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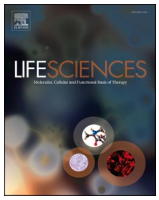

Impact of *Lactobacillaceae* supplementation on the multi-organ axis during MASLD

André A. Santos [a,*], Raquel Duarte [a], Madalena Duarte [a], Fabiola Arella [a], Vanda Marques [a], Stefan Roos [b], Cecília M.P. Rodrigues [a]

[a] Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Portugal
[b] Department of Molecular Sciences, Uppsala BioCenter, Swedish University of Agricultural Sciences, Sweden

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ABSTRACT

The gut-liver axis plays a pivotal role in maintaining body homeostasis. Disruption of the gut-liver axis is linked to a multitude of diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD). Probiotic strains from the *Lactobacillaceae* family are commonly used to mitigate experimental MASLD. Over the years, numerous studies have demonstrated the efficacy of these probiotics, often focusing on the outcome of liver disease. This review aims to further understand MASLD as a systemic metabolic dysfunction and to highlight the effects of probiotics on multi-organ axis, including organs such as the gastrointestinal tract, pancreas, muscle, adipose tissue, and the immune system. We specifically discuss evidence on how supplementation with *Lactobacillaceae* strains may alleviate MASLD by not only restoring liver health but also by modulating the physiology of other organ systems.

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major cause of chronic liver disease worldwide and is becoming a recurrent indication for liver transplantation in Europe and the USA [1,2]. The recent renaming from non-alcoholic fatty liver disease MASLD aimed to categorize more accurately patients who have liver disease and metabolic dysfunction simultaneously [3]. This reinforces MASLD as a manifestation of disrupted all-body homeostasis.

MASLD is widespread in developed countries and found in approximately 30 % of the adult population, with a predicted 21 % increase in prevalence from 2015 to 2030 [4]. Disease pathogenesis is particularly complex with etiology involving an interplay between genetics and environmental factors. The development of MASLD is intimately driven by the Western diet (WD) coupled with reduced physical activity and exercise [5]. WD is characterized by excessive consumption of calorie-dense food enriched in simple carbohydrates and saturated fats. Importantly, this diet modulates the gut microbiota, largely contributing to altered diversity and function.

The gut microbiota is a highly dynamic and complex consortium of microorganisms including bacteria, archaea, fungi, protozoa, and viruses that coexist in an equilibrium known as eubiosis [6]. Dysbiosis or unbalanced gut microbiota equilibrium is associated with MASLD and leads to changes in intestinal permeability, energy harvesting capacity, and production of microbial products, which can alter host signaling pathways [7,8].

Only recently, Resmetirom has been approved by the FDA as the first drug for the treatment of MASLD [9], together with lifestyle interventions still considered key in the clinical management of MASLD [5]. Nevertheless, the long-term sustainability of these interventions is poor and modulation of the gut microbiota has emerged as a novel strategy to alleviate the disease [10].

2. Probiotics in MASLD alleviation

As defined by the World Health Organization, probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [11]. In recent years, there has been increasing interest in the use of probiotics for the treatment or prevention of liver disease.

2.1. *Lactobacillaceae* strains

Among several probiotics, *Lactobacillaceae* strains have been

* Corresponding author.
E-mail address: afasantos@ff.ulisboa.pt (A.A. Santos).

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frequently used as probiotics due to their health-promoting effects. Their main characteristics are adhesion and aggregation, competitive adherence, auto- and co-aggregation, and stimulation of the immune system. The adhesion and aggregation traits inherent to *Lactobacillaceae* strains help host organisms prevent disease-causing bacteria from settling in the intestinal tract. The effectiveness of this adhesion factor is influenced by the species and origin of the strain. In terms of competitive adherence, certain strains such as *L. rhamnosus* and *L. acidophilus* have demonstrated their ability to effectively decrease the presence of harmful bacteria in adherence competition tests. This contributes to the prevention and removal of pathogenic bacteria in the gastrointestinal tract. *Lactobacillaceae* strains possess varying levels of auto-aggregation and co-aggregation abilities. These abilities can influence the prevention of harmful bacteria colonization and their removal from the gastrointestinal tract. These properties make *Lactobacillaceae* strains effective as probiotics in the treatment of various conditions, including MASLD. However, the effectiveness can vary depending on the specific strain and the individual health condition [12].

2.2. *Lactobacillaceae* impact on liver disease

Lactiplantibacillus plantarum strains have been shown to alleviate liver disease outcomes, reducing lipopolysaccharide (LPS)-induced oxidative stress [13] and body weight, and lowering serum liver enzymes [14]. In mouse models supplemented with *Lactobacillaceae* strains, the administration of *L. plantarum* ZJUIDS14 decreased the concentration of plasma triglycerides (TG), free fatty acids, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), together with an increase in high-density lipoprotein cholesterol levels when compared to the high-fat diet (HFD) (45 %) control group [15]. On the other hand, single supplementation of *Limosilactobacillus reuteri* MJM60958 or *L. plantarum* ZJUIDS14 also resulted in decreased blood total TG levels, while no significant change was observed in TC. Notably, *L. reuteri* MJM60668, *L. plantarum* Q16, *Lacticaseibacillus paracasei* N1115, *Lactobacillus acidophilus* LA5 and *L. plantarum* dfa1 supplementations contributed to decreased TG and TC levels (Table 1) [15–22]. Other studies have shown that the ability of *Lactobacillaceae* strains to reduce liver fat accumulation and obesity was not exclusively attributed to *L. plantarum*, but was rather observed in other strains, such as *Lacticaseibacillus rhamnosus* GG and *Limosilactobacillus reuteri* GMLN-263 [23]. Recently, it was demonstrated that *L. rhamnosus* GG competes with the host for fatty acid absorption in the intestine, resulting in decreased weight gain and body fat mass, as well as hepatic lipid accumulation. These results suggest that *Lactobacillaceae* strains would not directly influence liver disease but rather contribute to reducing the total fat reaching the liver while also ameliorating MASLD features such as liver fibrosis and inflammation. We have also recently reported that *L. reuteri* supplementation reduced liver fibrosis in acute bile duct-ligated mice and that D-lactate, a main metabolite of *Limosilactobacillus*, decreased macrophage transforming growth factor-β (TGF-β) production that may link to reduced liver fibrosis [24]. Consequently, supplementation with *Limosilactobacillus* may not only direct influence lipid metabolism, but also modulate other host metabolic pathways.

Considerable effort has been devoted to understanding the role of *Lactobacillaceae* in liver modulation, resulting in several reviews discussing the probiotic effects on liver phenotype. However, there remains a scarcity of understanding regarding the influence of *Lactobacillaceae* in other organ systems. Thus, in this review we aim to address the impact of *Lactobacillaceae* in gut, adipose, and muscle tissues, as well as immune system response within the context of MASLD, thereby elucidating its holistic therapeutic potential.

3. Modulation of the gut environment

As a symbiotic entity, the gut microbiota plays a crucial role in digestion, metabolism, immune function, and energy homeostasis. A

Table 1
Effects of *Lactobacillaceae* strains on the gut environment under dietary animal models.

Tissue and effect	Dietary model	*Lactobacillaceae* strains	Ref.
Serum/plasma			
TG decrease	HFD, 60 %	*L. acidophilus* KLDS1.0901	[16]
		L. plantarum dfa1	[22]
		L. plantarum Q16	[19]
	HFD, 45 %	*L. acidophilus* LA5	[21]
		L. plantarum ZJUIDS14	[15]
		L. reuteri ATCC 6475 and VPL 3461	[93]
		L. reuteri MJM60668	[18]
		L. sakei MJM60958	[17]
	HFD[a]	*L. paracasei* N1115	[20]
TC decrease	HFD, 60 %	*L. acidophilus* KLDS1.0901	[16]
		L. plantarum dfa1	[22]
		L. plantarum Q16	[19]
	HFD, 45 %	*L. acidophilus* LA5	[21]
		L. reuteri MJM60668	[18]
	HFD[a]	*L. paracasei* N1115	[20]
LPS decrease	HFD, 60 %	*L. acidophilus* KLDS1.0901	[16]
		L. rhamnosus GG	[64]
	HFD, 45 %	*L. lactis*	[30]
		L. plantarum ZJUIDS14	[15]
	HFD, 40 %	*L. gasseri* SBT2055	[33]
	HFHFD, 65 %	*L. plantarum* NA136	[29]
	HFHFD, 45 %	*L. fermentum* CQPC06	[25]
	HFHCD, 42 %	*L. rhamnosus* L7-1	[31]
	HFD[a]	*L. paracasei* N1115	[20]
		L. plantarum ATCC 14917	[39]
Intestine			
Lipogenic transcripts amelioration	HFD, 45 %	*L. plantarum* ZJUIDS14	[15]
	HFHFD, 45 %	*L. fermentum* CQPC06	[25]
Tight junctions increase	HFD, 60 %	*L. acidophilus* KLDS1.0901	[16]
	HFD, 45 %	*L. lactis*	[30]
		L. plantarum ZJUIDS14	[15]
	HFHFD, 65 %	*L. plantarum* NA136	[29]
	HFHFD, 45 %	*L. fermentum* CQPC06	[25]
Mucosal function increase	HFD, 60 %	*L. acidophilus* KLDS1.0901	[16]
		L. rhamnosus GG	[64]
	HFD, 45 %	*L. acidophilus* LA5	[21]
	HFHFD, 45 %	*L. fermentum* CQPC06	[25]
	HFHCD, 42 %	*L. rhamnosus* L7-1	[31]
		L. rhamnosus L10-1	[31]
Inflammation amelioration	HFD, 60 %	*L. plantarum* dfa1	[22]
	HFD, 45 %	*L. plantarum* ZJUIDS14	[15]
Permeability improvement	HFD, 60 %	*L. plantarum* dfa1	[15]
	HFD, 45 %	*L. acidophilus* LA5	[21]
	HFD, 40 %	*L. gasseri* SBT2055	[33]
Gut microbiota			
Microbial diversity increase	HFD, 60 %	*L. plantarum* Q16	[19]
		L. reuteri ATCC 6475	[94]
	HFD, 45 %	*L. plantarum* ZJUIDS14	[15]
	HFHFD, 65 %	*L. plantarum* NA136	[29]
	HFD[a]	*L. plantarum* ATCC 14917	[39]
F/B ratio restoration	HFD, 60 %	*L. acidophilus* KLDS1.0901	[16]
		L. plantarum Q16	[19]
	HFD, 45 %	*L. lactis*	[30]
	HFHFD, 45 %	*L. fermentum* CQPC06	[25]
	HFHCD, 42 %	*L. rhamnosus* L7-1	[31]
	HFD[a]	*L. paracasei* N1115	[20]
		L. plantarum ATCC 14917	[39]
		L. reuteri ATCC 6475	[82]

[a] Calories from fat percentage not disclosed. Abbrev: HFD, high-fat diet; HFHFD, high-fat diet high fructose diet; HFHCD, high-fat, high-cholesterol diet; LPS, lipopolysaccharide; TC, total cholesterol; TG, triglycerides.

potential imbalance of the microbiota stimulates altered bile acid homeostasis and intestinal barrier dysfunction, which later can contribute to increased intestinal permeability. This disruption allows bacteria and their metabolites to translocate into the liver, triggering the release of inflammatory cytokines and promoting the progression of liver disease (Fig. 1) [10].

3.1. Lipid metabolism in intestinal cells

A prolonged and excessive intake of calories, particularly from lipid- and sugar-rich diets such as a WD is associated with disruption in gut barrier function, inflammation, and alterations in the gut microbiome and serum lipids. Several intestinal mRNA markers have been used to evaluate the efficacy of *Lactobacillaceae* strains in modulating the gut environment during MASLD. Considering intestinal lipid metabolism, cluster of differentiation 36 (*Cd36*) mRNA expression is usually used to evaluate the absorption of long-chain fatty acids (LCFA) during HFD (45 %). Interestingly, the use of *Limosilactobacillus fermentum* CQPC06 in this dietary model significantly decreased small intestine *Cd36* mRNA expression [25]. Similarly, the expression of lipogenic genes in ileum tissue, including fatty acid transport protein 2 (*Fatp2*), fatty-acid-binding protein 2 (*Fabp2*), and *Cd36* was downregulated by *L. plantarum* ZJUIDS14 compared to the HFD (45 %) group [15]. Moreover, using radioactive oleic acid (OA), it was shown that *L. rhamnosus* GG can accumulate extracellular OA. This was observed by a decrease in the radioactivity of the medium, along with increased radioactivity in the bacterial pellet, suggesting the incorporation of OA into bacterial cells (~60 %). The same occurred with *L. gasseri* and *L. acidophilus*, but to a lesser extent (~20 %) [26]. Consequently, *L. rhamnosus* GG may limit the availability of exogenous OA by retaining fatty acids, potentially leading to a direct decrease in the intestinal absorption of fatty acids. *Lactobacillaceae* strains consume dietary fatty acids and, thus, reduce the total fatty acids that reach the intestinal tissue, contributing to ameliorating HFD-induced intestinal damage. Nevertheless, due to the high intake of fatty acids during HFD and the relatively low number of *Lactobacillaceae* used in a probiotic intervention, a beneficial effect of probiotics must majorly rely on the regulatory effect of the bacteria (e.g. modulation of host fat metabolism, immunity, and controlling gut microbiota dysbiosis).

3.2. Intestinal integrity

The preservation of host homeostasis relies heavily on the integrity of the intestinal epithelial barrier. At the core of this barrier are tight junctions, complexes formed by proteins such as zonula occludens (ZO), occludin, claudins, and junctional adhesion molecules (JAMs). Together, they regulate intestinal permeability, ensuring paracellular passage of ions, nutrients, and solutes between adjacent epithelial cells, thereby maintaining integrity and function. ZO-1 acts as a cytoskeletal linker protein, playing an important role in the assembly of tight junctions. In turn, occludin and claudins are the major integral membrane proteins, while JAMs regulate cell-cell adhesion [27].

In the past, several studies have demonstrated that MASLD is associated with decreased expression of tight junction proteins in the intestine [28]. Of note, supplementation with *Lactococcus lactis*, *L. acidophilus* KLDS1.0901, *L. fermentum* CQPC06, and *L. plantarum* (strains NA136 and ZJUIDS14) in experimental MASLD mouse models has been shown to modulate this host-bacteria physical barrier contributing to ameliorating liver disease [15,16,25,29,30]. In HFD-fed mice, supplementation with *L. plantarum* NA136 improved intestinal

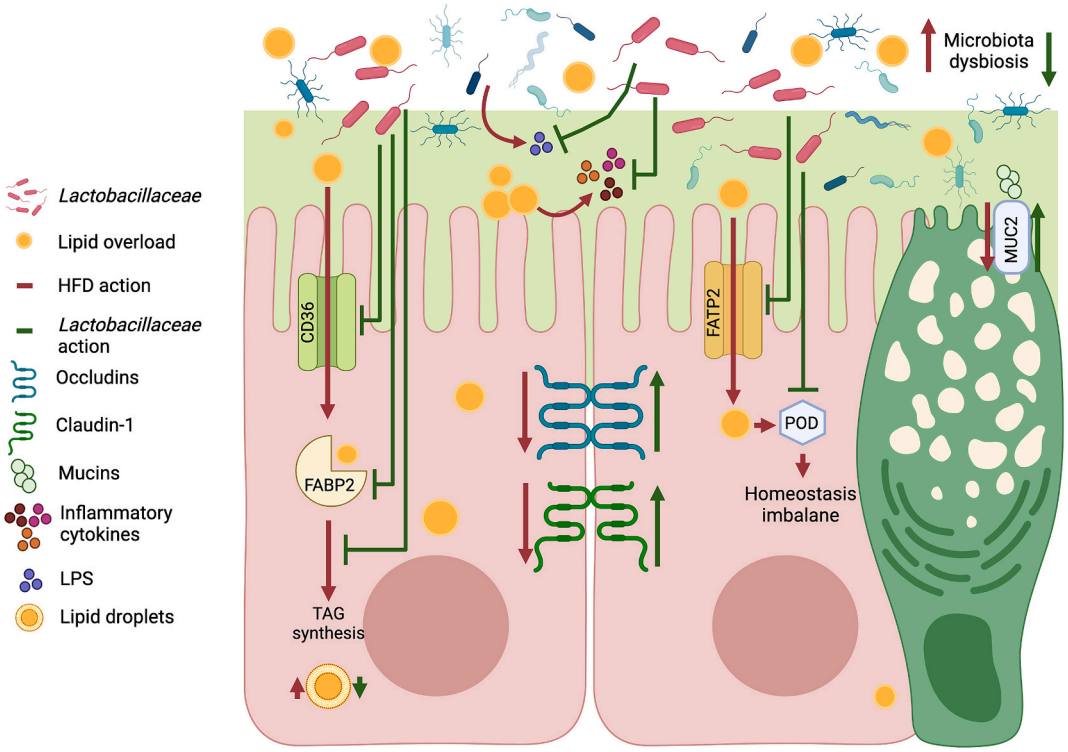

Fig. 1. Gut modulatory effects of *Lactobacillaceae* strains under HFD. Lipid overload leads to increased lipid transport and storage. Impairment of lipid transporters CD36, FATP2, and FABP2 by *Lactobacillaceae* limit the HFD-induced triglyceride synthesis and upregulation of diamine peroxidase. Moreover, HFD-associated microbiota dysbiosis promotes increased pro-inflammatory environment in the gut. Through the recovery of microbiota dysbiosis, *Lactobacillaceae* decrease bacterial LPS and intestinal inflammatory cytokine release, thus ameliorating intestinal inflammation. Additionally, *Lactobacillaceae* counteract the HFD-induced decrease of epithelial barrier defense, though the modulation of MUC2 and intestinal tight junctions occludins and claudin.

permeability by increasing *Zo-1* and *Occludin* mRNA expression. Similarly, in WD (42 %)-fed mice, supplementation with *L. lactis* also increased *Zo-1* and *Occludin* mRNA expression [30]. Furthermore, the administration of *L. plantarum* ZJUIDS14 to HFD-fed mice substantially increased ZO-1 and CLAUDIN-1 protein expression levels in the ileum compared to the non-treated HFD (45 %) group [15]. Similar results were obtained in a more specific high-fat (45 %) high-fructose (10 %) diet (HFHFD) mouse model, where *L. fermentum* CQPC06 treatment increased *Zo-1*, *Occludin*, and *Claudin-1* mRNA expression in the ileal tissues in a dose-dependent manner [25]. In the colon, administration of *L. acidophilus* KLDS1.0901 upregulated the expression of *Zo-1*, *Occludin*, and *Claudin-1* mRNA expression [16]. Conversely, administration of *L. rhamnosus* (strains GG, L7-1, and L10-1) failed to modulate the levels of tight junction proteins ZO-1, CLAUDIN-1, and OCCLUDIN promoted by high-fat (42 %) high-choline deficient diet (HFHCD) [31].

Using the 4-kDa fluorescein isothiocyanate dextran method [32] to evaluate intestinal epithelial barrier permeability in mice, the individual administration of *L. gasseri* SBT2055, *L. plantarum* dfa1 and *L. acidophilus* LA5 reduced HFD-induced permeabilization. This suggests the potential of *Lactobacillaceae* strains in preventing intestinal barrier disruption induced by HFD intake [21,22,33]. Similarly, in *in vitro* studies, human adenocarcinoma Caco-2 cells subjected to interferon gamma (IFN-γ) and TNF-α stimulation, and treated with *L. gasseri* SBT2055 or *L. lactis*, presented increased transepithelial electrical resistance (TEER) values, thus indicating an improvement in barrier impairment promoted by the pro-inflammatory stimuli [30,33].

3.3. Intestinal mucosa

Another crucial aspect of a functional intestinal barrier is the mucosal layer, which is composed of mucins secreted by goblet cells. This layer creates a protective environment that shields the intestinal tissue from the microbiota located near the epithelial cells [34]. Recently, it was demonstrated that *L. acidophilus* KLDS1.0901 and LA5 ameliorated *Muc-2* mRNA levels, counteracting the severely down-regulation induced by HFD (60 %) alone [16]. Nevertheless, it should be noted that the decrease in *Muc-2* mRNA expression during HFD (60 %) is not unanimous, as it has been found increased in other studies [21].

On the other hand, diamine peroxidase, an intracellular enzyme abundantly found on the villi of the small intestinal mucosa, plays a crucial role in regulating the synthesis of nucleic acids and proteins within mucosal cells, serving as a direct indicator of the overall integrity and extent of damage to the intestinal barrier. It has been demonstrated that the significant increase in diamine peroxidase serum levels observed in HFHFD (45 %|10 %)-fed mice can be restored by *L. fermentum* CQPC06 [25]. Moreover, this *Lactobacillaceae* strain was also able to minimize not only the thinning of the small intestinal mucosal epithelium, but also the decrease in the height and width of villi, and the reduction in the abundance of goblet cells induced by the HFHFD[25]. Furthermore, the administration of *L. rhamnosus* (*L. rhamnosus* GG, L7–1, and L10–1) during HFHCD increased the mucosubstances and length of intestinal villi in the ileum. It also restored the structure integrity of the colon, which was compromised in the untreated group. This intervention prevented the HFHCD-induced alterations and dysregulation in both the ileum and colon [31].

3.4. Intestinal immune response

HFD-induced changes in intestinal function together with microbiota modulation have been shown to be crucial to MASLD onset and progression. Indeed, the most known inflammatory bacterial marker is by far the Gram-negative bacterial LPS [35,36]. Due to its association with intestinal barrier disruption, the serum concentration of LPS is a standard indicator of intestinal barrier damage [16]. Interestingly, several *Lactobacillaceae* strains have been shown to ameliorate LPS blood concentration during HFD (Table 1). Nevertheless, this is a strain-specific feature, as *L. rhamnosus* L10-1, for instance, was not able to reduce serum LPS levels [31]. The MASLD inflammatory profile may start immediately at the gut site. Here, *L. plantarum* dfa1 was observed to normalize tumor necrosis factor-alpha (TNF-α) and inerleukin-6 (IL-6) cytokine levels in the colon, which were upregulated in HFD (60 %)-fed mice [22]. Additionally, the increased *Il-1β*, *Tnf-α*, and Cathelicidin-related antimicrobial peptide (*Cramp*) mRNA levels induced by the HFD (45 %), were restored by *L. plantarum* ZJUIDS14 administration [15]. CRAMP is an innate immune system effector molecule known for its distinct antimicrobial and immunomodulatory properties. This antimicrobial peptide is primarily synthesized by colonic epithelial cells in the gut, where it assumes a crucial role in the modulation of gut microbial communities [37]. Collectively, *Lactobacillaceae* supplementation plays a protective effect in intestinal barrier function and permeability against the infiltration of bacterial LPS from the intestine, possibly modulating the overgrowth of Gram-negative bacteria induced by the HFD or improving immunomodulatory functions (Table 2).

3.5. Gut microbiome

When assessing gut microbiota variations, the overall community behavior is evaluated using both α- and β-diversity. In a microbial community, α-diversity estimates species richness and evenness, while β-diversity compares the diversity between different communities, providing insights into how communities differ in terms of species composition [38]. Dietary mice models have shown that HFHFD induces a reduction in gut microbiota richness. Interestingly, the intestinal bacterial diversity can be restored with the administration of different *L. plantarum* strains (NA136, ZJUIDS14, ATCC14917, and Q16) [15,19,29,39]. However, this feature is not extensive to all *Lactobacillaceae* as *L. acidophilus* KLDS1.0901, and *L. rhamnosus* (strain L7-1, and L10-1) revealed no significant impact on gut bacterial diversity modulation [16,31]. In contrast, *L. rhamnosus* GG presented lower α-diversity compared to both control and HFHCD (42 %) groups [31].

Considering bacterial composition, Bacteroidetes (now renamed Bacteroidota) and Firmicutes (now renamed Bacillota) are the most prominent phyla in the mammal gut microbiota, crucial for host energy metabolism [40,41]. An increase in the Firmicutes/Bacteroidetes ratio (F/B) has been associated with HFD, accompanied by enhanced calorie absorption, increased harvestable energy, and presence of biomarkers related to obesity [40,42–46]. Similar F/B trends have been observed in patients with MASLD [47]. Interestingly, several studies have shown that *Lactobacillaceae* supplementation in MASLD dietary mice models typically results in a decrease in Firmicutes, and consequently, a decrease in the F/B ratio [40]. However, this cannot be generalized to all *Lactobacillaceae* species, as *L. plantarum* ZJUIDS14 for instance, showed no significant impact on F/B[15].

4. Gut-pancreas axis

The pathogenesis of MASLD is largely heterogeneous, with insulin resistance being a prevalent factor. This metabolic alteration is characterized by reduced glucose disposal in non-hepatic tissues, including the pancreas, muscle, and adipose tissue. Although hepatic steatosis is closely associated with systemic insulin resistance, it is noteworthy that insulin resistance also predicts the development of MASLD [48]. Insulin is produced in the pancreas, particularly by beta cells of the islets of Langerhans, and it plays an essential role in regulating glucose metabolism and insulin secretion by responding to changes in nutrients under various metabolic circumstances [49].

4.1. Insulin resistance

Obesity and HFD are closely linked with MASLD and type II diabetes, which induces insulin resistance and accelerates fat accumulation in the pancreas, causing islets of Langerhans cell death and compromising

Table 2
Effects of *Lactobacillaceae* strains on muscle, pancreas, and adipose tissue under dietary animal models.

Tissue and effect	Dietary model	*Lactobacillaceae* strains	Ref.
Muscle			
Insulin resistance improvement	HFD, 60 %	*L. acidophilus* NX2-6	[66]
		L. rhamnosus GG	[64]
	HFD, 45 %	*L. acidophilus* NS1	[63]
	HFD, 60 %	*L. rhamnosus* GG	[64]
Lipid metabolism improvement	HFD, 57 %	*L. fermentum* MTCC5689	[65]
		L. plantarum MTCC5690	[65]
	HFD, 45 %	*L. acidophilus* NS1	[63]
ER stress levels restoration	HFD, 57 %	*L. fermentum* MTCC5689	[65]
		L. plantarum MTCC5690	[65]
Inflammation suppression	HFD, 60 %	*L. acidophilus* NX2-6	[66]
Mitochondrial biogenesis improvement	HFD, 60 %	*L. acidophilus* NX2-6	[66]
Gluconeogenesis suppression	HFD, 60 %	*L. acidophilus* NX2-6	[67]
Pancreas			
Insulin resistance improvement	HFD, 60 %	*L. plantarum* CCFM0236	[52]
		L. plantarum-pMG36e-GLP-1	[59]
		L. plantarum SHY130	[54]
	HFD, 40 %	*L. gasseri* SBT2055	[33]
	HFD[a]	*L. paracasei* NL41	[53]
α-Cells decreased proliferation	HFD, 60 %	*L. plantarum* SHY130	[54]
	HFD[a]	*L. paracasei* NL41	[54]
β-Cells loss protection	HFD, 60 %	*L. plantarum* CCFM0236	[52]
		L. plantarum-pMG36e-GLP-1	[59]
		L. plantarum SHY130	[54]
Oxidative damage reduction	HFD[a]	*L. paracasei* NL41	[54]
	HFD, 60 %	*L. plantarum* SHY130	[54]
	HFD[a]	*L. paracasei* NL41	[54]
		L. plantarum CCFM0236	[52]
		L. plantarum HAC01	[56]
Islets of Langerhans protection and repair	HFD, 60 %	*L. plantarum* SHY130	[54]
		L. plantarum-pMG36e-GLP-1	[59]
	HFD, 58 %	*L. rhamnosus* ATCC 53103	[50]
	HFD, 45 %	*L. casei* Q14	[55]
		L. paracasei G15	[55]
	HFD, 10 %	*L. plantarum* HJ-S2	[58]
	HFD[a]	*L. paracasei* NL41	[54]
Fat accumulation	HFD, 10 %	*L. plantarum* HJ-S2	[58]
Inflammation improvement	HFD, 60 %	*L. plantarum*-pMG36e-GLP-1	[59]
	HFD, 10 %	*L. plantarum* HJ-S2	[58]
	HFD[a]	*L. gasseri* SBT2055	[33]
Adipose tissue			
Lipid metabolism improvement	HFD, 60 %	*L. gasseri* MG4524	[70]
		L. plantarum Shinshu N-07	[69]
		L. rhamnosus LRH05	[73]
		L. rhamnosus MG4502	[70]
		L. reuteri MG5149	[70]
	HFD, 45 %	*L. acidophilus* NS1	[63]
	HFD, 55 %	*L. plantarum* Ln4	[61]
Insulin resistance improvement	HFD, 45 %	*L. acidophilus* NS1	[63]
	HFD[a]	*L. plantarum* L-14 extract	[72]
Weight gain reduction	HFD, 60 %	*L. gasseri* MG4524	[70]
		L. paracasei L9	[74]
		L. reuteri MG5149	[70]
		L. rhamnosus MG4502	[70]
	HFD, 55 %	*L. plantarum* Ln4	[61]
Fat/lipid accumulation improvement	HFD, 60 %	*L. acidophilus* NX2-6	[67]
		L. gasseri MG4524	[70]
		L. reuteri MG5149	[70]
		L. rhamnosus MG4502	[70]
	HFD, 55 %	*L. plantarum* Ln4	[61]
Glucose metabolism improvement	HFD[a]	*L. plantarum* L-14 extract	[72]
	HFD, 60 %	*L. gasseri* MG4524	[70]
		L. reuteri MG5149	[70]
		L. rhamnosus MG4502	[70]
	HFD, 55 %	*L. plantarum* Ln4	[61]
Inflammation improvement	HFD, 60 %	*L. brevis* OPK-3	[71]
		L. fermentum LM1016	[68]
		L. paracasei L9	[74]
		L. plantarum Shinshu N-07	[69]
		L. rhamnosus LRH05	[73]
	HFD[a]	*L. plantarum* L-14 extract	[61]
Oxidative phosphorylation induction	HFD, 60 %	*L. fermentum* LM1016	[68]
Balanced adipocyte differentiation	HFD, 60 %	*L. brevis* OPK-3	[71]
		L. rhamnosus LRH05	[73]
	HFD[a]	*L. plantarum* L-14 extract	[61]
Adipose tissue browning	HFD, 60 %	*L. acidophilus* NX2-6	[67]
		L. plantarum Shinshu N-07	[69]

[a] Calories from fat percentage not disclosed. Abbrev: HFD, high-fat diet.

pancreatic function. This process increases monocyte infiltration and expression of proinflammatory cytokines, inducing inflammation and β-cell failure, resulting in insulin resistance and ectopic fat deposition in other tissues [49,50]. On the other hand, this forms a self-perpetuating loop, where hepatic fat accumulation further promotes insulin resistance and consequently the synthesis of free fatty acids released into the pancreas [51]. Although most studies involving the pancreas and HFD are associated with type II diabetes, there is a great lack of information regarding MASLD and pancreatic cell failure [52,53]. Several studies have shown that *Lactobacillaceae* strains may have protective effects on the pancreas by reducing oxidative damage and, consequently, improving insulin resistance (Fig. 2A). In this regard, the administration of *L. plantarum* CCFM0236 in high-fat and streptozotocin-induced type II diabetes mice protected β-cells and islets of Langerhans, thereby improving insulin resistance and contributing to ameliorating pancreatic function [52]. Moreover, both *L. paracasei* NL41 and *L. plantarum* SHY130 administration in mice fed HFD and streptozotocin-induced type II diabetes mellitus rats, besides reducing islets of Langerhans damage, also protected against β-cell loss and α-cell expansion [53,54]. Furthermore, in both mice and rat type II diabetes models, treatment with *Lactobacillaceae* strains, such as *L. paracasei* subsp. paracasei G15, *L. casei* Q14, and *L. plantarum* HAC01, improved histological abnormalities, increased the number of normal β cells, and normalized the shape of islet cell clusters [55,56]. In turn, *L. gasseri* SBT2055 supplementation increased insulin secretion by suppressing of pancreatic and systemic inflammation [57], while *L. rhamnosus* significantly reduced islets of Langerhans size and *L. plantarum* HJ-S2 reduced fat accumulation and inflammatory cell infiltration in the liver and pancreas [50,58].

4.2. Pancreatic modulation

Next-generation probiotics are currently being investigated as therapeutic agents with an impact on gut microbiota and liver disease development. Glucagon-like peptide-1 (GLP-1) shows excellent therapeutic effects on diabetes but has an extremely short half-life *in vivo* [59]. To solve GLP-1 short half-life and consider the potential therapeutic effects of *L. plantarum*, a novel and diabetes-specific *Lactobacillaceae* strain transformed with the pMG36e-GLP-1 plasmid was developed, which could persistently express GLP-1 and showed a good curative effect in an obese diet-induced mouse model. Administration of

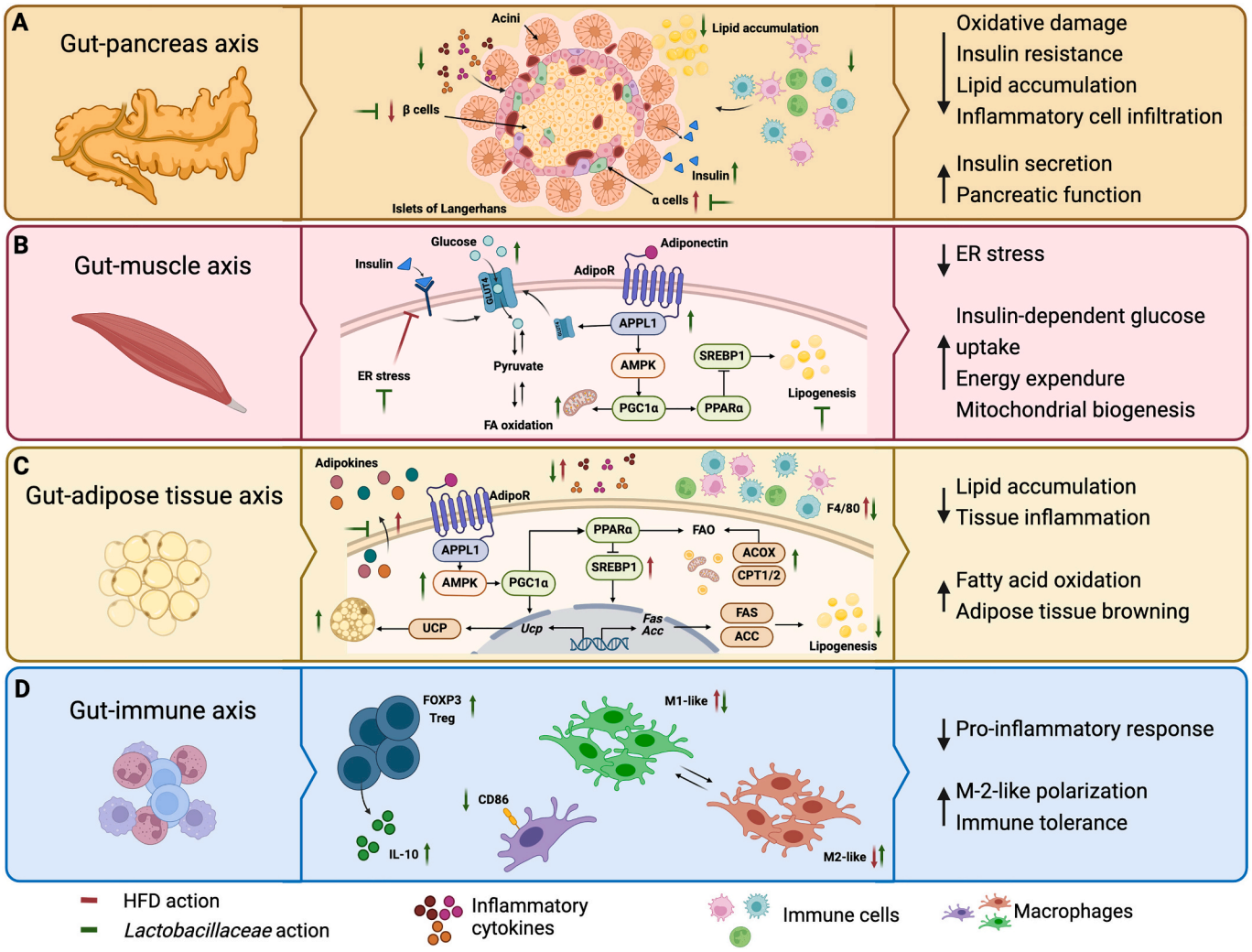

Fig. 2. Modulatory effects of *Lactobacillaceae* strains in the gut-tissue specific axis under HFD. A) In the pancreas, *Lactobacillaceae* have been shown to reduce cell damage in the islets of Langerhans, as well as keep α-cell and β-cell homeostasis. Also, by reducing fat accumulation and the immune cell infiltration, *Lactobacillaceae* promote pancreatic function. B) In the muscle, *Lactobacillaceae* reduce ER stress, thus improving insulin-dependent glucose uptake and consequent fatty acid oxidation. Through APPL1/AMPK signaling, *Lactobacillaceae* promote mitochondrial function and inhibit lipogenesis. C) Similarly to the muscle, in adipose tissue, through APPL1/AMPK/PGC1-α signaling *Lactobacillaceae* inhibit lipogenesis and increase adipocyte browning. The increase of PPAR-α, ACOX, CPT1 and CPT2 expression promote fatty acid oxidation (FAO). Moreover, *Lactobacillaceae* inhibit adipokine release, and decrease a pro-inflammatory cytokines and immune recruitment. D) *Lactobacillaceae* are general modulators of immune response by stimulating an anti-inflammatory environment by promoting M2-like macrophage polarization, increased levels of IL-10 and decreased T cell activation.

L. plantarum-pMG36e-GLP-1 regulated the intestinal microbiota, reduced the inflammatory reaction in the pancreatic tissue, and inhibited apoptosis in the islets of Langerhans. Furthermore, *L. plantarum*-pMG36e-GLP-1 promoted islet β-cell proliferation and insulin secretion [59]. Despite, the promising results associated with genetically modified probiotics, particularly in humans, the challenges of safety and higher costs must be clearly defined. Therefore, although these *Lactobacillaceae* strains exhibit an anti-diabetic effect in the pancreas, more studies are needed to assess their effectiveness during MASLD.

5. Gut-muscle axis

During MASLD, the integrity of muscle tissue is compromised due to an imbalance in lipid and glucose metabolism, which increases oxidative stress in cells, stimulating cellular inflammation and consequently insulin resistance [60,61]. Furthermore, lipid accumulation and mitochondrial dysfunction induce endoplasmic reticulum stress and lipotoxicity, which are also involved in insulin resistance [62].

Administration of *L. rhamnosus* GG and *L. acidophilus* NS1 in HFD (45 %)-fed mice increased glucose transporter type 4 (*Glut4*) mRNA expression and AMP-activated protein kinase (AMPK) activation in skeletal muscle, thus improving insulin resistance *via* AKT phosphorylation [63]. GLUT4 is responsible for insulin-stimulated glucose uptake, and AMPK activation results in GLUT4 translocation from the cytosol to the cell membrane, consequently leading to glucose uptake in the skeletal muscle. This may also suggest an improvement in lipid metabolism and insulin resistance through an AMPK/SREBP-1c/PPAR-α signaling pathway, resulting in reduced lipogenesis and increase in fatty acid oxidation [63,64]. On the other hand, the endoplasmic reticulum stress inhibits insulin signaling by interfering with the insulin receptors on the cell surface, leading to insulin resistance and potentially serving as a precursor to MASLD. Indeed, the effect of *Lactobacillaceae* strains of Indian intestinal origin on mice fed an HFD (67 %) was shown to restore normal levels of endoplasmic reticulum stress factors such as GRP78, protein kinase R-like ER kinase (PERK), and IRE1α, thereby improving insulin resistance in skeletal muscle [65].

Recent data reinforce that administration of *L. acidophilus* NX2-6 in HFD (60 %) increased insulin sensitivity and improved mitochondrial

biogenesis in the skeletal muscle, activating the adiponectin/AdipoR1/APPL1/AMPKα/PGC-1α pathway, leading to increased energy expenditure [66]. By activating this pathway, the probiotic enhanced cell mitochondrial biogenesis and energy expenditure which could be translated into improvements in insulin resistance and lipid metabolism [67] (Fig. 2B).

6. Gut-adipose tissue axis

Different *Lactobacillaceae* strains have been shown to mitigate diet-induced body weight gain, fat accumulation, adiposity, and low-grade inflammation, while also contributing to decreased levels of serum metabolic biomarkers, such as blood glucose, insulin, and triglycerides [68,69].

6.1. Lipid accumulation

In HFD (55 %)-fed mice, *L. plantarum* Ln4 administration inhibited the increase in organ weight, including epididymal fat and brown adipose tissue, which are features highly associated with MASLD [61]. Administration of *L. acidophilus* NS1 in HFD (45 %)-fed mice counteracted diet-induced lipogenesis, as evidenced by decreased Srebp-1c and its target genes *Fas* and *Acc*, while fully restoring the expression of genes involved in fatty acid oxidation such as *Ppar-α, Acox,* and *Cpt1,* in both liver and adipose tissue [63] (Fig. 2C). Furthermore, *L. plantarum* Ln4 supplementation was also able to downregulated abnormal levels of several adipokines, including leptin, lipocalin-2, monocyte chemoattractant protein-1 (MCP-1), and insulin-like growth factor binding proteins, all associated with insulin action, as well as glucose and lipid metabolism [61]. In turn, in an HFD (60 %) mouse model, *L. fermentum* LM1016 ameliorated inflammation and induced oxidative phosphorylation in the adipose tissue, resulting in increased energy expenditure and protecting against diet-induced obesity [68]. Recent data indicated that the consumption of three *Lactobacillaceae* strains, namely *L. rhamnosus* MG4502, *L. gasseri* MG4524, and *L. reuteri* MG5149 impacted body weight gain, inhibited lipid accumulation, and improved glucose tolerance, thereby preventing fatty liver disease in obese mice. However, only supplementation with *L. reuteri* MG5149 significantly prevented weight gain. Furthermore, the intake of the three lactic acid bacteria strains normalized lipogenic protein expression, such as PPARγ, C/EBPα, and FAS in the liver and adipose tissue [70].

6.2. Adipose tissue immune modulation

Regulating adipose tissue inflammation is crucial for improving MASLD. In an HFD (60 %) mouse model, supplementation with *Lactobacillus brevis* OPK-3 inhibited adipose tissue inflammation, by decreasing mRNA expression of pro-inflammatory cytokines, such as *Il-6* and *Tnf-α*. Moreover, in mice epididymal adipose tissue, *L. brevis* OPK-3 balanced the mRNA expression of adipocyte differentiation genes *Ppar-γ, Cebpa*, *Lpl*, and *Ap2* [71]. *In vitro* treatment with *L. plantarum* L-14 extract significantly inhibited both lipid accumulation and cell differentiation of mouse 3T3-L1 cells and Human bone marrow stem cells into mature adipocytes *via* AMPK and PPAR signaling pathways. Furthermore, supplementation of HFD (60 %) with *L. plantarum* L-14 extract significantly decreased the fat mass of epididymal white adipose tissue (eWAT) and controlled eWAT dysfunction by inhibiting hypertrophic adipocytes and polarization to M1 eWAT macrophages [72]. On the other hand, *in vivo* administration of HFD (60 %) with *L. plantarum* Shinshu N-07 induced eWAT browning by upregulating of uncoupling protein 1 [69]. These data suggest that *Lactobacillaceae* strains may act in two distinct pathways, either by decreasing eWAT, or by stimulating eWAT differentiation to beige adipose tissue, both contributing to ameliorating liver disease.

MASLD is also known to induce adipocyte tissue hypertrophy and hyperplasia, which can be restored by some *Lactobacillaceae* strains [67,73,74]. In a HFD mouse model, *L. rhamnosus* LRH05 administration significantly reduced the infiltration of pro-inflammatory macrophages in white adipose tissue, by regulating the expression of *Igf-1*, *Mcp-1*, and *F4/80* genes involved in lipid metabolism and inflammation. These outcomes were consistent with the reduction in the size of adipocytes in adipose tissue, reinforcing the beneficial effects on adipogenesis [73]. In adipose tissue, *L. acidophilus NX2–6* suppressed lipid accumulation by decreasing the protein expression of FAS, SREBP-1c, C/EBPα, and PPAR-α, while increasing CPT2 expression. This inhibition of *de novo* lipogenesis and adipogenesis, coupled with enhanced fatty acid oxidation contributed to the suppression of fat accumulation. Moreover, *L. acidophilus NX2-6* treatment promoted fat browning and energy expenditure in adipose tissue, by activating the adiponectin/AMPKα/PGC-1α/UCP1 pathway [67]. Additionally, supplementation with *L. paracasei* L9 reduced body and adipose tissue weight, as well as inflammation of adipose tissue, partially justified *via* reduced serum LPS levels and adipose tissue *Tlr4* mRNA expression. Ultimately, *L. paracasei* L9 was shown to reduce fat accumulation in the adipose tissue through decreased *Fas* and *Acc* mRNA expression which consequently diminished adipocyte size [74].

7. Liver immune system function

The efficacy of the immune response is closely intertwined with the development and composition of the gut microbiota. This relationship is evidenced by studies comparing germ-free and conventionally raised mice, which demonstrate that gut microbiota is required for the normal generation and maturation of gut-associated lymphoid tissues and for host protection from infection [75,76]. In this regard, probiotics are one approach to support microbial growth and play an essential role in intestinal mucosa immunomodulation [77].

Kupffer cells (KCs), the liver resident macrophages, play a pivotal role in the pathogenesis of MASLD and are involved in hepatic injury, inflammation, infection, immune response, ischemia, and stress [78]. During liver inflammation, KCs recruit monocytes that can differentiate into two distinct phenotypes based on specific surface markers: activated macrophages (M1-like phenotype) with a pro-inflammatory role, and alternatively activated macrophages (M2-like phenotype) involved in inflammation resolution and tissue repair [79]. In MASLD, the pro-inflammatory M1-like phenotype appears to contribute to disease progression and severity. In this regard, it has been shown that supplementation with *L. paracasei* in an HFD mouse model reduced KCs infiltration and inhibited the pro-inflammatory M1-like response while promoting the anti-inflammatory M2-like response, thus inducing M2-like KC polarization in MASLD (Fig. 2D). Similarly, administration of *Lactobacillaceae* influenced hepatic macrophage polarization and alleviated inflammation-associated liver disease. For example, *L. paracasei* increased the fraction of M2-like macrophages in MASLD mice and relived the inflammatory response [80]. In another study, administration of *Bifidobacterium breve*, *L. paracasei,* and *L. rhamnosus* to Zucker-Lepr$^{fa/fa}$ rats, an obese rat model of insulin resistance syndrome, resulted in decreased expression of the pro-inflammatory marker Cd86 in hepatic macrophages, accompanied by improved liver damage [81]. These findings suggest that probiotics exert an immune-modulatory effect by influencing macrophage polarization. In addition, fast-food-fed mice supplemented with *L. reuteri* ATCC 6475 contributed to immune tolerance. This was achieved by promoting the induction of Foxp3^{+} regulatory T cells (Treg) and IL-10 [82].

8. Clinical translation of *Lactobacillaceae* effects

Although translating preclinical to clinical data is always a challenge, some authors have already tried to assess the benefits of *Lactobacillaceae* strains to alleviate MASLD or obesity related diseases. In a human trial, adults with metabolic syndrome supplemented their diet with *L. reuteri* for 18 weeks, with only a subset of the supplemented

participants showing improvements in TG and diastolic blood pressure. Also, those that responded to supplementation presented a different gut microbiota profile than participants in the non-responder and placebo groups. Interestingly, dietary sugar consumption was higher in the *L. reuteri* responders group, having been identified as a key differentiating factor between responders and non-responders [83]. In another study, the effect of probiotic supplementations in 21 glucose-tolerant humans was tested. Results showed that four-weeks of daily administration of *L. reuteri* SD5865 in glucose-tolerant humans increased glucose-stimulated GLP-1 and GLP-2 release, along with higher insulin and C-peptide secretion. However, *L. reuteri* SD5865 failed to alter peripheral and hepatic insulin sensitivity, body mass, ectopic fat content, or circulating cytokines [84]. Similarly, in patients with type II diabetes on insulin therapy subjected to *L. reuteri* DSM 17938 supplementation for 12 weeks, *L. reuteri* SD5865 also failed to affect liver steatosis, adiposity, or microbiota composition. However, insulin sensitivity was improved in a subset of participants, particularly those with high diversity of the gut microbiota at baseline [85]. Also, in type II diabetics, probiotics reduced fasting glucose, glycated haemoglobin, insulin, and homeostatic model of insulin resistance, while in patients with fatty liver diseases, probiotics reduced alanine and aspartate aminotransferases [86]. Interestingly, an integrative study suggested that an additional 100 g intake of microbe-containing foods was associated with a lower systolic blood pressure, C-reactive protein, plasma glucose, plasma insulin, triglyceride, waist circumference, and BMI levels, and also with a higher level of high-density lipoprotein cholesterol [87]. Accordingly, two systematic reviews using meta-analysis comprising data from 1990 to 2018 showed that probiotics improved body weight, body mass index, waist circumference, body fat mass, and visceral adipose tissue mass in overweight but not obese subjects [86,87].

Collectively, these results may suggest that the use of *Lactobacillaceae* may depend not only on the strain but also on the patient's gut microbiota baseline. Indeed, a systematic review showed that probiotic intake in patients with metabolic syndrome resulted in improved body mass index, blood pressure, glucose metabolism, and lipid profile, along with decreased inflammatory biomarkers. However, these beneficial effects seem to be marginal when compared to drug therapy and healthy lifestyles [88]. Indeed, a meta-analysis of randomized controlled trials found no significant differences in most anthropometric and biochemical outcomes between intervention and control groups while significant improvements were observed in body fat percentage and LDL-C [89]. These findings suggest that human trials for probiotic supplementation to alleviate MASLD should consider several key factors, such as the timing of probiotic supplementation, the stage of liver disease and even the use of probiotics before disease onset.

Of note, attention should also be given to kidney modulation during MASLD. Indeed, MASLD patients show a 1.5-fold increased risk of incident chronic kidney disease during a 10-year follow-up [90,91]. Recently, it was reported that mice under HFD (60 %) supplemented with *L. casei* LC-01 had significantly reduced serum aspartate aminotransferase and alanine transaminase together with decreased renal mRNA markers Lipocalin-2 (*Ngal*) and Hepatitis A Virus Cellular Receptor 1 (*Kim-1*). The study also verified an increase in kidney weight and volume compared to the HFD group, showing a protective effect of *L. casei* LC-01 [92]. In another study, kidney tissue HFD-induced damage was prevented by *L. paracasei* NL41 supplementation, with kidney-to-body weight maintenance and mitigation of pathological score [53]

9. Conclusion and future perspectives

MASLD is a metabolic disorder that disrupts whole-body homeostasis. Given the essential role of *Lactobacillaceae* strains in restoring homeostasis, we aimed to review information on the utilization of these strains for ameliorating MASLD outcome and progression. In contrast to the predominant focus on hepatic disease in most studies and reports, our attention shifted toward the gastrointestinal tract, pancreas, skeletal muscle, adipose tissue, and immune system. In addition to hepatic improvement, *Lactobacillaceae* strains contribute to systemic maintenance, spanning from the gastrointestinal tract to adipose tissue and skeletal muscle, with established effects on preventing insulin resistance and lipid accumulation. A more comprehensive understanding of the impact of gut microbiota modification remains elusive, and many questions remain unanswered.

Are the overall effects merely due to the improvement in hepatic disease? Or do they indeed reflect systemic amelioration of the disease? How do intestinal bacteria communicate with distant organs such as the skeletal muscle or brown adipose tissue? Which metabolites do these probiotics generate, or indirectly stimulate in other bacteria, that could potentially contribute to improve MASLD? Is the probiotic effect solely linked to immune system modulation, or does it also involve effects on gut permeability? Are we potentially losing the efficacy of gut microbiota modulation in human trials due to issues with sample collection or the duration of the trials? Should the microbiota of the small intestine be assessed instead of relying solely on stool microbiota analysis?

Although many questions remain unanswered, gaining a comprehensive understanding of the overall impact of *Lactobacillaceae* supplementation will enhance our knowledge of metabolic diseases like MASLD. In the future, combining nutritional and pharmacologic therapies with probiotic supplementation could help mitigate the outcomes and progression of MASLD. This underscores the importance of adopting a holistic, multi-organ approach to further understand and potentially treat MASLD.

Abbreviations

AMPK	AMP-activated protein kinase
C/EBPα	CCAAT-enhancer-binding proteins alpha
Cd36	Cluster of differentiation 36
FAS	Fas Cell Surface Death Receptor
Fatp2	Fatty acid transport protein 2
Fabp2	Fatty-acid-binding protein 2
GLP-1	Glucagon-like peptide-1
Glut4	Glucose transporter type 4
HFD	High-fat diet
HFHFD	High-fat high-fructose diet
Igf-1	Igf-1Insulin-like growth factor 1
KCs	Kupffer cells
LPS	Çipopolysaccharide
LDL-C	Low-density lipoprotein cholesterol
MASLD	Metabolic dysfunction-associated steatotic liver disease
Mcp-1	Monocyte chemoattractant protein 1
Muc-2	Mucin-2
APPL1	Phosphotyrosine interacting with PH domain and leucine zipper 1
PERK	Protein kinase R-like ER kinase
SREBP-1c	Sterol regulatory element-binding transcription factor 1
TC	Total cholesterol
TG	Triglycerides
WD	Western diet
ZO	Zonula occludens

CRediT authorship contribution statement

André A. Santos: Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Funding acquisition, Conceptualization. **Raquel Duarte:** Writing – original draft, Investigation. **Madalena Duarte:** Writing – original draft, Investigation. **Fabiola Arella:** Writing – review & editing, Writing – original draft, Investigation. **Vanda Marques:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Stefan Roos:** Writing – review & editing, Validation, Investigation. **Cecília M.P. Rodrigues:** Writing – review & editing, Validation, Supervision, Funding acquisition.

Declaration of competing interest

Stefan Roos has a part time employment in the company BioGaia AB. No potential conflicts of interest were reported by any other authors.

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