REDOX EXPERIMENTAL MEDICINE

A Das, A J De, T Mohanty *et al.* | 2023:1 | e230016

REVIEW

Role of oxidative stress, gut microbiota and derived metabolites in the etiology and progression of nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease or NAFLD is a complex and multifactorial liver disease that is affecting a majority of the world's population now more than ever. The review focuses on two major contributing factors in the etiology of the disease – oxidative stress and the gut microbiota. There is a complex interplay between oxidative stress and the gut microbiota in the pathogenesis of NAFLD. Oxidative stress in NAFLD can result from both the accumulation of lipids in the liver and the interactions between gut-derived metabolites and the liver. Dysbiosis in the gut microbiota can contribute to oxidative stress by promoting the production of reactive oxygen species and altering the balance of antioxidant systems. This interplay between oxidative stress and the gut microbiota can create a vicious cycle, where dysbiosis contributes to oxidative stress, and oxidative stress further promotes dysbiosis, exacerbating liver damage in NAFLD. Understanding the intricate relationship between oxidative stress, the gut microbiota, and NAFLD is essential for developing targeted therapeutic strategies. In this context, more scientific research is required to unravel the complex and interconnecting pathways underlying NAFLD pathogenesis and progression. Modulating the gut microbiota through dietary interventions, prebiotics, probiotics, and change in lifestyle may help restore microbial balance and reduce oxidative stress in NAFLD.

Keywords

- oxidative stress
- ROS
- gut microbiota
- dysbiosis
- metabolites
- NAFLD
- extrahepatic manifestation
- obesity
- T2DM
- CVD
- CKD
- IBD
- cognitive impairment

Redox Experimental Medicine (2023) **2023**, e230016

Introduction

With the growing prevalence of obesity and diabetes worldwide, liver diseases are becoming more frequent. Nonalcoholic fatty liver disease (NAFLD) is now the one of the most common forms of liver disease found across the globe. Currently, 12% of children and a third (70%) of adults are affected by this condition, particularly the ones suffering from type 2 diabetes mellitus (T2DM), central obesity, and metabolic syndrome (MS). NAFLD is a condition that is characterized by excessive accumulation of lipids and triglycerides (TGs) in hepatocytes i.e. by more than 5%. Whereas NASH, an extended form of the NAFLD, is characterized by the presence of steatosis in more than 5% of hepatocytes along with signs of inflammation and ballooning, with or without the occurrence of fibrosis (Hamid *et al.* 2022). In Western nations, it is one of the leading causes of liver cirrhosis and hepatocellular

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carcinoma (HCC), especially in patients with nonalcoholic steatohepatitis (NASH) and severe fibrosis (Mantovani *et al.* 2020).

The MS, a cluster of metabolic abnormalities including excess weight or obesity, T2DM, dyslipidemia, and arterial hypertension, is closely connected pathophysiologically to the causes of this disorder (Ye *et al.* 2020). Hence, a suggested nomenclature change to metabolic-associated fatty liver disease from NAFLD was made in 2020 by a committee of worldwide experts. The primary goal of the nomenclature change was to emphasize the significance of metabolic abnormalities by making this disease an inclusive rather than an exclusive entity, like NAFLD (García-Compeán & Jiménez-Rodríguez 2022).

Currently, a number of animal studies are being conducted to better understand the development and pathophysiology of NAFLD/NASH with different diet-based models (high fructose, high fat, and methionine-deficient diet). These studies propose that the development of NAFLD/NASH is a two-step process, the first being insulin resistance due to the accumulation of fat in hepatocytes. The second stage of this process involves cellular and molecular alterations brought on by oxidative stress and the oxidation of fatty acids in the liver, and the production of reactive oxygen species (ROS) as a result of numerous factors (cytokine injury, hyperinsulinemia, hepatic lipid peroxidation, alteration in the extracellular matrix, altered energy homeostasis, and altered immunological function, to name a few) (Edmison & McCullough 2007, Erbas *et al.* 2018).

NAFLD has also been associated with alterations in the composition of the gut microbiota leading to gut dysbiosis. The gut microbiota is a community of commensal bacteria that inhabit our gut and play an instrumental role in normal physiology (Stražar *et al.* 2021, Fang *et al.* 2022). The dysbiosis is characterized by a decrease in beneficial bacteria (such as *Bifidobacterium* and *Lactobacillus*) and an increase in potentially harmful bacteria (such as *Escherichia coli* and *Enterococcus*). This imbalance can again contribute to metabolic dysfunction, inflammation, and insulin resistance, all of which are already known to be involved in the development and progression of NAFLD. An imbalanced gut microbiota can lead to the production of harmful metabolites, such as trimethylamine *N*-oxide (TMAO), which has been associated with liver injury and disease pathogenesis. Conversely, certain bacteria can produce short-chain fatty acids (SCFAs) through the fermentation of dietary fibers. SCFAs, such as acetate, propionate, and butyrate, have beneficial effects on the host's energy metabolism and can reduce inflammation (Hrncir *et al.* 2021).

Overall, the development of the entire disease spectrum of NAFLD to HCC is multifactorial with complex cellular- and molecular-level alterations brought about by oxidative stress and toxic host or gut microbiome-derived metabolites (meta-metabolites) that ultimately lead to liver injury, hepatic steatosis, and its further complications.

Overview of NAFLD pathogenesis at the molecular level

Transfer of dietary fat to the liver (contribution to liver fat: 5%), delivery of extrahepatic nonesterified fatty acids (NEFAs) to the liver (contribution to liver fat: 60%), and hepatic *de novo* lipogenesis are all factors that determine the formation of fatty liver (Byrne 2012). In various cell types, CD36 (also known as fatty acid translocase) promotes NEFA uptake and intracellular trafficking to (macrophages, hepatocytes, adipocytes, enterocytes, and myocytes). As a frequent target of the liver X receptor, pregnancy X receptor, and peroxisome proliferator-activated receptor (PPAR) gamma, CD36 has been observed to increase in mouse models of hepatic steatosis (Auguet *et al.* 2014, Bessone *et al.* 2019). Although the function of CD36 in human diseases is not entirely understood, the liver fat content and apoptosis have been linked to CD36 messenger RNA levels in individuals with NAFLD who are morbidly obese (Bechmann *et al.* 2009).

The role of gut microbiota seems essential in understanding the NAFLD etiology (Fig. 1). The so-called healthy gut microbiota usually regulates the expression of fasting-induced adipose factor, also known as angiopoietin-like protein 4 (ANGPTL4), an inhibitor of circulating lipoprotein lipase (LPL). Any perturbing agent inducing gut microbiota perturbation can be a causative factor for decreased expression of ANGPTL4. A crucial part of lipid metabolism and glucose homeostasis is played by the protein ANGPTL4, which is secreted by the liver and adipose tissue. In the lipid metabolism pathway, LPL is the primary rate-limiting enzyme. It mainly accelerates the hydrolysis of TGs into monoacylglycerol and free fatty acids (FFAs). Reduced ANGPTL4 can have multiple effects on the host physiology, one of them being increased transport of FFAs into the liver from adipose tissue, which ultimately increases the availability of long-chain fatty acyl-CoAs and leads to hepatic lipid accumulation. This buildup can significantly promote TG accumulation in NAFLD (Byrne 2012, Aragonès *et al.* 2019). Dysbiosis is

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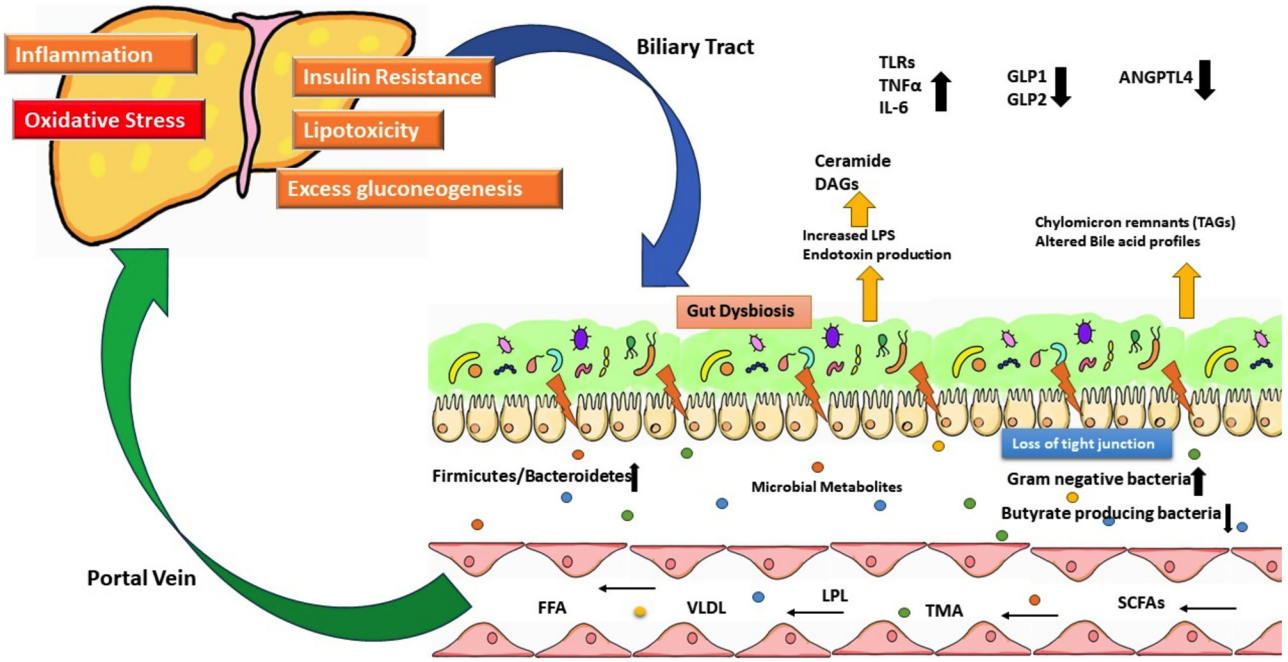

Figure 1
Molecular basis of NAFLD. The Firmicutes–Bacteroidetes ratio is frequently linked to the obesity phenotype. In addition, butyrate-producing bacterial depletion and gram-negative bacterial abundance lead to intestinal integrity barrier loss. This phenomenon allows endotoxins and lipopolysaccharides (LPS) to enter into the bloodstream, hence resulting in a chronic inflammatory response. The liver receives nonesterified fatty acids (NEFA), such as palmitic acid, from high-fat meals and dysfunctional adipose tissue from excessive lipolysis. The increasing circulating levels of NEFA leads to synthesis and accumulation of intrahepatic triglycerides (TGs). Angiopoietin-like protein 4 (ANGPTL4), a key regulator of LPL activity that ensures proper levels of circulating triacylglycerol (TAG) for transport to various tissues, including the adipose tissues (ATs), heart, muscle, and liver was found to be downregulated as well. Numerous lipotoxic mediators are produced when the hepatic mitochondria lose their ability to adapt. Diacylglycerols (DAGs) are lipid intermediates used in the production of TGs from NEFA and glycerol. They suppress proximal insulin signaling and promote hepatic insulin resistance. Activation of toll-like receptor 4 (TLR4) by lipopolysaccharides (LPS) causes inflammation, ceramide biosynthesis, and decreased insulin sensitivity. Meta-metabolites like trimethylamine-*N*-oxide (TMAO) are also observed to be increased in NAFLD.

also frequently accompanied by a rise in the production of endotoxins by gram-negative bacteria. These endotoxins can damage the intestinal barrier, interfere with the absorption of nutrients, increase gut permeability, and increase the risk of low-grade, chronic inflammation. Lipopolysaccharides (LPS) impair the tight connections between cells in the stomach, releasing pro-inflammatory cytokines into the bloodstream and, ultimately, into the liver. Because LPS production sends a direct inflammatory stimulant to the liver via the portal vein, we can infer that this LPS-mediated inflammatory response may increase the risk of inflammation and oxidative stress inside the liver (Miele *et al.* 2009). Gut dysbiosis as a driver of oxidative stress (OS) is discussed further in a later portion of this review. Excessive LPS can also promote the intrahepatic buildup of lipid intermediates, including ceramides and diacylglycerols, obstructing insulin signaling. For instance, increased ceramide levels in the liver activate inflammatory toll-like receptor 4 signaling pathways, impairing insulin signaling pathways by inhibiting RAC serine/threonine-protein kinase (AKT1) phosphorylation. Additionally, diacylglycerols can inhibit the activity of the insulin receptor through translocating protein kinase C-type, which will also result in decreased insulin signaling (Fig. 1) (Byrne 2012, Ilan 2012, Jasirwan *et al.* 2019).

Some studies have reported increased gluconeogenesis in individuals with high intrahepatic TG concentrations indicating dysregulation in insulin signaling (Sunny *et al.* 2011). Insulin resistance is now being considered as a distinct hit, which can escalate the process of NAFLD pathogenesis significantly. Studies at the molecular level now suggest insulin resistance, leading to excessive insulin, can inhibit hepatic sensitive lipase and also upregulate *de novo* lipogenesis by promoting the activity of sterol regulatory binding protein 1c (SREBP-1c). An incretin that improves insulin sensitivity and supports glucose metabolism is glucagon-like peptide 1 (GLP-1). In reaction to a meal being consumed, the small intestine's L cells produce an incretin GLP-1. Studies have also revealed

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that individuals with NAFLD secrete less endogenous GLP-1 (Fig. 1) (Nevola *et al.* 2023).

Oxidative stress causes cellular dysfunction and brings an anomaly at both structural and functional levels thus, appears to be one of the main factors in the development of liver damage and the advancement of NAFLD. However, gut dysbiosis is not the sole reason for oxidative stress in NAFLD, several other cellular pathways at the organelle level have a crucial role in maintaining the balance between oxidants and antioxidants. The intracellular balance of oxidants and antioxidants as well as their role in developing disease conditions is discussed in the preceding section of this review.

Oxidative stress

Perturbation in the equilibrium between oxidants and antioxidants may lead to oxidative stress at the cellular level. Oxidants include free radicals and other nonradical species. Free radicals are also known as ROS and reactive nitrogen species (RNS). Free radicals are molecules with unpaired electrons in the outer orbitals that are extremely reactive in the body and capable of oxidizing by taking an electron from atoms.

Radicals of superoxide anions can undergo a dismutation process (usually enzymatic) to form hydrogen peroxide. In the absence of catalase (CAT) or glutathione peroxidase (GSH-Px) and in the presence of transition metals, the end product hydrogen peroxide may go through an iron-catalyzed Fenton reaction to produce hydroxyl radicals (•OH) and water. Hydroxyl radicals either directly or indirectly promote the synthesis of other harmful pro-oxidants, such as peroxyl radicals, and hypochlorous acid. Nitric oxide and superoxide anion radicals can combine to generate peroxynitrite radicals, which are extremely reactive (Delli Bovi *et al.* 2021, Hong *et al.* 2021).

Cytosolic low-molecular-weight sulfhydryl molecules such as protein-bound thiol and nonprotein thiol, work as a reducing and protecting reagent against a variety of hazardous chemicals, including the majority of pollutants derived from an inorganic source, through the –SH group. Therefore, the first line of defense against oxidative stress is often thiol.

In order to prevent damage caused by free radicals, the defense mechanism is composed of a group of antioxidants. These include both enzymatic and nonenzymatic elements. Numerous enzymes in the enzymatic system detoxify ROS. Superoxide dismutases (SODs), CAT, GSH-Px and glutathione reductase are a few of the most important and well-studied enzymatic components of antioxidants. Small molecules like glutathione (GSH), ascorbic acid (vitamin C), retinol (vitamin A), and tocopherol (vitamin E), which function as electron acceptors, shield biomolecules and cell structures from ROS harm, are nonenzymatic components of the antioxidant system (Irie *et al.* 2016, Hadi *et al.* 2018).

Cellular pathways of oxidative stress

Mitochondria

The liver is an organ that uses up to 15% of the body's total oxygen, this is possible by the high abundance of mitochondria (500–4000 per hepatocyte), which have a fast turnover and are in charge of producing ATP. As an effect, any dysfunction in mitochondrial function can be a major driving force for the development of NAFLD. Steatosis in the liver leads to a metabolic hyperdrive state. A rise in the tricarboxylic acid cycle, oxidative phosphorylation, and electron transport chain activity is observed as a compensatory effort. Increased mitochondrial carnitine palmitoyltransferase (CPT)-1 and mitochondrial uncoupling protein (UCP)-2 activity, in particular, lowers blood levels of ROS and liver damage indicators, as a preventative measure against the development of NAFLD. However, if this anomaly goes on for a chronic period, higher mitochondrial respiration makes the mitochondria ineffective and causes structural and functional changes as a result of oxidative stress, so the hepatocyte can no longer adaptively adjust for the excess FFA (Ma *et al.* 2021).

Superoxides are produced when oxygen interacts with leaking electrons from electron transport chain complexes to cause oxidative stress in mitochondria.

Superoxides can drive an alteration in the structure and function of mitochondria by oxidizing electron transport chain complexes, phospholipid acyl chains, and mitochondrial DNA.

Most ROS are neutralized by being converted to water by redox molecules in the mitochondrial matrix under normal circumstances. Chronically elevated mitochondrial respiratory chain activity causes excessive electron leakage, which puts the liver under oxidative stress (Fig. 2) (Prasun *et al.* 2021).

An excess of mitochondrial calcium is another factor in generating mitochondrial ROS. Although Ca^{2+} is an established secondary messenger with a significant role in controlling various cellular physiological processes, Ca^{2+} excess is harmful to mitochondrial processes. Increased calcium flow encourages tricarboxylic acid cycle enzymes

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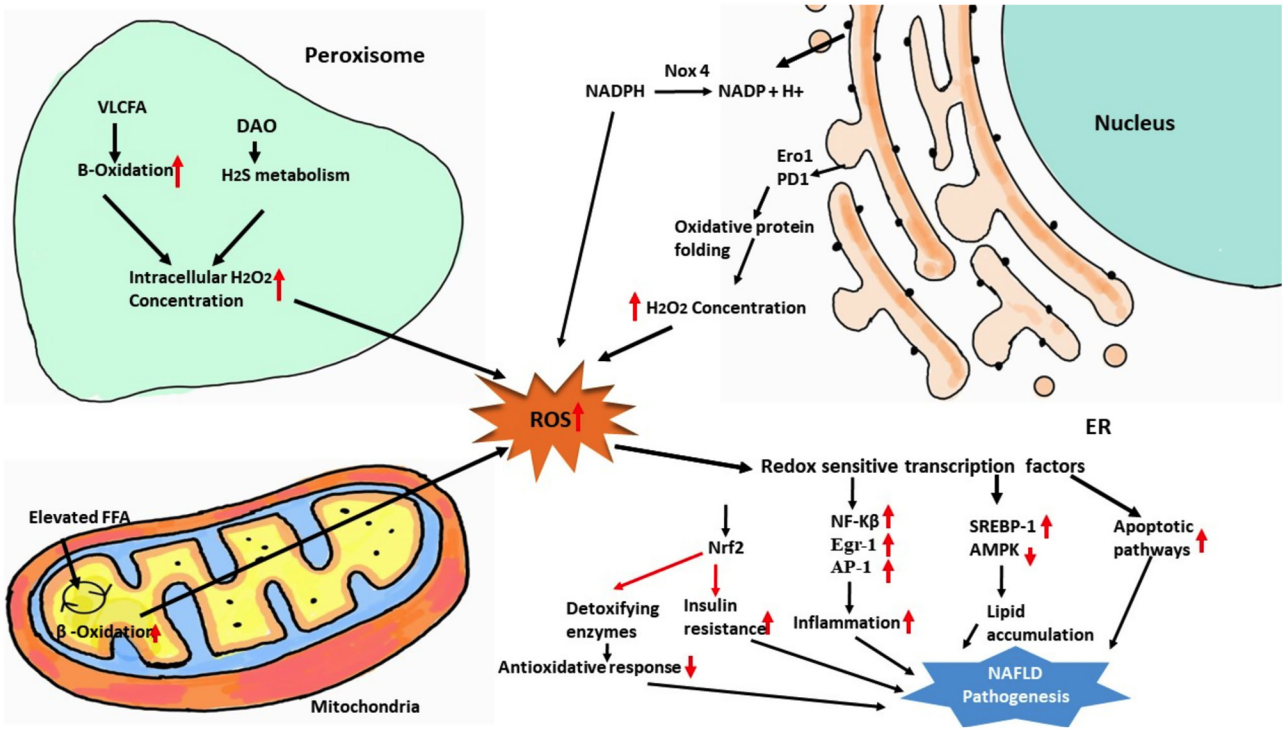

Figure 2
Intracellular pathways of oxidative stress. Oxidative stress is one of the key factors that are assumed to be responsible for the overall severity and progression of NAFLD. Multiple sources of oxidative stress are there at the cellular and organelle level, of which mitochondrial dysfunction, peroxisomal stress, and ER stress are major mediators. During steatosis, mitochondrial complex I and complex III tend to leak electrons (much more compared to basal level) and form superoxide radicals which contribute significantly to the overall cellular ROS. Excess free fatty acid pool leads to an elevation in beta-oxidation of very long-chain fatty acids (VLCFAs), other peroxisomal enzyme like D-amino acid oxidase (DAO) oxidizes polar D-amino acids, which leads to the production of H_2O_2 and other cytotoxic compounds as terminal products of this process. Endoplasmic reticulum (ER) stress is another major mediator of cellular ROS. Chronic activation of UPR can lead to inflammation and oxidative stress. Other ER-specific enzymes like endoplasmic reticulum oxidoreductin 1 (ERO1) and NADPH oxidase 4 protein (NOX4) also play a crucial role in generation of ROS. All of these organelle-based pathways activate redox sensitive transcription factors like NF-κB and Early growth response factor 1 (egr1) which leads to induction of proinflammatory and cell death pathways.

to produce NADH, which in turn boosts ATP synthesis and ROS generation. Additionally, elevated calcium levels in the mitochondrial matrix cause additional mitochondrial permeability transition pore opening, which promotes mitochondria-mediated apoptotic pathways over time.

Oxidative stress-mediated peroxidation of lipid intermediates and lipids are additional pathways of mitochondrial failure in advanced NAFLD like NASH; the levels of glycerophospholipids, sphingolipids, DAGs, ceramides, and free cholesterol are all elevated in NAFLD. Among them, cardiolipins fall under the category of phospholipid which is of recent interest to numerous researchers. It is complicated and currently being researched how exactly variations in cardiolipin content impact mitochondrial structure and function. However, it is understood that cytochrome c separates from cardiolipin when the acyl chain of cardiolipin is altered. The latter then moves to the outer mitochondrial membrane, where it destabilizes its lipid structure and encourages pore formation (Arroyave-Ospina *et al.* 2021).

Endoplasmic reticulum

Since protein folding requires a lot of energy, it is now assumed that around 25% of all cellular ROS originates from the forming of disulfide bonds while a peptide undergoes folding.

Different processes are used in the endoplasmic reticulum (ER) to produce ROS. First, endoplasmic reticulum oxidoreductin 1 (ERO1) mediates oxidation–reduction processes that are necessary for protein folding in the ER, which causes the formation of ROS and alters the redox balance of the ER. Furthermore, by its direct interaction with PDI, the ER-specific isoform of the NADPH oxidase 4 protein (Nox4) is directly connected to ROS production. Therefore, increased ROS production

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under ER stress is likewise linked to higher Nox4 levels. Finally, the NADPH-P450 reductase activity of the microsomal monooxygenase system plays a significant role in ROS generation in the ER. Depletion of GSH has also been linked to increased ROS production in the ER (Fig. 2).

RNA-dependent protein kinase-like ER eukaryotic initiation factor-2 kinase, activating transcription factor 6, and inositol-requiring ER-to-nucleus signaling protein 1 are components which activate the 'unfolded protein response' (UPR). At first, the activation of enzymes reduces ER stress. Still, continued activation of these pathways triggers pro-inflammatory reactions and increases the transcription and protein levels of the pro-apoptotic factor, the C/EBP homologous protein mediates the direct transcription of apoptotic BCL-2 protein family members, resulting in hepatocyte cell death (Cao & Kaufman 2014).

When it comes to the involvement of ER in the metabolism of lipids, the primary site for *de novo* lipogenesis is ER. Excess saturated fatty acids (SFA) result in ER stress, which disrupts regular ER function and leads to the buildup of unfolded and misfolded proteins, which sets off the UPR. Excess free SFAs are then incorporated into the phospholipids of the ER membrane, which causes Ca^{2+} to be released. As an effect of calcium-mediated mitochondrial dysfunction, pro-inflammatory and cell death pathways are activated (Hong *et al.* 2021, Ma *et al.* 2021).

Peroxisomes

Peroxisomes are multifunctional organelles that contribute to purine catabolism, glycolipid and bile acid production, fatty acid beta-oxidation, and beta-oxidation of very long-chain fatty acids (VLCFA). Approximately 35% of all intracellular ROS are produced by peroxisomes.

Aryl-CoA oxidase, which contains flavin adenine dinucleotide (FAD), facilitates the initial stage of the peroxisomal oxidation cycle by directly supplying electrons to molecular oxygen, which produces hydrogen peroxide (H_2O_2). This process starts in the traditional regulatory and inducible oxidation helices of the peroxisome PPAR, which deals with straight-chain acyl-CoA and is mediated by the same enzyme, AOX in all species. When the straight-chain acyl-CoA oxidase gene is disrupted, mice develop substantial microvascular hepatic steatosis. The outcomes of this are hepatomegaly, steatohepatitis, and excessive amounts of fatty acid chains in the serum. This could hasten the onset of NAFLD. The oxidation pathway is likewise activated in stimulated peroxisomes, but antioxidant enzymes are not concurrently elevated like oxidants, leading to a rise in the intracellular concentration of H_2O_2.

Another important source of oxidative stress, D-amino acid oxidase (DAO), an FAD-containing peroxisomal enzyme that catalyzes the oxidation of neutral and polar D-amino acids, is abundantly present in the kidney and liver. Amino acids are broken down to form 2-oxo acid (-keto acid) and ammonia when DAO is present, and the reduced flavin is reoxidized to form H_2O_2. These DAO reaction by-products are cytotoxic (Fig. 2) (Ucar *et al.* 2013, Ma *et al.* 2021).

Effectors of oxidative stress

It is essential to note that ROS are molecules capable of diverse functions that can modulate cell signaling and cellular stress response. The inflammatory response additionally contributes to OS. OS induces the activation of redox-sensitive transcription factors, such as nuclear factor kappa B (NF-κB), early growth response factor 1 (Egr-1), and activator protein 1 (AP-1), in the aftermath of liver injury, resulting in an inflammatory response and the induction of cell death pathways in hepatocytes.

Nuclear factor E2-related factor 2 (Nrf2) is a redox-sensitive transcription factor and the principal modulator of oxidative stress. High levels of ROS result in the expression of Nrf2 and its localization to the nucleus, promoting the transcription of target genes specific to antioxidants regulated by antioxidant response elements (ARE). Nrf2 regulates GSH levels and maintains the ratio of reduced GSH to oxidized GSH (GSH/GSSG), among other functions. In addition, Nrf2 regulates the production of numerous detoxifying enzymes that eliminate H_2O_2 and peroxide radicals from the cytosol, mitochondria, and ER. Yet the function of the Nrf2 pathway in lipid metabolism appears to be strongly condition-dependent, as there is distinct evidence supporting and against the Nrf2 pathway in relation to hepatic steatosis (Kang *et al.* 2017, Ma *et al.* 2021).

ROS can regulate NF-κB activation by inducing the pro-inflammatory cytokine TNFα, whereas antioxidants such as *N*-acetyl-L-cysteine inhibit NFκB activation. Similarly, it has been reported that *in vitro* or *in vivo* activation of Nrf2 by various antioxidants prevents inflammation via inhibition of the NF-κB pathway. In the context of NAFLD, it has been shown that the absence of Nrf2 results in hepatic insulin resistance through an NF-κB-dependent mechanism (Fig. 2) (Farzanegi *et al.* 2019, Ma *et al.* 2021).

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Gut microbiome and gut-derived metabolites as a regulatory component of oxidative stress in NAFLD

The importance of gut microbiome became more apparent after an experiment where wild type mice developed NAFLD upon fecal transplantation from diseased mice. Moreover, clinical studies have shown an increased abundance of circulating LPS in NAFLD patients. Since then, numerous researchers have attempted to comprehend the function of various gut bacteria in controlling the oxidative stress linked to the pathophysiology of the illness (Jones *et al.* 2012, Ferro *et al.* 2020). Some of the phylum level variations in different NAFLD clinical studies are summarized in Table 1.

Some antioxidant pathways, such as the AMP-activated protein kinase (AMPK) and Nrf2 pathways, are severely dysregulated in NAFLD (Solano-Urrusquieta *et al.* 2020). Cellular oxidative stress is further exacerbated by mitochondrial malfunction and ER stress (Zhang 2014, Meex & Blaak 2021). Numerous studies have drawn attention to the connection between the gut microbiome and its metabolites to redox equilibrium (Bellanti *et al.* 2023).

According to certain research, a high-fat diet disrupts the tight junction protein at the epithelial barrier, thereby rendering easy LPS translocation (Ferro *et al.* 2020). These bacterial cell wall products are sensed by hepatic stellate cells (HSCs), which activate the toll-like receptor 4 (TLR-4) pathway for the secretion of chemokines (Bigorgne *et al.* 2016). Reports suggest upregulation of cytokine receptors like TNFα upon endocytosis of LPS by Kupffer cells, which ultimately leads to ROS production (Delli Bovi *et al.* 2021). Additionally, LPS have been demonstrated to activate NADPH oxidase variation Nox2, which results in liver damage brought on by oxidative stress (Ferro *et al.* 2020).

There are some nuclear receptors known as peroxisome proliferator-activated receptors which prevent the progression of the disease by controlling both cellular and ER stress (Wang *et al.* 2020). However, research has emphasized on the role of gut microbiome in modulating the activity of these receptors. The population of Bacteroidetes, Firmicutes, and Streptococcaceae was found to be positively associated with NAFLD progression via the PPAR-γ signaling pathway. Since this pathway is downregulated in the diseased condition, some of the gut microbiota act as probiotic and upregulate the activity of the receptors. *Lactobacillus casei*, being one of them, ameliorates hepatic steatosis by inhibiting TLR4 pathway and elevating PPAR-γ activity. Few other strains of *Lactobacillus* have been found to cause similar activity (Wu *et al.* 2021*a*, Cao *et al.* 2023). The majority of research emphasizes the growth of butyrate-producing bacteria for improved signaling by these receptors, suggesting the metabolite's favorable connection with PPAR signaling (Wu *et al.* 2021*a*).

PPAR-β/δ receptors are also associated with another important antioxidant signaling, i.e. AMPK Pathway (Aguilar-Recarte *et al.* 2021). These pathways usually redirect ROS produced by mitochondria into antioxidant mechanisms (Rabinovitch *et al.* 2017). Metabolite acetate and propionate have been found to decrease the severity of the disease by activating AMPK pathways. Circulating acetate reduces macrophage infiltration, whereas propionate reduces the gluconeogenic gene expression in HepG2 cells (Carvalho *et al.* 2012, Yoshida *et al.* 2019). With the exception of butyrate, which has consistently shown a positive connection with AMPK activation, the impact of SCFAs on pathways is, however, widely debated (Anand & Mande 2022). Some probiotics are designed to stimulate the AMPK and SIRT1 pathways, which would otherwise be inactive. This downregulates liver autophagy and aids in the promotion of NAFLD (Pant *et al.* 2023). In certain experiments, lactic acid bacteria have been used to demonstrate their importance in activating the AMPK pathway (Wei *et al.* 2023). Some gut microbiomes release metabolites to stimulate the AMPK pathway for maintaining iron homeostasis and thus prevent NAFLD (González-Bosch *et al.* 2021). Many experimental studies have verified the role of hepatic iron

Table 1 Summary of studies on phylum level distribution in NAFLD patients.

	Shen *et al.* (2017)	Jiang *et al.* (2015)	Del Chierico *et al.* (2017)	Wang *et al.* (2016)	Behary *et al.* (2021)
Study size, *n*					
NAFLD cases	25	53	27	43	60
Control	22	32	54	83	30
Phylum					
Bacteroidetes	↓	↓	↓	↑	↓
Firmicutes		↑		↓	↓
Proteobacteria	↑	↑			↑
Actinobacteria		↑	↑		↑

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load in promoting insulin resistance by ROS production. Increase in iron accumulation has led to increment in fat deposits (Sumida *et al.* 2009). While *Bifidobacterium* and *Lactobacillus* species have shown a negative correlation, microbes like *Bacteroides* and *Prevotella* spp. are activated upon an increase in ferritin content (Mayneris-Perxachs *et al.* 2021).

Another key metabolic pathway for regulating cellular oxidative stress is the Keap1–Nrf2 pathway which stimulates antioxidant enzymes and detoxifying mechanisms to alleviate hepatic injury (Luo *et al.* 2022). This pathway is also regulated by the gut microbiome and gut-derived products. It has been demonstrated that some *Lactobacillus* species can downregulate oxidative stress by activating Nrf2 (Teng *et al.* 2020). Additionally, 5-methoxyindoleacetate, one of the metabolites this bacterium produces, has been found to activate hepatic Nrf2 (Luo *et al.* 2022). However, probiotic *Bacillus* aid in the degradation of Keap 1, but no effect was seen on Nrf2 (Wu *et al.* 2022). Among SCFAs, butyrate has been a promising candidate as it facilitates Nrf2 transport to the nucleus and in some cases activates the pathway by altering Nrf2's epigenetic state (González-Bosch *et al.* 2021).

It has been observed that the onset of the disease has been linked with imbalanced gut flora and altered intestinal permeability. This provides an opportunity for microbiome-derived metabolites to enter the liver via lymphatic circulation. This stimulates the liver to release components into systemic circulation via the biliary duct and affects the distant organs (Anand & Mande 2022).

Understanding extrahepatic manifestation in NAFLD through oxidative stress and gut microbiome

In-depth studies over the last few decades have revealed that NAFLD is a 'multisystems disease'. Although this disease is increasing at an alarming rate, extrahepatic consequences account for the majority of morbidity and mortality (as shown in Fig. 3) (Byrne & Targher 2015, Tomeno *et al.* 2020). Moreover, extrahepatic organs including the brain, heart, gut, and kidneys might suffer damage from systemic oxidative stress brought on by liver illness (Li *et al.* 2015). Hepatokines, proteins derived from the liver, have been the subject of extensive investigation

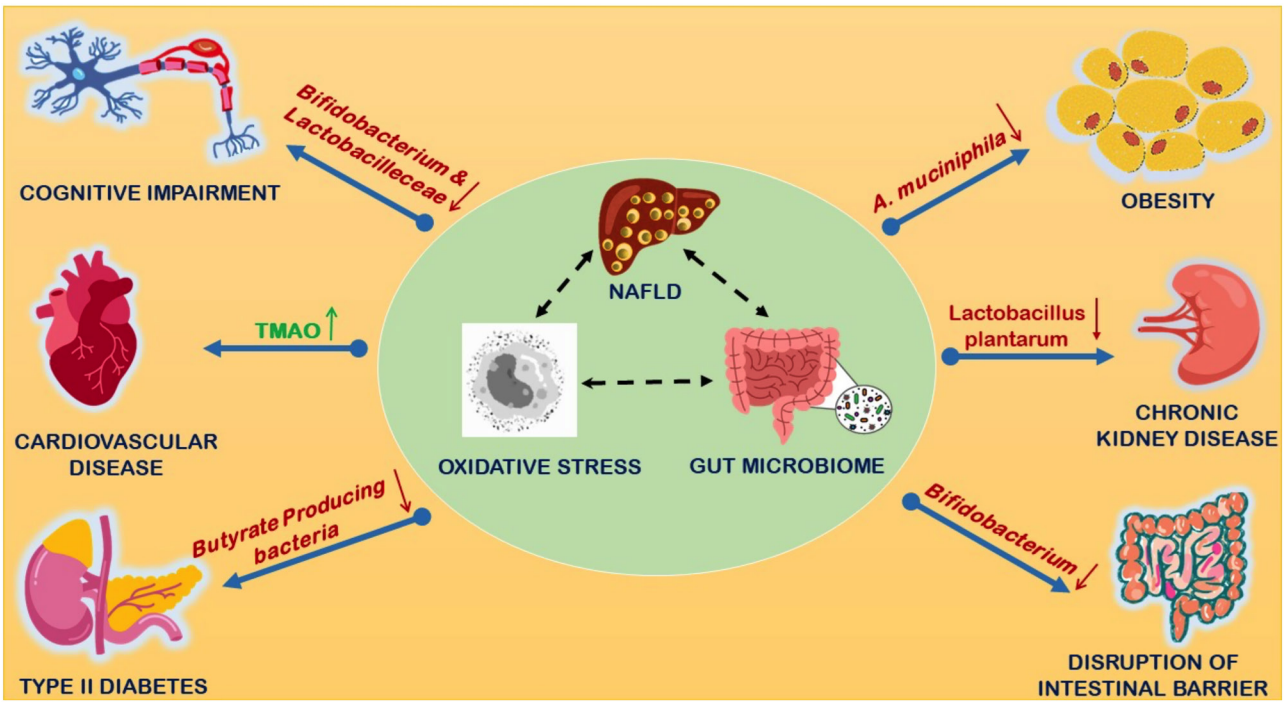

Figure 3
Association of gut microbiome and oxidative stress with extrahepatic abnormalities in NAFLD. A tripartite link exists between ROS, microbiome, and NAFLD. The inflammation arising due to this association is not only limited to liver but also occurs at the systemic level, thereby leading to extrahepatic manifestations of cardiovascular diseases (CVD), chronic kidney disease (CKD). However, at the same time it has been observed that extrahepatic disorders also contribute to the onset of NAFLD, thereby indicating a bidirectional association. Along with ROS, gut microbiome (acting as a probiotic) and gut-derived products also play a vital role in establishing such connectivity.

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for unraveling multiorgan communication. The three major hepatokines, i.e. fetuin A, angiopoietin-like protein (ANGPTL)8/betatrophin, and fibroblast growth factor 21 (FGF21), have been the subject of a thorough investigation (Iroz *et al.* 2015). For example, fetuin A has been observed to work in collaboration with other proteins to promote Insulin resistance by regulating pathways linked to oxidative stress (Ix & Sharma 2010). In addition to pro-inflammatory substances, compromised gut permeability brought on by an unbalanced gut flora serves as an additional connecting factor between the liver and other distant organs. The gut-derived metabolites can travel via portal circulation and activate the immune cells in the liver. These immune cells also commute to the liver via lymphatic circulation. In response to this interaction, the liver is prompted to release bile acids and other metabolites into the biliary tract, from which they travel to the systemic circulation (Anand & Mande 2022). It has been observed that both excess calorie intake and altered gut microbiome lead to adipocyte dysfunction. When adipocytes reach the limit of fat storage, it promotes ectopic fat storage, i.e. fat buildup in distant organs like the liver, skeletal muscles, and pancreas, ultimately causing lipotoxicity and systemic insulin resistance (Sears & Perry 2015, Martínez-Montoro *et al.* 2022).

Obesity

Obesity and NAFLD have recently been linked to ER stress-induced alteration in insulin sensitivity and concomitant inflammation. The results of liver biopsies showed a substantial elevation of NAFLD prevalence with increase in body mass index (BMI), adding support to the idea that these two metabolic disorders can co-occur (Fabbrini *et al.* 2010). The development of persistent low-grade inflammation linked to obesity has also been linked to the gut microbiota. Hence, it is safe to assume that gut microbiome perturbation can be strongly correlated with the disease. In contrast, some have found no difference or even the opposite, which can be attributable to experimental variations. It's interesting to note that there is growing evidence of particular bacteria at the species level that may have a role in preventing the development of NAFLD and obesity. *Akkermansia muciniphila,* a gram-negative bacterium that degrades mucin, is one of them. *A. muciniphila* was demonstrated to have a reasonable correlation with a healthier metabolic status in investigations on mice and people who were overweight and had diabetes. Numerous studies have highlighted this bacterium's capability to downregulate oxidative damage. The administration of *A. muciniphila* to several animal models has resulted in an improvement in glucose tolerance and antioxidant parameters (Zhang *et al.* 2018). All this evidence suggests that the microbiome plays an essential role in the pathogenesis of NAFLD, especially in obese people. As the direct correlation between obesity and NAFLD is quite established, most of the individuals either suffering from one or both shows a decrease in the expression of SOD (Liu *et al.* 2013). Fat accumulation along with insulin resistance can drive a shift in the balance of oxidative stress markers and antioxidative defense. One study has demonstrated this imbalance can be restored by calorie restriction for 8 weeks in obese patients, changes were also seen in insulin tolerance. Oxidative stress-induced dysregulated autophagy can also develop an Obesogenic microenvironment, this can be achieved in a mitochondrial alteration independent or dependent way. Some studies have demonstrated the role of mitochondrial antioxidants (MitoQ) in preventing oxidative stress-associated changes in obese rats (Feillet-Coudray *et al.* 2014). As discussed earlier, there are also evidence of gut dysbiosis as a contributing factor for NAFLD and obesity both. However, what is severely lacking in this field is the integration and number of unified studies linking all these risk factors. Gut dysbiosis induced oxidative stress or vice versa might aid in the progression of diseases like NAFLD and obesity.

Type 2 diabetes

When NAFLD coexists with obesity and insulin resistance (as it frequently does), the risk of incident T2DM increases noticeably. Thus, NAFLD as a potential cause of T2DM and T2DM as a causal factor of liver disease in NAFLD are interdependent (Scorletti & Byrne 2016). Just like most other metabolic disorders, T2DM also forms a triad with NAFLD and gut dysbiosis, as changes in the gut microbiome have been observed with the emergence of both NAFLD and T2DM (Canfora *et al.* 2019, Motta *et al.* 2019). The gut microbiome and its related metabolites contribute through several metabolic (like glucose metabolism) and immunologic pathways to T2DM (Tanase *et al.* 2020). Some studies have reported a decrease in the population of butyrate-producing microbes like *A. muciniphila*, *Bifidobacterium breve*, *Faecalibacterium prausnitzii*, *Coprococcus*, *Roseburia intestinalis*, and an increase in LPS-producing gram-negative bacteria like Ruminococcaceae *(Faecalibacterium) and Lactobacillus gasser* in T2DM (Ebrahimzadeh Leylabadlo *et al.* 2021). According to previous studies, SCFAs blocked insulin

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signaling by activating G protein-coupled receptor 43 in adipocytes, which prevented fat from accumulating in adipose tissue and encouraged energy metabolism in other tissues. Additionally, SCFAs slowed the growth of L cells by inhibiting neurogenin 3 expression through forkhead box O1 O-GlcNAcylation. Therefore, adipogenesis will be aided by a decrease in butyrate-producing bacteria after the onset of T2DM (Zhou *et al.* 2022). Notably, several antidiabetic treatments that target the gut microbiome are being investigated. Probiotics and prebiotics stand out among them as the most promising ones for use in therapeutic settings. By controlling the makeup of the gut microbiome in T2DM mice, *Lactobacillus rhamnosus LRa05* decreased fasting blood glucose and insulin resistance. By reversing gut microbiome dysbiosis and maintaining intestinal barrier integrity, Chang *et al.* showed that polysaccharides from *Ganoderma lucidum* reduced insulin resistance and inflammation in mice fed a high-fat diet, suggesting that they may be an effective prebiotic for the treatment of diabetes (Wu *et al.* 2021*b*). Thus, a triangular relationship between T2DM, NAFLD, and gut dysbiosis can be established, which can provide novel therapeutic approaches.

Lean NAFLD

However, some recent publications have reported that impaired insulin sensitivity occurs in some individuals independent of BMI, which led to lean NAFLD (Bilic-Curcic *et al.* 2021). Lean NAFLD is mainly associated with high visceral fat (Xu *et al.* 2022). In a different study, lean NAFLD mice had an increase in liver weight but a decrease in epididymal WAT (Huang *et al.* 2022). Reduction in subcutaneous adipose tissue can be one of the reasons for an increase in intrahepatic fat accumulation (Younes & Bugianesi 2019). Moreover, the gut microbiota of obese and nonobese NAFLD patients significantly differ (Wang *et al.* 2016). However, it is important to note that lean NAFLD is not benign because it can develop into cirrhosis and more severe liver diseases like NASH. Furthermore, several studies show that, compared to persons with obesity and NAFLD, those with lean NAFLD have a higher chance of developing T2DM and a higher all-cause mortality (Younes & Bugianesi 2019).

Cardiovascular disease (CVD)

Hyperglycemia and lipotoxicity triggered by insulin resistance have been observed to elevate oxidative stress, thereby leading to vascular injury and atherosclerosis (D'Archivio *et al.* 2012). This stress drives the conversion of macrophage into foam cells aiding in plaque formation. Similarly, ROS in NAFLD patients cause progression of the disease to advanced stages. Thus, oxidative stress can be one of the significant components for increasing the risk of CVD in NAFLD Patients (Polimeni 2015). Genetic predisposition and gut microbiome are also found to be linked with oxidative stress increment. Some clinical studies have found that loss of function mutation in genes lead to NAFLD by causing mitochondrial dysfunction (Longo *et al.* 2022). Furthermore, research has shown that some hepatic enzymes convert the gut microbiome-derived metabolite trimethylamine into TMAO, which further raises the level of ROS. Both illnesses exhibit endothelial impairment that is mediated by TMAO. These compounds cause the production of pro-inflammatory cytokines including interleukin 6 (IL-6) and TNFα by activating common inflammatory pathways like the NF-κB pathway (Shanmugham *et al.* 2023).

Inflammatory bowel disease (IBD)

The TNFα produced is responsible for the formation of superoxide in the colon with the help of NOX1 and NADPH oxidase organizer 1 (NOXO1), thereby leading to IBD (Tian *et al.* 2017). Additionally, ulcerative colitis (UC) patients have an increased level of inducible nitric oxide synthase caused by the NF-κB pathway (Schreiber 2005). Excessive ROS production in the gut manipulates the functions of protein and aids in lipid peroxidation which is also observed in the case of NAFLD (Tian *et al.* 2017). Malondialdehyde, a lipid peroxidation marker, has been found to be elevated in IBD patients by clinical studies (Achitei *et al.* 2013). Even certain probiotics like *Bifidobacterium* have been found to be ameliorating colitis in mice by downregulating lipid peroxidation (Lee *et al.* 2010). However, certain microbes are highly deleterious as they have been proven to trigger the neutrophils in ROS production or because they produce such reactive species themselves (Lundberg *et al.* 2004). Radical imbalances cause the cytoskeleton proteins to be disrupted and the tight junction proteins to be altered, which results in the loss of barrier integrity (Tian *et al.* 2017). Moreover, clinical studies have also highlighted the NAFLD-like increment of visceral adipose tissue volume in Crohn's disease patients (Simon *et al.* 2018). Thus, all of these factors have acted as a connecting thread between NAFLD and IBD, indicating the likelihood that these two diseases may co-occur (McGowan *et al.* 2012, Gaidos & Fuchs 2017, Lin *et al.* 2021).

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Chronic kidney disease (CKD)

Coming to the nonmetabolic disorders linked to NAFLD, more recent studies have shown people suffering from noncirrhotic NAFLD, and more particularly NASH, are at a higher risk of developing a form of kidney disorder known as CKD. CKD and NASH can aggravate one another mostly via insulin resistance, dyslipidemia, renin–angiotensin system, and proinflammatory pathways. Several scientific studies show that patients with NAFLD have higher rates of CKD regardless of their age, sex, BMI, or other factors such as diabetes, obesity, or hypertension (Yasui *et al.* 2011). Oxidative stress has been a key contributing factor that leads to renal failure and disease pathogenesis. Superoxides like NADPH oxidase and xanthine oxidase are upregulated leading to excess production of ROS, while SOD has been found to be downregulated in the case of CKD as well as in NAFLD. One major cause for oxidative disbalance could be the overproduction of TLR4 and proinflammatory cytokines like IL-6 in both these diseased conditions. Loss of intestinal barrier integrity (leaky gut) significantly increases the expression of these proinflammatory factors. In addition, oxidative stress can worsen renal function through fibrosis, hypertension, glomerular filtration barrier degradation, and inflammation (NF-κB activation) (Whaley-Connell *et al.* 2006).

Disrupted gut microbiome and their derived metabolites like indole, *p*-cresol, and their sulfates have significant effects in increasing both liver and kidney toxicity (Liu *et al.* 2016). A probiotic combination of *Lactobacillaceae* and *Bifidobacteriales* has been found to mitigate NAFLD by reducing systemic inflammation while *Lactobacillaceae* supplementation alone was found to mitigate CKD by reducing both systemic inflammation and proteinuria (Yoshifuji *et al.* 2016, Liang *et al.* 2018).

Metabolites like cystatin-C, gamma glutamyl transferase in serum, and urine albumin have been found to be elevated in both CKD and NAFLD (Stevens *et al.* 2013). The prognosis of patients who are diagnosed with both illnesses may significantly be impacted by the relationship between NAFLD and CKD, which is a growing association. This link can be explained by the fact that both diseases share similar metabolic risk factors. Extended research can better bridge the link between these two diseases (Ling & Kuo 2018, Kiapidou *et al.* 2020).

Cognitive impairment

Another nonmetabolic extrahepatic complication that has currently gained attention is the altered cognitive state and higher risks of cognitive impairment associated with NAFLD pathogenesis. Dysbiosis of the gut–liver–brain axis has been found to have a huge impact in the development of neuropsychiatric disorders with the progression of liver disease. Recent studies suggest up to 70% of NAFLD cases have memory, attention, focus, forgetfulness, and confusion issues, which have a detrimental effect on daily functioning and quality of life (Kennedy-Martin *et al.* 2018). One study showed that NAFLD was associated with a reduction in psychomotor speed and deficits in visuospatial function (Seo *et al.* 2016). Some studies have reported memory deficits in individuals with NAFLD, particularly in the domain of episodic memory. Cognitive changes in NAFLD can also be accompanied by mood and affective disturbances, such as depression and anxiety. These psychological symptoms can further exacerbate cognitive impairments.

NAFLD and cognitive impairment appear to be linked by one molecular mechanism, oxidative stress. Both conditions share several pathophysiological mechanisms, including systemic inflammation, mitochondrial dysfunction, insulin resistance, and lipid peroxidation. These mechanisms can contribute to oxidative stress in both the liver and the brain, potentially leading to liver injury, neuroinflammation, and cognitive impairment.

Another mechanistic link suggests NAFLD at the noncirrhotic stage is associated with hyperammonemia due to an altered nitrogen cycle. This excess ammonia acts as a neurotoxin, can easily cross the blood–brain barrier, and plays a key role in the pathophysiology of hepatic encephalopathy (Aldridge *et al.* 2015, De Chiara *et al.* 2018).

An altered gut microbial state like an enriched Firmicutes–Bacteroidetes ratio has long been associated with leaky gut. It has now been proposed that bacterial metabolites, endotoxins, ammonia, and DNA of these bacteria can initiate and spread systemic and neurological inflammation. Another study used the probiotic *Lactobacillus plantarum* to treat control and diet-induced NASH mice for 2 weeks while examining alterations in cognitive activity and hippocampus histology. The probiotic treatment in this case restored the decline in memory and spatial learning that was linked to NASH. The NASH group also experienced an increase in hippocampus viable cells and a reversal of hepatic steatosis, ballooning, and fibrosis following probiotic medication. These studies suggest that progressive stages of NAFLD are linked with cognitive loss whereas supplementation of probiotics and a better lifestyle can help improve the condition (Mohammed *et al.* 2020).

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Conclusion

NAFLD, a multifactorial liver disease, is becoming widely common not just in the United States but also around the world as a result of obesity and insulin resistance, leading to TG and free fatty acid accumulation in the liver. There are several risk factors for the development of NAFLD, and the pathophysiology of the majority of these risk factors centers around some or the other form of metabolic disorder or insulin resistance.

Now that it has been established that oxidative stress, and overproduction of ROS can be major leading factors for the pathogenesis of NAFLD, future studies can focus on application of antioxidants as a therapeutic measure.

Gut dysbiosis and altered gut microbiota facilitate NAFLD pathogenesis and progression. These bacteria can take advantage of altered intestinal permeability and the circulating bacterial endotoxins can enhance systemic alterations as well as extrahepatic manifestations. To counter this, a healthy lifestyle and a healthy diet consisting of probiotics, prebiotics, and vitamin E supplementation could potentially contribute to NAFLD prevention.

Although a lot of research is being focused to understand this complex disease and its underlying mechanisms, a lot is yet to be uncovered as regards how the disease progression can be halted and comorbidity with extrahepatic diseases can be prevented.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

We thank NISER, DAE, Government of India, for providing the funds and infrastructural support. We thank the University Grants Commission (UGC), Government of India, for fellowship support to TM.

Author contribution statement

AD, AJD, and TM contributed equally and wrote the manuscript. PA conceptualized, supervised, and finalized the manuscript.

References

Achitei D, Ciobica A, Balan G, Gologan E, Stanciu C & Stefanescu G 2013 Different profile of peripheral antioxidant enzymes and lipid peroxidation in active and non-active inflammatory bowel disease patients. *Digestive Diseases and Sciences* **58** 1244–1249. (https://doi.org/10.1007/s10620-012-2510-z)

Aguilar-Recarte D, Palomer X, Wahli W & Vázquez-Carrera M 2021 The PPARβ/δ-AMPK connection in the treatment of insulin resistance. *International Journal of Molecular Sciences* **22** 8555. (https://doi.org/10.3390/ijms22168555)

Aldridge DR, Tranah EJ & Shawcross DL 2015 Pathogenesis of hepatic encephalopathy: role of ammonia and systemic inflammation. *Journal of Clinical and Experimental Hepatology* **5**(Supplement 1) S7–S20. (https://doi.org/10.1016/j.jceh.2014.06.004)

Anand S & Mande SS 2022 Gut-Liver axis and its connection with other organs. *npj Biofilms and Microbiomes* **8** 89. (https://doi.org/10.1038/s41522-022-00352-6)

Aragonès G, González-García S, Aguilar C, Richart C & Auguet T 2019 Gut microbiota-derived mediators as potential markers in nonalcoholic fatty liver disease. *BioMed Research International* **2019** 8507583. (https://doi.org/10.1155/2019/8507583)

Arroyave-Ospina JC, Wu Z, Geng Y & Moshage H 2021 Role of oxidative stress in the pathogenesis of non-alcoholic fatty liver disease: implications for prevention and therapy. *Antioxidants* **10** 174. (https://doi.org/10.3390/antiox10020174)

Auguet T, Berlanga A, Guiu-Jurado E & Porras JA 2014 Molecular pathways in non-alcoholic fatty liver disease. *Clinical and Experimental Gastroenterology* **7** 221–239. (https://doi.org/10.2147/CEG.S62831)

Bechmann LP, Gieseler RK, Sowa JP, Kahraman A, Erhard J, Wedemeyer I, Emons B, Jochum C, Feldkamp T, Gerken G, *et al.* 2009 Apoptosis is associated with CD36/fatty acid translocase upregulation in non-alcoholic steatohepatitis. *Liver International* **30** 850–859. (https://doi.org/10.1111/j.1478-3231.2010.02248.x)

Behary J, Amorim N, Jiang X-T, Raposo A, Gong L, McGovern E, Ibrahim R, Chu F, Stephens C, Jebeili H *et al.* 2021 Gut microbiota impact on the peripheral immune response in non-alcoholic fatty liver disease related hepatocellular carcinoma. *Nature Communications* **12** 187. (https://doi.org/10.1038/s41467-020-20422-7)

Bellanti F, Lo Buglio A & Vendemiale G 2023 Hepatic mitochondria-gut microbiota interactions in metabolism-associated fatty liver disease. *Metabolites* **13** 322. (https://doi.org/10.3390/metabo13030322)

Bessone F, Razori MV & Roma MG 2019 Molecular pathways of nonalcoholic fatty liver disease development and progression. *Cellular and Molecular Life Sciences* **76** 99–128. (https://doi.org/10.1007/s00018-018-2947-0)

Bigorgne AE, John B, Ebrahimkhani MR, Shimizu-Albergine M, Campbell JS & Crispe IN 2016 TLR4-Dependent Secretion by Hepatic Stellate Cells of the Neutrophil-Chemoattractant CXCL1 Mediates Liver Response to Gut Microbiota. *PloS One*. Ed. M Samson **11** e0151063. (https://doi.org/10.1371/journal.pone.0151063)

Bilic-Curcic I, Cigrovski Berkovic M, Virovic-Jukic L & Mrzljak A 2021 Shifting perspectives – interplay between non-alcoholic fatty liver disease and insulin resistance in lean individuals. *World Journal of Hepatology* **13** 80–93. (https://doi.org/10.4254/wjh.v13.i1.80)

Byrne CD 2012 Dorothy Hodgkin Lecture 2012* Non-alcoholic fatty liver disease, insulin resistance and ectopic fat: a new problem in diabetes management. *Diabetic Medicine* **29** 1098–1107. (https://doi.org/10.1111/j.1464-5491.2012.03732.x)

Byrne CD & Targher G 2015 NAFLD: A multisystem disease. *Journal of Hepatology* **62**(1)(Supplement) S47–S64. (https://doi.org/10.1016/j.jhep.2014.12.012)

Canfora EE, Meex RCR, Venema K & Blaak EE 2019 Gut microbial metabolites in obesity, NAFLD and T2DM. *Nature Reviews. Endocrinology* **15** 261–273. (https://doi.org/10.1038/s41574-019-0156-z)

Cao SS & Kaufman RJ 2014 Endoplasmic reticulum stress and oxidative stress in cell fate decision and human disease. *Antioxidants and Redox Signaling* **21** 396–413. (https://doi.org/10.1089/ars.2014.5851)

Cao F, Ding Q, Zhuge H, Lai S, Chang K, Le C, Yang G, Valencak TG, Li S & Ren D 2023 Lactobacillus plantarum ZJUIDS14 alleviates non-alcoholic fatty liver disease in mice in association with modulation in the gut microbiota. *Frontiers in Nutrition* **9** 1071284. (https://doi.org/10.3389/fnut.2022.1071284)

Carvalho BM, Guadagnini D, Tsukumo DML, Schenka AA, Latuf-Filho P, Vassallo J, Dias JC, Kubota LT, Carvalheira JBC & Saad MJA 2012 Modulation of gut microbiota by antibiotics improves insulin signalling in high-fat fed mice. *Diabetologia* **55** 2823–2834. (https://doi.org/10.1007/s00125-012-2648-4)

D'Archivio M, Annuzzi G, Varì R, Filesi C, Giacco R, Scazzocchio B, Santangelo C, Giovannini C, Rivellese AA & Masella R 2012 Predominant role of obesity/insulin resistance in oxidative stress development. *European Journal of Clinical Investigation* **42** 70–78. (https://doi.org/10.1111/j.1365-2362.2011.02558.x)

De Chiara F, Heebøll S, Marrone G, Montoliu C, Hamilton-Dutoit S, Ferrandez A, Andreola F, Rombouts K, Grønbæk H, Felipo V, *et al.* 2018 Urea cycle dysregulation in non-alcoholic fatty liver disease. *Journal of Hepatology* **69** 905–915. (https://doi.org/10.1016/j.jhep.2018.06.023)

Del Chierico F, Nobili V, Vernocchi P, Russo A, De Stefanis C, Gnani D, Furlanello C, Zandonà A, Paci P, Capuani G *et al.* 2017 Gut microbiota profiling of pediatric nonalcoholic fatty liver disease and obese patients unveiled by an integrated meta-omics-based approach. *Hepatology* **65** 451–464. (https://doi.org/10.1002/hep.28572)

Delli Bovi AP, Marciano F, Mandato C, Siano MA, Savoia M & Vajro P 2021 Oxidative stress in non-alcoholic fatty liver disease. An updated mini review. *Frontiers in Medicine* **8** 595371. (https://doi.org/10.3389/fmed.2021.595371)

Ebrahimzadeh Leylabadlo H, Samadi Kafil H, Farajnia S, Shanehbandi D, Yaghoub Moaddab S, Feizabadi MM & Ghotaslou R 2021 Gut microbiota in nonalcoholic fatty liver diseases with and without type-2 diabetes mellitus. *European Journal of Gastroenterology and Hepatology* **33** e548–e554. (https://doi.org/10.1097/MEG.0000000000002140)

Edmison J & McCullough AJ 2007 Pathogenesis of non-alcoholic steatohepatitis: human data. *Clinics in Liver Disease* **11** 75–104. (https://doi.org/10.1016/j.cld.2007.02.011)

Erbas O, Erdogan MA, Khalilnezhad A, Gürkan FT, Yiğittürk G, Meral A & Taskiran D 2018 Neurobehavioral effects of long-term maternal fructose intake in rat offspring. *International Journal of Developmental Neuroscience* **69** 68–79. (https://doi.org/10.1016/j.ijdevneu.2018.07.001)

Fabbrini E, Sullivan S & Klein S 2010 Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology* **51** 679–689. (https://doi.org/10.1002/hep.23280)

Fang J, Yu CH, Li XJ, Yao JM, Fang ZY, Yoon SH & Yu WY 2022 Gut dysbiosis in nonalcoholic fatty liver disease: pathogenesis, diagnosis, and therapeutic implications. *Frontiers in Cellular and Infection Microbiology* **12** 997018. (https://doi.org/10.3389/fcimb.2022.997018)

Farzanegi P, Dana A, Ebrahimpoor Z, Asadi M & Azarbayjani MA 2019 Mechanisms of beneficial effects of exercise training on non-alcoholic fatty liver disease (NAFLD): roles of oxidative stress and inflammation. *European Journal of Sport Science* **19** 994–1003. (https://doi.org/10.1080/17461391.2019.1571114)

Feillet-Coudray C, Fouret G, Ebabe Elle R, Rieusset J, Bonafos B, Chabi B, Crouzier D, Zarkovic K, Zarkovic N, Ramos J, *et al.* 2014 The mitochondrial-targeted antioxidant MitoQ ameliorates metabolic syndrome features in obesogenic diet-fed rats better than apocynin or allopurinol. *Free Radical Research* **48** 1232–1246. (https://doi.org/10.3109/10715762.2014.945079)

Ferro D, Baratta F, Pastori D, Cocomello N, Colantoni A, Angelico F & Del Ben M 2020 New insights into the pathogenesis of non-alcoholic fatty liver disease: gut-derived lipopolysaccharides and oxidative stress. *Nutrients* **12** 2762. (https://doi.org/10.3390/nu12092762)

Gaidos JKJ & Fuchs M 2017 Increased prevalence of NAFLD in IBD patients. *Digestive Diseases and Sciences* **62** 1362–1362. (https://doi.org/10.1007/s10620-017-4552-8)

García-Compeán D & Jiménez-Rodríguez AR 2022 NAFLD VS MAFLD. The evidence-based debate has come. Time to change?' *Annals of Hepatology* **27** 100765. (https://doi.org/10.1016/j.aohep.2022.100765)

González-Bosch C, Boorman E, Zunszain PA & Mann GE 2021 Short-chain fatty acids as modulators of redox signaling in health and disease. *Redox Biology* **47** 102165. (https://doi.org/10.1016/j.redox.2021.102165)

Hadi H, Vettor R & Rossato M 2018 Vitamin E as a treatment for nonalcoholic fatty liver disease: reality or myth?' *Antioxidants* **7** 12. (https://doi.org/10.3390/antiox7010012)

Hamid O, Eltelbany A, Mohammed A, Alsabbagh Alchirazi K, Trakroo S & Asaad I 2022 The epidemiology of non-alcoholic steatohepatitis (NASH) in the United States between 2010–2020: a population-based study. *Annals of Hepatology* **27** 100727. (https://doi.org/10.1016/j.aohep.2022.100727)

Hong T, Chen Y, Li X & Lu Y 2021 The role and mechanism of oxidative stress and nuclear receptors in the development of NAFLD. *Oxidative Medicine and Cellular Longevity*. Ed. J Pu **2021** 6889533. (https://doi.org/10.1155/2021/6889533)

Hrncir T, Hrncirova L, Kverka M, Hromadka R, Machova V, Trckova E, Kostovcikova K, Kralickova P, Krejsek J & Tlaskalova-Hogenova H 2021 Gut microbiota and NAFLD: pathogenetic mechanisms, microbiota signatures, and therapeutic interventions. *Microorganisms* **9** 957. (https://doi.org/10.3390/microorganisms9050957)

Huang X, Yao Y, Hou X, Wei L, Rao Y, Su Y, Zheng G, Ruan XZ, Li D & Chen Y 2022 Macrophage SCAP contributes to metaflammation and lean NAFLD by activating STING–NF-κB signaling pathway. *Cellular and Molecular Gastroenterology and Hepatology* **14** 1–26. (https://doi.org/10.1016/j.jcmgh.2022.03.006)

Ilan Y 2012 Leaky gut and the liver: A role for bacterial translocation in nonalcoholic steatohepatitis. *World Journal of Gastroenterology* **18** 2609–2618. (https://doi.org/10.3748/wjg.v18.i21.2609)

Irie M, Sohda T, Anan A, Fukunaga A, Takata K, Tanaka T, Yokoyama K, Morihara D, Takeyama Y, Shakado S, *et al.* 2016 Reduced glutathione suppresses Oxidative Stress in Nonalcoholic Fatty Liver Disease. *Euroasian Journal of Hepato-Gastroenterology* **6** 13–18. (https://doi.org/10.5005/jp-journals-10018-1159)

Iroz A, Couty JP & Postic C 2015 Hepatokines: unlocking the multi-organ network in metabolic diseases. *Diabetologia* **58** 1699–1703. (https://doi.org/10.1007/s00125-015-3634-4)

Ix JH & Sharma K 2010 Mechanisms linking obesity, chronic kidney disease, and fatty liver disease: The roles of fetuin-A, adiponectin, and AMPK. *Journal of the American Society of Nephrology* **21** 406–412. (https://doi.org/10.1681/ASN.2009080820)

Jasirwan COM, Lesmana CRA, Hasan I, Sulaiman AS & Gani RA 2019 The role of gut microbiota in non-alcoholic fatty liver disease: pathways of mechanisms. *Bioscience of Microbiota, Food and Health* **38** 81–88. (https://doi.org/10.12938/bmfh.18-032)

Jiang W, Wu N, Wang X, Chi Y, Zhang Y, Qui X, Hu Y & Liu Y 2015 Dysbiosis gut microbiota associated with inflammation and impaired mucosal immune function in intestine of humans with non-alcoholic fatty liver disease. *Scientific Reports* **5** 8096. (https://doi.org/10.1038/srep08096)

Jones RM, Mercante JW & Neish AS 2012 Reactive oxygen production induced by the gut microbiota: pharmacotherapeutic implications. *Current Medicinal Chemistry* **19** 1519–1529. (https://doi.org/10.2174/092986712799828283)

Kang HH, Kim IK, Lee HI, Joo H, Lim JU, Lee J, Lee SH & Moon HS 2017 Chronic intermittent hypoxia induces liver fibrosis in mice with diet-induced obesity via TLR4/MyD88/MAPK/NF-kB signaling pathways. *Biochemical and Biophysical Research Communications* **490** 349–355. (https://doi.org/10.1016/j.bbrc.2017.06.047)

Kennedy-Martin T, Bae JP, Paczkowski R & Freeman E 2018 Health-related quality of life burden of nonalcoholic steatohepatitis: a robust pragmatic literature review. *Journal of Patient-Reported Outcomes* **2** 28. (https://doi.org/10.1186/s41687-018-0052-7)

Kiapidou S, Liava C, Kalogirou M, Akriviadis E & Sinakos E 2020 Chronic kidney disease in patients with non-alcoholic fatty liver disease: what the Hepatologist should know?' *Annals of Hepatology* **19** 134–144. (https://doi.org/10.1016/j.aohep.2019.07.013)

Lee IA, Bae EA, Lee JH, Lee H, Ahn YT, Huh CS & Kim DH 2010 Bifidobacterium longum HY8004 attenuates TNBS-induced colitis by inhibiting lipid peroxidation in mice. *Inflammation Research* **59** 359–368. (https://doi.org/10.1007/s00011-009-0108-5)

Li S, Tan HY, Wang N, Zhang ZJ, Lao L, Wong CW & Feng Y 2015 The role of oxidative stress and antioxidants in liver diseases. *International Journal of Molecular Sciences* **16** 26087–26124. (https://doi.org/10.3390/ijms161125942)

Liang Y, Lin C, Zhang Y, Deng Y, Liu C & Yang Q 2018 Probiotic mixture of Lactobacillus and Bifidobacterium alleviates systemic adiposity and inflammation in non-alcoholic fatty liver disease rats through Gpr109a and the commensal metabolite butyrate. *Inflammopharmacology* **26** 1051–1055. (https://doi.org/10.1007/s10787-018-0479-8)

Lin A, Roth H, Anyane-Yeboa A, Rubin DT & Paul S 2021 Prevalence of nonalcoholic fatty liver disease in patients with inflammatory bowel disease: A systematic review and meta-analysis. *Inflammatory Bowel Diseases* **27** 947–955. (https://doi.org/10.1093/ibd/izaa189)

Ling XC & Kuo K-L 2018 Oxidative stress in chronic kidney disease. *Renal Replacement Therapy* **4** 53. (https://doi.org/10.1186/s41100-018-0195-2)

Liu Y, Qi W, Richardson A, Van Remmen H, Ikeno Y & Salmon AB 2013 Oxidative damage associated with obesity is prevented by overexpression of CuZn- or Mn-superoxide dismutase. *Biochemical and Biophysical Research Communications* **438** 78–83. (https://doi.org/10.1016/j.bbrc.2013.07.029)

Liu H, Narayanan R, Hoffmann M & Surapaneni S 2016 The uremic toxin Indoxyl-3-Sulfate induces CYP1A2 in primary human hepatocytes. *Drug Metabolism Letters* **10** 195–199. (https://doi.org/10.2174/1872312810666160719143703)

Longo M, Meroni M, Paolini E, Erconi V, Carli F, Fortunato F, Ronchi D, Piciotti R, Sabatini S, Macchi C, *et al.* 2022 TM6SF2/PNPLA3/MBOAT7 loss-of-function genetic variants impact on NAFLD development and progression both in patients and in in vitro models. *Cellular and Molecular Gastroenterology and Hepatology* **13** 759–788. (https://doi.org/10.1016/j.jcmgh.2021.11.007)

Lundberg JO, Weitzberg E, Cole JA & Benjamin N 2004 Nitrate, bacteria and human health. *Nature Reviews. Microbiology* **2** 593–602. (https://doi.org/10.1038/nrmicro929)

Luo D, Yang L, Pang H, Zhao Y, Li K, Rong X & Guo J 2022 Tianhuang formula reduces the oxidative stress response of NAFLD by regulating the gut microbiome in mice. *Frontiers in Microbiology* **13** 984019. (https://doi.org/10.3389/fmicb.2022.984019)

Ma Y, Lee G, Heo SY & Roh YS 2021 Oxidative stress is a key modulator in the development of nonalcoholic fatty liver disease. *Antioxidants* **11** 91. (https://doi.org/10.3390/antiox11010091)

Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD & Targher G 2020 Complications, morbidity and mortality of nonalcoholic fatty liver disease. *Metabolism: Clinical and Experimental* **111S** 154170. (https://doi.org/10.1016/j.metabol.2020.154170)

Martínez-Montoro JI, Damas-Fuentes M, Fernández-García JC & Tinahones FJ 2022 Role of the gut microbiome in Beta cell and adipose tissue crosstalk: a review. *Frontiers in Endocrinology* **13** 869951. (https://doi.org/10.3389/fendo.2022.869951)

Mayneris-Perxachs J, Cardellini M, Hoyles L, Latorre J, Davato F, Moreno-Navarrete JM, Arnoriaga-Rodríguez M, Serino M, Abbott J, Barton RH, *et al.* 2021 Iron status influences non-alcoholic fatty liver disease in obesity through the gut microbiome. *Microbiome* **9** 104. (https://doi.org/10.1186/s40168-021-01052-7)

McGowan CE, Jones P, Long MD & Barritt AS 2012 Changing shape of disease: nonalcoholic fatty liver disease in Crohn's disease-a case series and review of the literature. In Crohn's disease—A case series and review of the literature. *Inflammatory Bowel Diseases* **18** 49–54. (https://doi.org/10.1002/ibd.21669)

Meex RCR & Blaak EE 2021 Mitochondrial dysfunction is a key pathway that links saturated fat intake to the development and progression of NAFLD. *Molecular Nutrition and Food Research* **65** e1900942. (https://doi.org/10.1002/mnfr.201900942)

Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, Mascianà R, Forgione A, Gabrieli ML, Perotti G, *et al.* 2009 Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* **49** 1877–1887. (https://doi.org/10.1002/hep.22848)

Mohammed SK, Magdy YM, El-Waseef DA, Nabih ES, Hamouda MA & El-Kharashi OA 2020 Modulation of hippocampal TLR4/BDNF signal pathway using probiotics is a step closer towards treating cognitive impairment in NASH model. *Physiology and Behavior* **214** 112762. (https://doi.org/10.1016/j.physbeh.2019.112762)

Motta BM, Grander C, Gögele M, Foco L, Vukovic V, Melotti R, Fuchsberger C, De Grandi A, Cantaloni C, Picard A, *et al.* 2019 Microbiota, type 2 diabetes and non-alcoholic fatty liver disease: protocol of an observational study. *Journal of Translational Medicine* **17** 408. (https://doi.org/10.1186/s12967-019-02130-z)

Nevola R, Epifani R, Imbriani S, Tortorella G, Aprea C, Galiero R, Rinaldi L, Marfella R & Sasso FC 2023 GLP-1 receptor agonists in non-alcoholic fatty liver disease: current evidence and future perspectives. *International Journal of Molecular Sciences* **24** 1703. (https://doi.org/10.3390/ijms24021703)

Pant R, Sharma N, Kabeer SW, Sharma S & Tikoo K 2023 Selenium-enriched probiotic alleviates western diet-induced non-alcoholic fatty liver disease in rats via modulation of autophagy through AMPK/SIRT-1 pathway. *Biological Trace Element Research* **201** 1344–1357. (https://doi.org/10.1007/s12011-022-03247-x)

Polimeni L, Del Ben M, Baratta F, Perri L, Albanese F, Pastori D, Violi F & Angelico F 2015 Oxidative stress: new insights on the association of non-alcoholic fatty liver disease and atherosclerosis. *World Journal of Hepatology* **7** 1325–1336. (https://doi.org/10.4254/wjh.v7.i10.1325)

Prasun P, Ginevic I & Oishi K 2021 Mitochondrial dysfunction in nonalcoholic fatty liver disease and alcohol related liver disease. *Translational Gastroenterology and Hepatology* **6** 4–4. (https://doi.org/10.21037/tgh-20-125)

Rabinovitch RC, Samborska B, Faubert B, Ma EH, Gravel SP, Andrzejewski S, Raissi TC, Pause A, St-Pierre J & Jones RG 2017 AMPK maintains cellular metabolic homeostasis through regulation of mitochondrial reactive oxygen species. *Cell Reports* **21** 1–9. (https://doi.org/10.1016/j.celrep.2017.09.026)

Schreiber S 2005 The complicated path to true causes of disease: role of nuclear factor B in inflammatory bowel disease. *Gut* **54** 444–445. (https://doi.org/10.1136/gut.2004.051797)

Scorletti E & Byrne CD 2016 Extrahepatic diseases and NAFLD: the triangular relationship between NAFLD, type 2-diabetes and dysbiosis. *Digestive Diseases* **34**(Supplement 1) 11–18. (https://doi.org/10.1159/000447276)

Sears B & Perry M 2015 The role of fatty acids in insulin resistance. *Lipids in Health and Disease* **14** 121. (https://doi.org/10.1186/s12944-015-0123-1)

Seo SW, Gottesman RF, Clark JM, Hernaez R, Chang Y, Kim C, Ha KH, Guallar E & Lazo M 2016 Nonalcoholic fatty liver disease is associated with cognitive function in adults. *Neurology* **86** 1136–1142. (https://doi.org/10.1212/WNL.0000000000002498)

Shanmugham M, Bellanger S & Leo CH 2023 Gut-derived metabolite, trimethylamine-N-oxide (TMAO) in cardio-metabolic diseases: detection, mechanism, and potential therapeutics. *Pharmaceuticals* **16** 504. (https://doi.org/10.3390/ph16040504)

Shen F, Zheng R-D, Sun X-Q, Ding W-J, Wang X-Y & Fan J-G 2017 Gut microbiota dysbiosis in patients with non-alcoholic fatty liver disease. *Hepatobiliary & Pancreatic Diseases International* **16** 375–381. (https://doi.org/10.1016/S1499-3872(17)60019-5)

Simon TG, Van Der Sloot KWJ, Chin SB, Joshi AD, Lochhead P, Ananthakrishnan AN, Xavier R, Chung RT & Khalili H 2018 IRGM gene variants modify the relationship between visceral adipose tissue and NAFLD in patients with Crohn's disease. *Inflammatory Bowel Diseases* **24** 2247–2257. (https://doi.org/10.1093/ibd/izy128)

Solano-Urrusquieta A, Morales-González JA, Castro-Narro GE, Cerda-Reyes E, Flores-Rangel PD & Fierros-Oceguera R 2020 NRF-2 and nonalcoholic fatty liver disease. *Annals of Hepatology* **19** 458–465. (https://doi.org/10.1016/j.aohep.2019.11.010)

Stevens PE, Levin A & Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members 2013 Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Annals of Internal Medicine* **158** 825–830. (https://doi.org/10.7326/0003-4819-158-11-201306040-00007)

Stražar M, Temba GS, Vlamakis H, Kullaya VI, Lyamuya F, Mmbaga BT, Joosten LAB, van der Ven AJAM, Netea MG, de Mast Q, *et al.* 2021 Gut microbiome-mediated metabolism effects on immunity in rural and urban African populations. *Nature Communications* **12** 4845. (https://doi.org/10.1038/s41467-021-25213-2)

Sumida Y, Yoshikawa T & Okanoue T 2009 Role of hepatic iron in non-alcoholic steatohepatitis. *Hepatology Research* **39** 213–222. (https://doi.org/10.1111/j.1872-034X.2008.00442.x)

Sunny NE, Parks EJ, Browning JD & Burgess SC 2011 Excessive hepatic mitochondrial TCA cycle and gluconeogenesis in humans with nonalcoholic fatty liver disease. *Cell Metabolism* **14** 804–810. (https://doi.org/10.1016/j.cmet.2011.11.004)

Tanase DM, Gosav EM, Neculae E, Costea CF, Ciocoiu M, Hurjui LL, Tarniceriu CC, Maranduca MA, Lacatusu CM, Floria M, *et al.* 2020 Role of gut microbiota on onset and progression of microvascular complications of Type 2 diabetes (T2DM). *Nutrients* **12** 3719. (https://doi.org/10.3390/nu12123719)

Teng Y, Wang Y, Tian Y, Chen Y, Guan W, Piao C & Wang Y 2020 Lactobacillus plantarum LP104 ameliorates hyperlipidemia induced by AMPK pathways in C57BL/6N mice fed high-fat diet. *Journal of Functional Foods* **64** 103665. (https://doi.org/10.1016/j.jff.2019.103665)

Tian T, Wang Z & Zhang J 2017 Pathomechanisms of oxidative stress in inflammatory bowel disease and potential antioxidant therapies. *Oxidative Medicine and Cellular Longevity* **2017** 4535194. (https://doi.org/10.1155/2017/4535194)

Tomeno W, Imajo K, Takayanagi T, Ebisawa Y, Seita K, Takimoto T, Honda K, Kobayashi T, Nogami A, Kato T, *et al.* 2020 Complications of non-alcoholic fatty liver disease in extrahepatic organs. *Diagnostics* **10** 912. (https://doi.org/10.3390/diagnostics10110912)

Ucar F, Sezer S, Erdogan S, Akyol S, Armutcu F & Akyol O 2013 The relationship between oxidative stress and nonalcoholic fatty liver disease: its effects on the development of nonalcoholic steatohepatitis. *Redox Report: Communications in Free Radical Research* **18** 127–133. (https://doi.org/10.1179/1351000213Y.0000000050)

Wang B, Jiang X, Cao M, Ge J, Bao Q, Tang L, Chen Y & Li L 2016 Altered fecal microbiota correlates with liver biochemistry in nonobese patients with non-alcoholic fatty liver disease. *Scientific Reports* **6** 32002. (https://doi.org/10.1038/srep32002)

Wang Y, Nakajima T, Gonzalez FJ & Tanaka N 2020 PPARs as metabolic regulators in the liver: lessons from liver-specific PPAR-null mice. *International Journal of Molecular Sciences* **21** 2061. (https://doi.org/10.3390/ijms21062061)

Wei B, Peng Z, Xiao M, Huang T, Yang S, Liu K, Wu M, Zheng W, Xie M & Xiong T 2023 Modulation of the microbiome–fat–liver axis by lactic acid bacteria: A potential alleviated role in high-fat-diet-induced obese mice. *Journal of Agricultural and Food Chemistry* **71** 10361–10374. (https://doi.org/10.1021/acs.jafc.3c03149)

Whaley-Connell AT, Chowdhury NA, Hayden MR, Stump CS, Habibi J, Wiedmeyer CE, Gallagher PE, Tallant EA, Cooper SA, Link CD, *et al.* 2006 Oxidative stress and glomerular filtration barrier injury: role of the renin-angiotensin system in the Ren2 transgenic rat. *American Journal of Physiology-Renal Physiology* **291** F1308–F1314. (https://doi.org/10.1152/ajprenal.00167.2006)

Wu L, Li J, Feng J, Ji J, Yu Q, Li Y, Zheng Y, Dai W, Wu J & Guo C 2021*a* Crosstalk between PPARs and gut microbiota in NAFLD. *Biomedicine and Pharmacotherapy* **136** 111255. (https://doi.org/10.1016/j.biopha.2021.111255)

Wu T, Zhang Y, Li W, Zhao Y, Long H, Muhindo EM, Liu R, Sui W, Li Q & Zhang M 2021*b* Lactobacillus rhamnosus LRa05 ameliorate hyperglycemia through a regulating glucagon-mediated signaling pathway and gut microbiota in Type 2 diabetic mice. *Journal of Agricultural and Food Chemistry* **69** 8797–8806. (https://doi.org/10.1021/acs.jafc.1c02925)

Wu Y, Wang B, Tang L, Zhou Y, Wang Q, Gong L, Ni J & Li W 2022 Probiotic Bacillus alleviates oxidative stress-induced liver injury by modulating gut-liver axis in a rat model. *Antioxidants* **11** 291. (https://doi.org/10.3390/antiox11020291)

Xu R, Pan J, Zhou W, Ji G & Dang Y 2022 Recent advances in lean NAFLD. *Biomedicine and Pharmacotherapy* **153** 113331. (https://doi.org/10.1016/j.biopha.2022.113331)

Yasui K, Sumida Y, Mori Y, Mitsuyoshi H, Minami M, Itoh Y, Kanemasa K, Matsubara H, Okanoue T & Yoshikawa T 2011 Nonalcoholic steatohepatitis and increased risk of chronic kidney disease. *Metabolism: Clinical and Experimental* **60** 735–739. (https://doi.org/10.1016/j.metabol.2010.07.022)

Ye Q, Zou B, Yeo YH, Li J, Huang DQ, Wu Y, Yang H, Liu C, Kam LY, Tan XXE, *et al.* 2020 Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Lancet. Gastroenterology and Hepatology* **5** 739–752. (https://doi.org/10.1016/S2468-1253(20)30077-7)

Yoshida H, Ishii M & Akagawa M 2019 Propionate suppresses hepatic gluconeogenesis via GPR43/AMPK signaling pathway. *Archives of Biochemistry and Biophysics* **672** 108057. (https://doi.org/10.1016/j.abb.2019.07.022)

Yoshifuji A, Wakino S, Irie J, Tajima T, Hasegawa K, Kanda T, Tokuyama H, Hayashi K & Itoh H 2016 Gut Lactobacillus protects against the progression of renal damage by modulating the gut environment in rats. *Nephrology, Dialysis, Transplantation* **31** 401–412. (https://doi.org/10.1093/ndt/gfv353)

Younes R & Bugianesi E 2019 NASH in lean individuals. *Seminars in Liver Disease* **39** 86–95. (https://doi.org/10.1055/s-0038-1677517)

Zhang XQ, Xu CF, Yu CH, Chen WX & Li YM 2014 Role of endoplasmic reticulum stress in the pathogenesis of nonalcoholic fatty liver disease. *World Journal of Gastroenterology* **20** 1768–1776. (https://doi.org/10.3748/wjg.v20.i7.1768)

Zhang L, Qin Q, Liu M, Zhang X, He F & Wang G 2018 Akkermansia muciniphila can reduce the damage of gluco/lipotoxicity, oxidative stress and inflammation, and normalize intestine microbiota in streptozotocin-induced diabetic rats. *Pathogens and Disease* **76** (https://doi.org/10.1093/femspd/fty028)

Zhou Z, Sun B, Yu D & Zhu C 2022 Gut microbiota: an important player in type 2 diabetes mellitus. *Frontiers in Cellular and Infection Microbiology* **12** 834485. (https://doi.org/10.3389/fcimb.2022.834485)

Received 20 January 2023
Accepted 31 August 2023
Available online 31 August 2023
Version of Record published 5 October 2023