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Review

# Metabolic Restoration through Nutritional Detoxification in Non-Alcoholic Fatty Liver: A Mini-Review

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## Abstract

About a third of the global population suffers from non-alcoholic fatty liver disease (NAFLD). The disease develops with no specific signs along with other co-morbidities. Both genetic polymorphisms and external risk factors are correlated with the disease. NAFLD is characterized by the accumulation of fat within hepatocytes that precede its progression to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma/hepatic failure. The standard management involves compliance with a fat and sugar-poor diet as well as other lifestyle alterations. Nonetheless, recent studies have shown that some foods and nutraceuticals exhibited beneficial effects toward NAFLD. This paper offers a short review of the pathophysiology, risk factors, and nutritional detoxification of NAFLD.

**Keywords:** NAFLD, free fatty acids, metabolic syndrome, detoxification, xenobiotics, synbiotics.

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On a daily basis, the human liver is predisposed to a wide array of xenobiotics that need to be continually metabolized and excreted to protect the body from their adverse effects. The liver is a pivotal, powerful organ that can eliminate almost every possible compound but the problem lies if its clearance capacity got overwhelmed. If so, the liver itself is negatively impacted and therefore many of its fundamental functions are interrupted and excessive fats accumulate within resulting in fatty liver disease (FLD).[1] FLD is considered the most common leading cause of chronic liver diseases. There are two common patterns of FLD, alcoholic FLD (AFLD) and non-alcoholic FLD (NAFLD) based on whether or not alcohol is the driving cause.[2] This review aims to highlight the prevalence, risk factors, and pathophysiology of NAFLD. Moreover, foods, as well as nutraceuticals demonstrating positive action on NAFLD, are also discussed.

## Prevalence

It has been estimated that approximately a third (32.4%) of the f global population has NAFLD. This number increased markedly within a decade, i.e. it increased from 25.5% in 2005 and attained maximum prevalence in 2016 (37.8%). Gender difference is a significant risk factor as women are less susceptible than men (39.7% vs 25.6%).[3] Concerning its geographic distribution, Middle-East and South America are the major hotspots (>30%) while Africa is the least (13%).[4] Overall mortality related to NAFLD was estimated to be 15–20 per 1000 people.[5] Such extremely high prevalence rates hit an alarming medical alert so that contradictory health measures should take place so as to alleviate its incidence.

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## Risk Factors

### Genetics

Multiple genetic mutations contribute to the pathogenesis of NAFLD as inferred from identical twins, familial inheritance, and predisposition variation studies. Whole exome sequencing studies conducted on obese individuals indicated that the Bardet-Biedl syndrome 1 gene and Melanocortin 3 receptor gene were associated with the pathology of NAFLD.[6] In addition, PNPLA3 single nucleotide polymorphisms were shown to promote NAFLD, with some variants are at greater risk of severe fibrosis and even hepatocellular carcinoma.[7] Currently, seven gene families were implicated in different stages of the pathogenesis of NAFLD as summarized in Table 1. This includes hepatic lipid and glucose metabolic pathways, insulin signaling, steatosis oxidative stress, and cytokines.[8,9] This interprets the complex interplay observed in this disease and the absence of potential radical intervention.

### External Factors

Given the fact that the liver a is a central organ, especially in food and toxicants metabolism, numerous risk factors were linked to the excessive accumulation of fat in it and, thus, the development NAFLD. Several non-genetic risk factors were correlated with NAFLD such as sex, age, race, diet, exercise, sleep, and the existence of comorbidities[10] as illustrated in Figure 1. Men are more susceptible to NAFLD than women.[11,12] It has a low prevalence in middle-aged people and peaks at the age of 60 following a bell-like curve.[13] Also, a high-fat diet that is rich in triglycerides and cholesterol is associated with NAFLD incidence. Sugars (primarily fructose), on the other hand, in the form of sucrose or high-fructose corn syrup added into commercial syrups and drinks can induce lipogenesis in high doses. At the same time, they also trigger an inflammatory response that results in liver cell apoptosis via the c-Jun-N-Terminal pathway.[14] A large body of evidence confirmed that the co-existence of type 2 diabetes is highly correlated with the incidence of NAFLD.[15] Likewise, about half of hypertension patients develop NAFLD.[16] Furthermore, recent researches suggested an important link between dysbiosis, an imbalance of the gut microflora composition, and the incidence of NAFLD through the so-called gut-liver axis.[17]

**Table 1.** Genes implicated in the pathogenesis of NAFLD

| Pathway | Implicated genes |
|---|---|
| Hepatic lipid export/oxidation | *PNPLA3, TM6SF2, NR1I2, PPAR-α, PEMT, MTTP, APOC3 and APOE* |
| Glucose metabolism and insulin resistance | *ENPP1/IRS1, GCKR, SLC2A1, GOAT, TCF7L2 and PPARG* |
| Steatosis-hepatic lipid import/ synthesis | *SLC27A5, FADS1, and LPIN1* |
| Steatohepatitis-oxidative stress | *HFE, GCLC/GCLM, ABCC2, and SOD2* |
| Steatohepatitis-endotoxin response | *TLR4 and CD14* |
| Cytokines | *TNF and IL6* |
| Fibrosis | *AGTR1 and KLF6* |

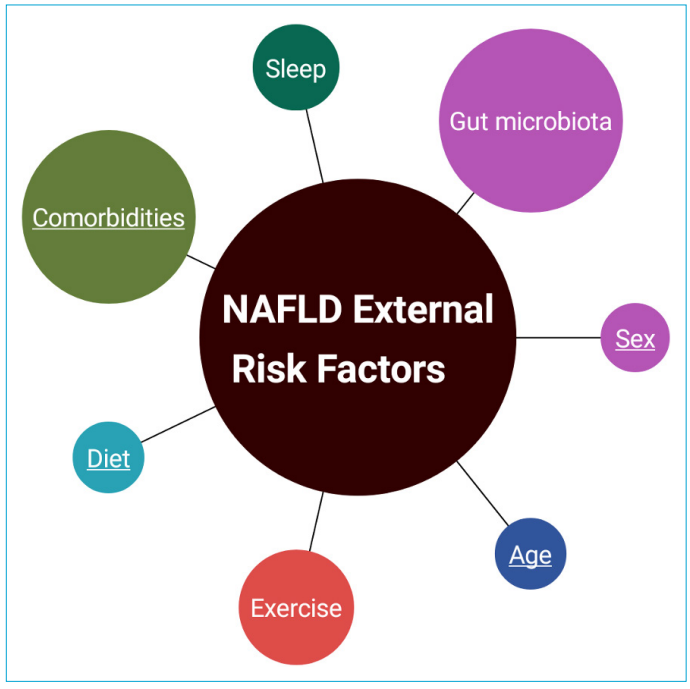


**Figure 1.** External risk factors of NAFLD pathogenesis.

### Pathophysiology

The first step leading to the development of NAFLD is the accumulation of fatty acids within hepatocytes which is usually accompanied by the emergence of metabolic syndrome.[18] The accumulated fatty acids came from three distinguished sources: (i) lipolysis of the stored fats in the adipose tissues, (ii) de novo lipogenesis (DNL) of fat, or (iii) derived from the diet macronutrients.[19] Isotope labeling to quantify the major route of fatty acids in the liver prioritized the lipolysis from adipose tissue as the major route (59%) followed by DNL (26%) and diet fat/sugar was the least (15%)[20] as depicted in Figure 2. Being the primary source of fat accumulation, excessive adipose tissue fat further promotes insulin resistance which aggravates the situation by decreasing peripheral fat acquisition and its redirection into the liver.[21,22] NAFLD is progressed to steatohepatitis, fibrosis, cirrhosis, portal HTN, and liver failure which is the major cause of liver-related death. Besides, patients with NAFLD may experience hepatocellular carcinoma if untreated.[23] Toxic lipids generated

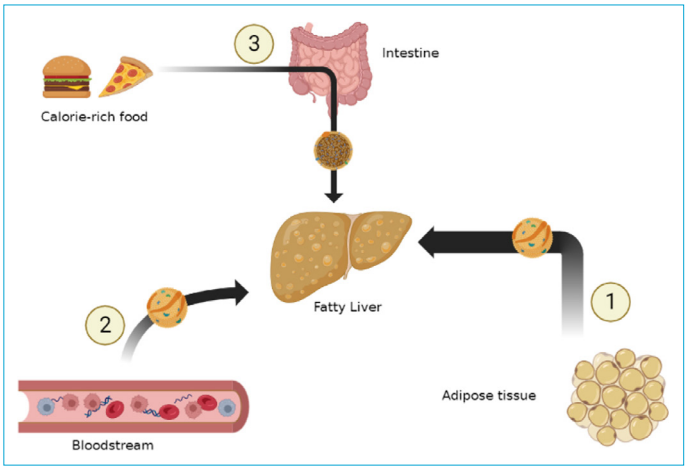


**Figure 2.** The three major sources of FFA. Numbers are ordered according to involvement. External fats are conveyed to the liver via chylomicron whereas the internal fat is via VLDL.

from the accumulated fats within hepatocytes can induce three cellular events that account for the aggressive behavior of NAFLD progression and complications, namely, mitochondria and endoplasmic reticulum stresses, disrupted intracellular signaling pathways, and activation of cellular/transmembrane proinflammatory cytokine kinases.[19,24]

The liver in normal circumstances can handle large quantities of fat and other macronutrients efficiently and no accumulated fat is seen. Indeed, the accumulated fat is a clinical sign denoting an overwhelmed, debilitated liver.[25,26] Therefore, accumulated hepatic fat can be deemed as a result and not a real causal agent as evidenced by the development of the disease in lean, non-obese individuals.[27]

So, what are the triggers of the first strike in NAFLD? To address this question, we should take a look at the chemicals we are exposed to every day. These include pesticides, drugs, plastics, smoking gases, petroleum products, caffeine, heavy metals, preservatives, cleaning chemicals, cosmetics from external sources and hydrogen peroxide, degraded hormones, and metabolic wastes from internal sources.[28,29] It should be noted that the majority of these xenobiotics are lipophilic in nature giving a clue about their involvement in NAFLD since they are stored in the liver in a similar scenario to lipid-soluble vitamins. Hence, it is no surprise such huge, various xenobiotics play a significant – if not causative – role in the development and progression of NAFLD. Indeed, xenobiotics can fasten the progression of NAFLD into further stages. In contrast, a pre-existing NAFLD disrupts the metabolism of xenobiotics creating a favorable environment for oxidative stress and inflammation, exacerbating the disease outcome.[30,31]

## Nutritional Detoxification

To understand the biochemical principle underlying the induction of the detoxification system of xenobiotics. Once a xenobiotic gets inside the hepatocyte, it undergoes successive three main phases that culminate with the rid of those toxic chemicals as elucidated in Figure 3. Phase I is the redox reaction that provisions the xenobiotic for the second reaction. Phase I is represented mainly by the inducible enzyme cytochrome P450 (CYP P450). Afterward, the activated xenobiotic enters phase II which is a conjugation reaction, i.e. loading a highly water-soluble moiety onto the activated xenobiotic, rendering it more suitable and readier for excretion (phase III). The conjugated xenobiotic is then excreted via two portals: the urinary tract (in urine) or the gastrointestinal tract (via bile).[29,32]

## Protein and Choline

The egg is considered a complete food that contains all essential amino acids, and micronutrients, particularly calcium. Meat and fish are another rich sources of protein and, being animal protein contains all the indispensable amino acids. In addition, meat contains high amounts of iron. The protein content of eggs and meats is essential for the synthesis of proteins and enzymes and in the case of NAFLD, the enzymes of the detoxification system are upregulated to cope with the exposed xenobiotics. The upregulation of biotransforming enzymes requires extra building blocks (amino acids) which are provided via eggs and meats.[33] Also, the amino acids will fuel the synthesis of extra glutathione, the most important antioxidant in the body, which is demanded by the conjugation reaction in phase II.[34] The eggs are unique in that has a good content of choline and the latter is important for the synthesis of very low-density lipoprotein (VLDL). Rodents fed with a choline-deficient diet not only developed NAFLD but also fibrosis was documented.[35]

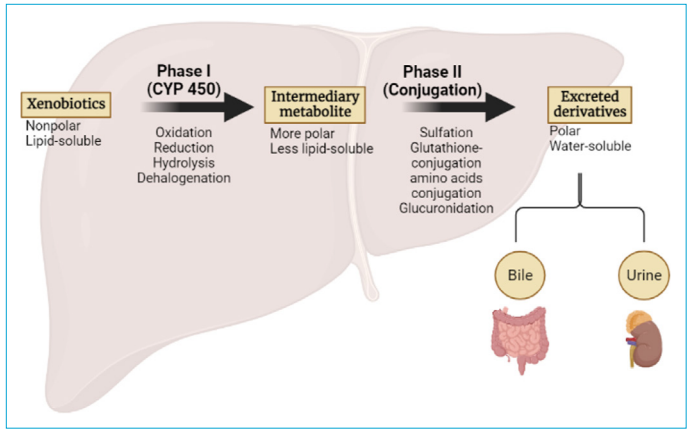


**Figure 3.** Overview of the xenobiotics detoxification system.

### Iron and Sulfur

The iron in the meat serves as a cofactor in the form of an iron-sulfur cluster of CYP 450, flavin monooxygenase, and the other phase I redox enzymes. As stated above, phase I enzymes contains iron-sulfur clusters for their redox reactions. The sulfur is provided in the diet from both onion and garlic. This strategy of treatment follows the principle of substrate flux in which the substrate supplied feeds a pathway or process. Iron-sulfur clusters participate in the electron-transfer process so that ensures the submission of electrons to the xenobiotics and, at the same time, minimizes the liberation of free radicals. Additionally, sulfation is another means of conjugation reaction occurs in phase II system to increase the solubility of the xenobiotics. Both garlic and onions pose good antioxidant as well as anti-inflammatory profiles.[36–38]

### Vitamins

In addition to the amino acids and iron and sulfur that satisfy the needs of over-expressed genes of the detoxification system upon xenobiotics exposure, other prosthetic groups and cofactors are also needed. Some reports proved the diminished activity of P4502C11 in retinol-deficient mice.[39] Vitamin E, on the other hand, besides its antioxidant activity, can induce phase I enzymes and it has been suggested as a promising choice for NAFLD.[40] Vitamin C, the other antioxidant, is required for reverting vitamin E activity after its reaction with free radicals. Vitamin C itself is demanding glutathione for restoring its active form.[41] Indeed, cysteine supplements in different formulations such as whey, N-acetylcysteine, and water soluble vitamins (B-complex and C) can compensate for the depleted glutathione.[42] This confirms the intricate network of the antioxidant system. In an in vitro system, both vitamin E and rifampicin, a known stimulator of xenobiotic metabolism, activated the pregnane X receptor (PXR). PXR forms a heterodimer with the retinoid X receptor (RXR), and binds to specific cis-elements in the promoter regions of genes. PXR/RXR instigates a gene array involved in the detoxification of xenobiotics, including oxidation/reduction (phase I), conjugation (phase II), and transporters (phase III). Most importantly, PXR/RXR regulates the first step of the detoxification system (CYP3A), the primary isoform implicated in the hepatic detoxification of >50% of taken medicines. Vitamin E acting as a PXR ligand could alter these PXR-mediated reactions. Unfortunately, the half-life of this action has not been determined.[43]

### Bile Salts

The risk of hepatic injury and dysfunction is doubled if bile salts metabolism was dysregulated in adult NAFLD patients.[44] After passing through phase I and II, the prepared xenobiotic is ready for excretion in urine or bile. To aid its elimination in the bile, bile salts supplements are a good medical intervention. Moreover, bile salts also facilitate the emulsification of fats during digestion and absorption. The body does not excrete bile salts unless its available in large quantities as provided in these supplements.[45] Some bile salts hydrolase-overexpressing Lactobacillus strains showed improvement in hepatic fat accumulation in vitro in a NAFLD cell model.[46]

### Cruciferous Vegetables

Cruciferous vegetables such as Brussels sprouts, broccoli, cauliflower, kale, cabbage, and spinach are rich in fibers which decrease fat absorption from the intestine besides their strong antioxidant properties.[47]. Most importantly, dietary nitrate (80-95% are from cruciferous vegetables) plays a crucial role in ameliorating the inflammation of the liver via inducing AMPK. Activation of AMPK a rise in the xanthine oxidase-dependent NO production, as well as cGMP signaling declines the levels of superoxide through NADPH oxidase enzymes.[48] The polyphenols of cruciferous vegetables inhibit DNL through the downregulation of SREBP1c and β-oxidation rate-limiting enzymes.[49]

### Probiotics and Prebiotics

It is now evident that the gut microbiome composition determines whether or not the individual is at risk of developing a certain disorder. The misuse of antibiotics, particularly broad-spectrum ones, negatively controls both beneficial and pathogenic bacteria, not to mention the emergence of antibiotic-resistant strains. The association between NAFLD and an altered gut microbiome is well-established. Therefore, the intake of both probiotics and prebiotics (now combined as synbiotics) reduced NAFLD severity as mirrored by the findings of corresponding biomarkers. The tested mechanism involves reducing obesity and relieving insulin resistance. Additionally, some microbial metabolites such as acetate, propionate, indole derivatives, and secondary bile acids act to epigenetically brake gluconeogenesis, lipogenesis, and activating nuclear X receptors.[50–52] Probiotics were demonstrated to degrade and eliminate the administered xenobiotics before reaching the liver owing to the versatile repertoire of enzymes they have.[53]

## Conclusion

NAFLD is a leading cause of morbidity and mortality. It usually coexists with other chronic diseases such as metabolic syndrome. Numerous genetic as well as external risk factors are associated with NAFLD. The real cause of the disease is not fully understood although the exposure to various toxic compounds daily is the most rational perspective. The

standard management available is lifestyle and diet modification. However, many reports utilized the biochemistry of some foods and nutraceuticals to empower the xenobiotics detoxification system. This includes high-protein diet, iron and sulfur-rich natural resources, cruciferous vegetables, bile salts supplements, multi-vitamin supplements, and synbiotics whose positive actions are promising.

**Disclosures**

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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