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Non-alcoholic fatty liver disease: pathogenesis and assessing the impact of dietary bioactive compounds on the liver

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a pathological condition ranging from simple steatosis to non-alcoholic steatohepatitis, cirrhosis, and liver cancer. NAFLD is a complex disease mediated by metabolic, environmental, and genetic mechanisms. Many factors such as insulin resistance, lipotoxicity, inflammation, mitochondrial dysfunction, endoplasmic reticulum stress, circadian rhythm, genetics, epigenetics, dietary factors, and gut microbiota play a crucial role in the pathogenesis of NAFLD. Lifestyle changes such as healthy diet, physical activity, avoiding alcohol and smoking are involved in the NAFLD treatment. Dietary bioactive compounds including curcumin, resveratrol, catechins, quercetin, sulforaphane, epigallocatechin-3-gallate, alkaloids, vitamins, and peptides have many health promoting effects such as antioxidant, anti-inflammatory, antihypertensive, chemopreventive, and hepatoprotective. In this review, the pathophysiology of NAFLD and the effects of dietary bioactive compounds on this disease will be discussed in detail with updated information.

Keywords: Non-Alcoholic Fatty Liver Disease, Pathogenesis, Dietary Bioactive Compounds

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as the pathological spectrum of the liver that can progress from simple steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis, and liver cancer [1]. Histopathologically, the absence of necroinflammatory activity is accepted as simple steatosis; however, the presence of a fibrosis caused by portal inflammation, ballooning and hepatocyte damage together with fatty liver is called NASH [2].

Non-alcoholic fatty liver disease has been accepted as a global public health issue, affecting 6 to 45% of the general population, increasing to 70% in patients with type 2 diabetes mellitus and up to 90% in morbidly obese patients [3].

Although, there is no licensed pharmacotherapy for NAFLD, antidiabetic drugs, drugs affecting the bile acid system and lipid-lowering agents are given for treatment according to the accompanying diseases. The most important treatment is mainly based on lifestyle changes such as healthy diet, body weight control, physical activity, smoking cessation and avoiding alcohol [4]. Diet is affordable and effective and does not have any adverse effects. Also, it does not include the metabolic burden that medications load on the body systems. In this respect, many different dietary components are being studied for their possible pharmacological activity in several pathophysiological conditions [5].

The most widely accepted definition of bioactive compounds is 'compounds which have the ability to interact with one or more component(s) of living tissue by presenting a wide range of probable effects [6]. Bioactive compounds which mainly include curcumin, resveratrol, catechins, quercetin, sulforaphane, epigallocatechin-3-gallate, alkaloids, vitamins, and peptides, are particullary present in small quantities in fruits, vegetables, whole grains, beverages and milk products. These bioactive compounds have anti-inflammatory, antioxidant and hepatoprotective properties [7]. In this review, we discussed the pathophysiology of NAFLD and the effects of dietary bioactive compounds on this disease.

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2. PATHOGENESIS

Non-alcoholic fatty liver disease is considered as a multifactorial disease and mediated by metabolic, environmental, and genetic mechanisms. Many factors such as insulin resistance, lipid metabolism, inflammation, mitochondrial dysfunction, endoplasmic reticulum stress, circadian rhythm, genetics, epigenetics, dietary factors, and gut microbiota play a crucial role in the pathogenesis of NAFLD (Figure 1).

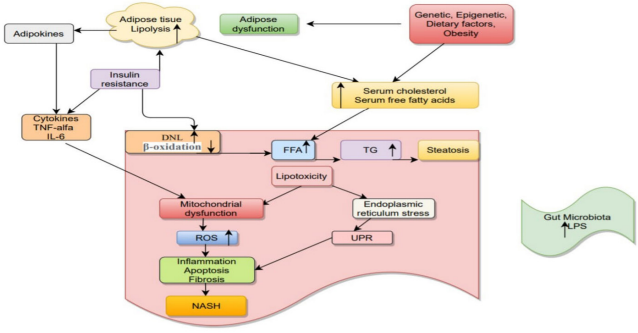

Figure 1. *The multi-hit hypothesis of non-alcoholic fatty liver disease (NAFLD) pathogenesis. The insulin resistance and lipid metabolism dysregulation lead to the development of simple steatosis and render hepatocytes susceptible to "multi-hit", which includes gut-derived bacterial toxins(lipopolysaccharides), adipocytokine imbalance, mitochondrial dysfunction, reactive oxygen species, endoplasmic reticulum stress, apoptosis, activation of pro-fibrogenic factors and pro-inflammatory mediators ultimately leading to non-alcoholic steatohepatitis (NASH). IL: Interleukin; TNF: Tumor necrosis factor; ROS: Reactive oxygen species; DNL: de novo lipogenesis; UPR: Unfolded protein response; TG: Triglyceride; FFA: Free fatty acids; LPS: lipopolysaccharides*

Insulin resistance

Insulin resistance has critical role in the activation of lipotoxicity, oxidative stress, and inflammatory processes in NAFLD and its progression to NASH [8]. Insulin resistance is associated with lipolysis in adipose tissue, it causes an increase in circulating free fatty acids (FFAs) and their uptake by the liver [9].

Increased glucose and insulin levels inhibit mitochondrial β-oxidation, suppress apolipoprotein B100 synthesis, and increase *de novo* lipogenesis (DNL) in the liver through glycolysis [10]. Hepatic DNL could be increased by activation of transcription factors such as sterol regulatory element binding protein (SREBP)-1, carbohydrate response element binding protein (ChREBP), and peroxisome proliferator activated receptor (PPAR). SREBP-1c which regulates DNL, is stimulated by insulin [11]. ChREBP is activated by glucose and increases DNL, it also provides more substrate for triglyceride and FFAs synthesis [12]. In general, PPARs are involved in glucose and fat metabolism as well as in immune response, inflammation, apoptosis, and cell proliferation [13].

Lipid metabolism

Fat accumulates in the liver of NAFLD patients in the form of triglycerides [11]. FFAs are obtained from diet, adipose tissue by lipolysis and/or liver by DNL. In hepatocytes, FFAs undergo acyl-CoA synthesis and form fatty acyl-CoAs that enter esterification or β-oxidation pathways [14]. Increased levels of FFAs in the liver lead to lipid peroxidation, which causes the release of inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and reactive oxygen species (ROS). Inflammation and oxidative stress resulting from the release of these molecules, cause cellular damage and inflammation seen in NASH [15].

Oxidative stress plays an important role in the beginning of hepatic and extrahepatic injuries. Increased levels of FFAs cause oxidative stress by increasing ROS production [16].

Inflammation

Lipotoxicity, insulin resistance, peripheral adipose tissue dysfunction, and gut-derived endotoxins due to increased levels of FFAs induce production and secretion of pro-inflammatory cytokines both systemically and locally in the liver. Also, adipose tissue produces pro-inflammatory cytokines such as IL-6 and TNF-α, which are responsible for the inflammatory and fibrogenic profile of the liver [16].

Adipokines (e.g. leptin, adiponectin) are hormones derived from adipose tissue that contribute to steatosis, NASH, cirrhosis, and carcinogenesis. Adipokines are in balance in healthy and normal weight individuals, but this balance is impaired in NAFLD [17]. Leptin appears to show an anti-steatotic effect in early stage of the NAFLD, but it can trigger hepatic inflammation and fibrosis when the disease progresses [18]. On the other hand, adiponectin, which has anti-steatotic, anti-inflammatory and anti-fibrotic effects, inhibits pro-inflammatory cytokines and stimulates anti-inflammatory cytokines, thus reduces oxidative stress and fibrogenesis [19].

Mitochondrial dysfunction

Structural and functional changes in mitochondria contribute to the pathogenesis of NAFLD. While structural changes occur with the reduction of mitochondrial DNA, functional changes include respiratory chain and mitochondrial β-oxidation [20]. ROS stimulate oxidative stress through the activation of inflammatory pathways and mitochondrial damage; together with oxidized LDL particles they activate Kupffer cells and hepatic stellate cells which lead to inflammation and fibrosis [21].

Endoplasmic reticulum stress

The accumulation of FFAs leads to endoplasmic reticulum stress by triggering an unfolded protein response (UPR). The factors which induce UPR include hyperglycemia, mitochondrial damage, hypercholesterolemia, and oxidative stress in NAFLD [22]. UPR activates c-jun terminal kinase, which is an activator of inflammation and apoptosis [23].

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Circadian rhythm

Animal studies have shown that there is a link between circadian rhythm genes and NAFLD pathogenesis. Environmental factors such as circadian disruption (jet lag or night shift work) and high fat diet (HFD) increase the risk of NAFLD in animal knockout models of circadian locomotor output cycles kaput (clock) and PPAR-α [24]. Treatment with PPAR agonists or melatonin could potentially prevent progression of NAFLD and even cause regression of the disease [25].

Genetics and epigenetics

Genetic variants affect the development and progression of NAFLD by playing a central role in different ways such as single nucleotide polymorphism, lipogenesis, lipoprotein transport, oxidation of FFAs, oxidative stress, and cytokine production by endotoxin [26]. Patatin-like phospholipase-3 (PNPLA3) gene encodes enzymes which are involved in lipid metabolism [27]. The PNPLA3 protein, which is also known as adiponutrin, exerts a lipolytic activity on triglycerides [27]. However, the role of genetics in NAFLD is needed to study more to understand the pathogenesis of the disease.

Epigenetic modifications include DNA methylation, histone modifications, and the activity of microRNAs (miRNAs) without altering the primary DNA sequence. These modifications exhibit a high degree of developmentally and environmentally oriented plasticity, and contribute to cell homeostasis [28].

Dietary factors

Dietary composition and high energy intake have important effects on NAFLD pathogenesis. High energy intake and fat accumulation that are associated with insulin resistance, result in the increase of inflammatory cytokines and fatty acids in the circulation [29]. In general, NAFLD is characterized by high intake of saturated fats, simple carbohydrates, foods containing fructose, cholesterol, and low intake of antioxidants, fiber, and omega-3 fatty acids [30].

In NAFLD pathogenesis, fructose has been suggested to increase DNL, inhibit β-oxidation, increase inflammation, and alter gut microbiota which potentially causes dysbiosis. It has been also shown that fructose is an important factor for increasing intestinal permeability and endotoxins in the portal blood [31].

Mediterranean diet which can reduce liver fat, has been recommended for the treatment of NAFLD by the EASL-EASD-EASO Clinical Practice Guideline and the European Society of Clinical Nutrition and Metabolism (ESPEN) Guidelines [4, 32].

Gut microbiota

Microbiota is thought to play an important role in the pathogenesis of NAFLD. Several mechanisms have been suggested for the role of microbiota in NAFLD including gut permeability, microbiome-induced regulation of gut barrier, inflammatory factors, and metabolites produced or altered by the microbiota such as bile acids, short chain fatty acids, and ethanol [33].

Intestinal bacterial overgrowth leads to a leaky mucosal barrier which allows bacterial translocation and increases microbial products such as lipopolysaccharides. These products, particularly pathogen-associated molecular pattern molecules, interact with receptors found not only on inflammatory cells but also on other cell types such as hepatic stellate cells and endothelial cells [34].

3. THE IMPACT OF DIETARY BIOACTIVE COMPOUNDS ON NAFLD

Dietary bioactive compounds are being investigated intensively to complement therapeutic strategies of many diseases including NAFLD [35]. They show many health-promoting effects such as antioxidant, anti-inflammatory, antihypertensive, chemopreventive, and hepatoprotective [36].

Some dietary bioactive compounds showing antioxidant and/or anti-inflammatory effects, and their mechanism of actions on NAFLD are summarized in Table I.

Table I. *The impact of dietary bioactive compounds in NAFLD*

Nutrient/Bioactive compound	Effects	Mechanism of action
Caffeine	Antioxidant	Weight gain ⇓ Oxidative stress ⇓
Epigallocatechin gallate	Antioxidant	Weight gain ⇓ Oxidative stress ⇓ Lipid accumulation ⇓
Probiotic	Anti-inflammatory	Lipid accumulation ⇓ Steatosis ⇓ Serum lipids ⇓
Omega-3	Anti-inflammatory Antioxidant	Steatosis ⇓ Lipid peroxidation ⇓
Prebiotic	Anti-inflammatory Antioxidant	β-oxidation ⇓ Lipogenesis ⇓ Serum lipids ⇓
Astaxanthin	Anti-inflammatory Antioxidant	Pro-inflammatory cytokines ⇓ Inhibition of lipogenesis
Quercetin	Anti-inflammatory Antioxidant	Pro-inflammatory cytokines ⇓ Inhibition of lipogenesis
Curcumin	Anti-inflammatory Antioxidant	Intestinal barrier function ⇓ Endotoxin ⇓ Toll-like receptor (TLR)4 / nuclear factor (NF)-κB inflammation ⇓
Resveratrol	Anti-inflammatory Antioxidant	Oxidative stress ⇓ Inflammation ⇓ Serum lipids ⇓

Yang et al., found that the co-administration of epigallocatechin-3-gallate and caffeine in low doses improved obesity and NAFLD in obese rats, suggesting the possible role of epigallocatechin-3-gallate and caffeine co-administration in reducing body weight, oxidative stress and inflammatory cytokines and improving serum lipid profiles [37].

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A study included 20 male and 20 female participants, aged between 19 and 64 years and diagnosed with NAFLD. Among them, those who consumed ≥250 mg/day of caffeine showed elevated ALT and AST levels, as well as a decrease in high-density lipoprotein cholesterol (HDL-C) levels [38].

Consumption of 50 mg green tea tablets containing 500 mg of standardized total polyphenols three times daily for three months was effective in reducing liver fat accumulation, attenuating fatty liver grading and improving liver function in 52 patients diagnosed with NAFLD aged 10 to 16 years [39].

Administration of both probiotic and omega-3 supplements to obese mice caused a significant reduction in hepatic steatosis and hepatic lipid accumulation [40]. Similarly, another study showed the beneficial effects of omega-3 fatty acids treatment in a mouse model of NAFLD by decreasing plasma cholesterol, plasma triglycerides, fasting plasma glucose and liver lipid peroxidation levels [41]. Patients diagnosed with NAFLD were given omega-3 fatty acids supplementation, improvements in hepatic steatosis were seen in contrast to those who received placebo. Omega-3 fatty acid supplementation resulted in a reduction in triglyceride and total cholesterol levels as well as a decrease in body mass index (BMI), while also increasing HDL-C concentrations among individuals with NAFLD [42].

It has been shown that prebiotic and synbiotic (prebiotic and probiotic) supplementation improved hepatic changes due to hypercholesterolemia in adult rats [43]. These changes appear to be mediated by altered gene expressions such as SREBP-1c and PPAR-α which are associated with β-oxidation and lipogenesis. Thus, prebiotic supplementation can modulate and decrease SREBP-1c expression in lipogenesis [43].

Behrouz et al., conducted a study investigating the effects of probiotics and prebiotics on individuals NAFLD. The results showed reductions in AST, ALT, triglycerides, and total cholesterol; however, there were no changes observed in inflammation biomarkers such as C-reactive protein. It is important to note that the trial had a relatively short duration, making it challenging to guarantee the sustained reduction of metabolic parameters. Moreover, the study did not include assessments for liver fibrosis to examine the severity and progression of liver disease [44].

Hernandez-Ortega et al. and Shen et al., found that hepatic marker levels such as alanine aminotransferase and aspartate aminotransferase were reduced by adding astaxanthin and quercetin to the diets of mice with liver fibrosis [45,46]. Also, decrease in pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β) in serum and liver tissue and antifibrotic effects have been associated with their anti-inflammatory capacities. In addition, quercetin and astaxanthin contribute to the improvement of lipid metabolism by inhibiting lipogenesis and stimulating fatty acid oxidation by affecting PPAR-α and adiponectin [45,46].

Administration of curcumin protects against HFD-induced hepatic steatosis in ApoE−/− mice by modulating intestinal barrier function and reducing endotoxin and toll-like receptor (TLR)4/nuclear factor (NF)-κB inflammation [47]. In a study involving 55 NAFLD individual, it was observed that administering a daily dose of 500 mg of curcumin resulted in a reduction in the serum concentrations of inflammatory cytokines such as TNF-α and interleukins [48].

In a 12-week clinical trial that randomized 90 participants aged 20 to 60 years with NAFLD, the subjects were divided into three distinct groups: the calorie-restricted (CR) diet group (n = 30), the resveratrol group (n = 30) receiving a daily dose of 600 mg pure trans-resveratrol, and the placebo group (n = 30) receiving placebo capsules. Findings from the trial demonstrated that the CR diet induced significant reductions in weight (4.5%), BMI, waist circumference, waist-to-hip ratio, as well as ALT, AST, and lipid profiles, surpassing the outcomes observed in both the resveratrol and placebo groups [49].

Conclusion

Non-alcoholic fatty liver disease has high morbidity and mortality rates worldwide as it has become the major cause of end-stage liver disease and liver transplantation. The pathogenesis of NAFLD is a complex process with multiple factors such as gut microbiota, insulin resistance, hormones secreted from adipose tissue, increased levels of FFAs, endoplasmic reticulum stress, mitochondrial dysfunction, inflammation, circadian rhythm, genetic and epigenetic factors. Dietary bioactive compounds, which modulate lipogenesis, lipid oxidation and lipid peroxidation, reduce endotoxin and inflammation and improve intestinal barrier function, represent a new attractive therapeutic approach for NAFLD. Further studies could provide insights into the role of dietary bioactive compounds in NAFLD treatment.

Compliance with Ethical Standards

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REFERENCES

[1] Cohen JC, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. Science 2011; 332:1519-23. doi:10.1126/science.1204265.

[2] Çolak Y, Tuncer İ. Nonalkolik karaciğer yağlanması ve steatohepatit. İst Tıp Fak Derg 2010; 73:85-9.

[3] Fazel Y, Koenig AB, Sayiner M, Goodman ZD, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. Metab 2016; 65:1017-25. doi: 10.1016/j.metabol.2016.01.012.

[4] EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64:1388-402. doi: 10.1016/j.jhep.2015.11.004.

[5] Cecchini M, Sassi F, Lauer JA, Lee YY, Guajardo – Barron V, Chisholm D. Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness. Lancet 2010; 376:1775-84. doi:10.1016/S0140-6736(10)61514-0.

[6] Guaadaoui A, Benaicha S, Elmajdoub N, Bellaoui M, Hamal A. What is a bioactive compound? A combined definition for a preliminary consensus. Int J Nutr Food Sci 2014; 3:74-9. doi: 10.11648/j.ijnfs.20140303.16.

[7] Gil-Chavez JG, Villa JA, Ayala-Zavala JF, et al. Technologies for extraction and production of bioactive compounds to be used as nutraceuticals and food ingredients: An overview. Compr Rev Food Sci Food Saf 2013; 12:5-23. doi: 10.1111/1541-4337.12005.

[8] Peverill W, Powell LW, Skoien R. Evolving concepts in the pathogenesis of NASH: beyond steatosis and inflammation. Int J Mol Sci 2014; 15:8591-638. doi: 10.3390/ijms15058591.

[9] Fabbrini E, Mohammed BS, Magkos F, Korenblat KM, Patterson BW, Klein S. Alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease. Gastroenterology 2008; 134:424-31. doi: 10.1053/j.gastro.2007.11.038.

[10] Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002; 346:1221-31. doi: 10.1056/NEJMra011775.

[11] Schultz JR, Tu H, Luk A, et al. Role of LXRs in control of lipogenesis. Genes Dev 2000; 14:2831-8. doi: 10.1101/gad.850400.

[12] Musso G, Gambino R, Cassader M. Cholesterol metabolism and the pathogenesis of non-alcoholic steatohepatitis. Prog Lipid Res 2013; 52:175-91. doi: 10.1016/j.plipres.2012.11.002.

[13] Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res 2011; 2:236. doi: 10.4103/2231-4040.90879.

[14] Ferramosca A, Zara V. Modulation of hepatic steatosis by dietary fatty acids. World J Gastroenterol 2014; 20:1746-755. doi: 10.3748/wjg.v20.i7.1746.

[15] Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 2006; 43:99-112. doi: 10.1002/hep.20973.

[16] Puntarulo S. Iron, oxidative stress and human health. Mol Aspects Med 2005; 26:299-312. doi: 10.1016/j.mam.2005.07.001.

[17] Adolph TE, Grander C, Grabherr F, Tilg H. Adipokines and non-alcoholic fatty liver disease: multiple interactions. Int J Mol Sci 2017; 18:1649. doi: 10.3390/ijms18081649.

[18] Polyzos SA, Kountouras J, Mantzoros CS. Leptin in nonalcoholic fatty liver disease: a narrative review. Metabolism 2015; 64:60-78. doi: 10.1016/j.metabol.2014.10.012.

[19] Saxena NK, Anania FA. Adipocytokines and hepatic fibrosis. Trends Endocrinol Metab 2015; 26:153-61. doi: 10.1016/j.tem.2015.01.002.

[20] Pessayre D, Fromenty B. NASH: a mitochondrial disease. J Hepatol 2005; 42:928-40. doi: 10.1016/j.jhep.2005.03.004.

[21] Begriche K, Igoudjil A, Pessayre D, Fromenty B. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. Mitochondrion 2006; 6:1-28. doi: 10.1016/j.mito.2005.10.004.

[22] Seki S, Kitada T, Sakaguchi H. Clinicopathological significance of oxidative cellular damage in non-alcoholic fatty liver diseases. Hepatol Res 2005; 33:132-4. doi: 10.1016/j.hepres.2005.09.020.

[23] Yung, JHM, Giacca, A. Role of c-Jun N-terminal kinase (JNK) in obesity and type 2 diabetes. Cells 2020; 9:706. doi: 10.3390/cells9030706.

[24] Mazzoccoli G, De Cosmo S, Mazza T. The biological clock: A pivotal hub in non-alcoholic fatty liver disease pathogenesis. Front Physiol 2018; 9:1-16. doi: 10.3389/fphys.2018.00193.

[25] Ip E, Farrell G, Hall P, Robertson G, Leclercq I. Administration of the potent PPAR alpha agonist, Wy-14,643, reverses nutritional fibrosis and steatohepatitis in mice. Hepatology 2004; 39:1286-96. doi: 10.1002/hep.20170.

[26] Anstee QM, Daly AK, Day CP. The Genetics of Nonalcoholic Fatty Liver Disease: Spotlight on *PNPLA3* and *TM6SF2*. Semin Liver Dis 2015; 35:270-90. doi: 10.1055/s-0035.156.2947.

[27] Anstee QM, Day CP. The genetics of NAFLD. Nat Rev Gastroenterol Hepatol 2013; 10:645-55. doi: 10.1038/nrgastro.2013.182.

[28] Zeybel M, Mann DA, Mann J. Epigenetic modifications as new targets for liver disease therapies. J Hepatol 2013; 59:1349-53. doi: 10.1016/j.jhep.2013.05.039.

[29] Dongiovanni P, Valenti LA. Nutrigenomic approach to nonalcoholic fatty liver disease. Int J Mol Sci 2017; 18:1534. doi: 10.3390/ijms18071534.

[30] Musso G, Gambino R, De Michieli F, et al. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology 2003; 37:909-16. doi: 10.1053/jhep.2003.50132.

[31] Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): A population based study. J. Hepatol 2007; 47:711-7. doi:10.1053/jhep.2003.50132.

[32] Bischoff SC, Bernal W, Dasarathy S, et al. ESPEN practical guidline: Clinical nutrition in liver disease. Clin Nut 2020; 39:3533-62. doi: 10.1016/j.clnu.2020.09.001.

[33] Bashiardes S, Shapiro H, Rozin S, Shibolet O, Elinav E. Non-alcoholic fatty liver and the gut microbiota. Mol Metab 2016; 5:782-94. doi: 10.1016/j.molmet.2016.06.003.

[34] Chakaroun RM, Massier L, Kovacs P. Gut microbiome, intestinal permeability, and tissue bacteria in metabolic disease: perpetrators or bystanders? Nutrients 2020; 12:1082. doi: 10.3390/nu12041082.

[35] Suárez M, Boqué N, Del Bas JM, Mayneris-Perxachs J, Arola L, Caimari A. Mediterranean Diet and Multi-Ingredient-Based Interventions for the Management of Non-Alcoholic Fatty Liver Disease. Nutrients 2017; 9:1052. doi: 10.3390/nu9101052.

[36] Ortega AMM, Campos MRS. Bioactive compounds as therapeutic alternatives. In: Bioactive compounds, Cambridge, England: Woodhead Publishing, 2019:247-64. ISBN: 978.012.8147757.

[37] Yang Z, Zhu MZ, Zhang YB, et al. Coadministration of epigallocatechin-3-gallate (EGCG) and caffeine in low dose ameliorates obesity and nonalcoholic fatty liver disease in obese rats. Phytother Res 2019;33:1019-1026. doi: 10.1002/ptr.6295.

[38] Uçar K, Kahramanoğlu K, Göktaş Z. Association between caffeine intake and liver biomarkers in non-alcoholic fatty liver disease. Cukurova Med J 2023; 48:177-86. doi: 10.17826/cumj.1171396.

[39] Rostampour N, Kasiri KA, Hashemi-Dehkordi E, et al. Therapeutic effects of green tea on nonalcoholic fatty liver disease in 10 – 16-year-old children. J Clin Diagn Res 2019; 13:4-7. doi: 10.7860/JCDR/2019/35236.12986.

[40] Kobyliak N, Falalyeyeva T, Bodnar P, Beregova T. Probiotics supplemented with omega-3 fatty acids are more effective for hepatic steatosis reduction in an animal model of obesity. Probiotics Antimicrob Proteins 2017; 9:123-30. doi: 10.1007/s12602.016.9230-1.

[41] Popescu LA, Vîrgolici B. Lixardu D, et al. Effect of diet and omega-3 fatty acids in NAFLD. Rom J Morphol Embryol 2013;54:785-90.

[42] Lee CH, Fu Y, Yang SJ, Chi CC. Effects of omega-3 polyunsaturated fatty acid supplementation on non-alcoholic fatty liver: A systematic review and meta-analysis. Nutrients 2020;12:9. doi: 10.3390/nu12092769.

[43] Alves CC, Waitzberg DL, de Andrade LS, et al. Prebiotic and synbiotic modifications of beta oxidation and lipogenic gene expression after experimental hypercholesterolemia in rat liver. Front Microbiol 2017; 8:2010. doi:10.3389/fmicb.2017.02010.

[44] Behrouz V, Aryaeian N, Zahedi MJ, Jazayeri S. Effects of probiotic and prebiotic supplementation on metabolic parameters, liver aminotransferases, and systemic inflammation in nonalcoholic fatty liver disease: A randomized clinical trial. J Food Sci 2020; 85: 3611-17. doi: 10.1111/1750-3841.15367.

[45] Hernandez-Ortega LD, Alcantar-Diaz BE, Ruiz-Corro LA, et al. Quercetin improves hepatic fibrosis reducing hepatic stellate cells and regulating pro-fibrogenic/anti-fibrogenic molecules balance. J Gastroenterol Hepatol 2012; 27:1865-72. doi:10.1111/j.1440-1746.2012.07262.x

[46] Shen M, Chen K, Lu J, et al. Protective effect of astaxanthin on liver fibrosis through modulation of TGF-beta1 expression and autophagy. Mediators Inflamm 2014; 2014:954502. doi: 10.1155/2014/954502.

[47] Feng Dan, Zou J, Mai H, et al. Curcumin prevents high-fat diet-induced hepatic steatosis in ApoE−/− mice by improving intestinal barrier function and reducing endotoxin and liver TLR4/NF-κB inflammation. Nutr Metab 2019; 16:79. doi: 10.1186/s12986.019.0410-3.

[48] Saberi-Karimian M, Keshvari M, Ghayour-Mobarhan M, et al. Effects of curcuminoids on inflammatory status in patients with non-alcoholic fatty liver disease: a randomized controlled trial. Complement Ther Med 2020; 49:102322. doi: 10.1016/j.ctim.2020.102322.

[49] Asghari S, Asghari-Jafarabadi M, Somi MH, Ghavami SM, Rafraf M. Comparison of calorie-restricted diet and resveratrol supplementation on anthropometric indices, metabolic parameters, and serum sirtuin-1 levels in patients with nonalcoholic fatty liver disease: a randomized controlled clinical trial. J Am Coll Nutr 2018; 37:223-33 doi: 10.1080/07315.724.2017.1392264.