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MOLECULAR TARGETS OF NATURAL POLYPHENOLS IN OXIDATIVE STRESS-MEDIATED NAFLD

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is a major global cause of chronic liver disease, ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), which may progress to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). NASH is now one of the fastest-growing indications for liver transplantation. Despite its increasing prevalence, no approved pharmacological therapy exists, and lifestyle modification remains the primary treatment strategy. Oxidative stress plays a central role in NAFLD pathogenesis by disrupting the balance between reactive oxygen species (ROS) and antioxidant defenses, leading to cellular damage and disease progression. Natural polyphenols, plant-derived bioactive compounds with strong antioxidant and anti-inflammatory properties, have emerged as potential therapeutic agents. These compounds may improve hepatic steatosis by modulating lipid metabolism, insulin resistance, oxidative stress, and inflammatory pathways. This review focuses on oxidative stress-mediated mechanisms in NAFLD progression and highlights the molecular targets of natural polyphenols that may offer promising therapeutic strategies for its management.

Keywords: Non-alcoholic fatty liver disease (NAFLD), Non-alcoholic steatohepatitis (NASH), Oxidative stress, Reactive oxygen species (ROS), Polyphenols.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease globally. It encompasses a spectrum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), which can progress to liver fibrosis and cirrhosis. NASH is now the fastest-rising cause of hepatocellular carcinoma worldwide and also the fastest-rising indication for liver transplantation [1]. NAFLD is divided into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) according to histological features. NAFL is defined as cases characterized by steatosis, with or without mild lobular inflammation. In contrast, NASH is additionally characterized by hepatocellular damage. Although simple steatosis is considered a “benign” condition, its association with liver fibrosis can lead to the development of cirrhosis and hepatocellular carcinoma (HCC) [2]. The molecular mechanisms leading to NASH and its progression to liver fibrosis and cirrhosis remain only partially understood. [3]. There is no globally recognized “first-line agent” for NAFLD, and lifestyle modifications remain the foundation of treatment. Recently, an increasing number of studies have focused on NAFLD-related therapeutic agents, particularly in clinical trials and future prospects, attracting significant attention [4]. Oxidative stress plays a crucial role in NAFLD pathogenesis and is defined as an imbalance between reactive species and antioxidant defenses. Reactive oxygen species (ROS) are highly reactive molecules that can cause cellular damage. Oxidative stress refers to an imbalance between the production of reactive species (RS) and antioxidant defenses [5]. Recent research indicates that incorporating diets rich in polyphenols may help prevent and treat chronic conditions, such as obesity, certain cancers, and diabetes. Polyphenols are a heterogeneous class of plant-

derived compounds that include several water-soluble antioxidants, reported to be health-promoting agents and proposed for the treatment of various metabolic disorders. In particular, polyphenols may exhibit hepatoprotective effects by increasing fatty acid oxidation and modulating insulin resistance, oxidative stress, and inflammation, which are the main pathogenetic factors driving progression from simple fat accumulation to NASH. Several studies, including in vitro, pre-clinical, and emerging clinical trials, have reported beneficial effects on liver steatosis and its pathogenic and clinical outcomes. Polyphenols can be considered a promising therapeutic approach in the treatment of NAFLD [6]. This review discusses oxidative stress-mediated NAFLD pathogenesis and the molecular targets of natural polyphenols that may offer therapeutic potential.

PATHOGENESIS OF NAFLD

NASH can arise through a variety of molecular mechanisms, and it is unclear whether NAFL is always present before NASH. Furthermore, patients are unlikely to share identical pathogenic factors. A useful conceptual framework for understanding the pathogenic drivers of NAFL and NASH is that the liver's ability to process major metabolic energy substrates, carbohydrates and fatty acids, becomes overburdened, leading to the accumulation of toxic lipid species. These metabolites contribute to hepatic stress, injury, and cell death, which may progress to fibrosis, cirrhosis, and hepatocellular carcinoma. This process is also associated with fibro genesis and genomic instability. Understanding the metabolic basis of NASH, therefore, requires elucidation of the origin and fate of fatty acids in hepatocytes. Fatty acids serve as substrates for the formation of lipotoxic species that induce endoplasmic reticulum (ER) stress and hepatocellular injury when they are present in excess or when their disposal is impaired. The pathways leading to lipotoxicity, ER stress, and cell injury have therefore emerged as rational therapeutic targets [7]. Several etiological factors (e.g., intestinal barrier dysfunction, gut dysbiosis, insulin resistance, lipotoxicity, and hepatic inflammation) act in an interdependent manner to exacerbate liver injury without a clearly defined sequence. Importantly, evidence suggests that hepatic activation of NF-κB–dependent inflammation serves as a convergence point for many of these factors and thus plays a central role in NASH pathogenesis [8].

ROLE OF OXIDATIVE STRESS IN NAFLD

Liver inflammation in NASH is associated with pro-inflammatory mediators such as leptin, resistin, IL-6, tumor necrosis factor-alpha (TNF-α), and intestinal lipopolysaccharides, which impair insulin signalling pathways, thereby reducing insulin-mediated glucose uptake in peripheral tissues and suppressing hepatic glucose production. Oxidative stress arising from the accumulation of free fatty acids and lipids in the liver contributes to mitochondrial dysfunction and activation of inflammatory signalling pathways, further exacerbating insulin resistance. Increased production of reactive oxygen species (ROS) promotes oxidation of nucleic acids, proteins, and lipids, thereby impairing cellular function and stimulating the release of pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, and TGF-β. This combined inflammatory and oxidative environment disrupts the insulin signalling cascade, leading to reduced tissue responsiveness to insulin and ultimately resulting in persistent hyper-glycemia and hyperinsulinemia. [9]. Increased ROS production further contributes to disease progression by inducing oxidative damage to the mitochondrial electron transport chain, reducing ATP production through oxidation of cardiolipin in the inner mitochondrial membrane, and activating pro-apoptotic and pro-inflammatory signaling pathways.

Excess adiposity leads to adipocyte dysfunction and cell death, resulting in the secretion of inflammatory cytokines and increased free fatty acid release to the liver, both of which contribute to insulin resistance. This promotes aberrant triglyceride synthesis in hepatocytes, mitochondrial uncoupling, and further ROS generation, thereby amplifying cellular injury. The antioxidant status in NAFLD/NASH remains controversial; some studies report reduced serum superoxide dismutase (SOD) levels, while others show increased antioxidant enzyme activity, suggesting a possible compensatory response [10].

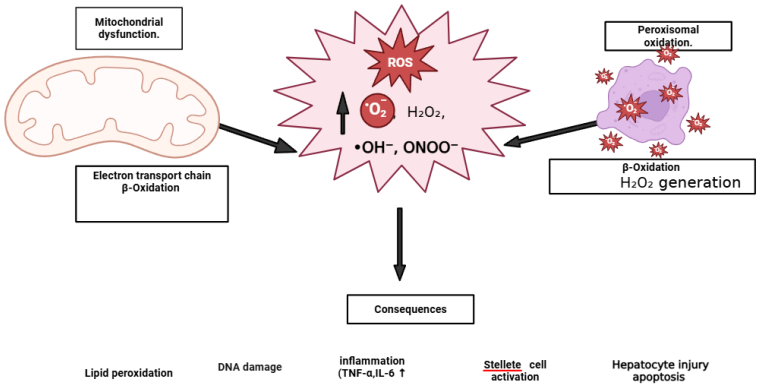

Fig 1: Sources and effects of oxidative stress.

Increased fatty acids lead to mitochondrial and β- oxidation, producing reactive oxygen peroxidation, DNA damage, producing reactive oxygen species (ROS). Lipid peroxidation, DNA damage, inflammation, stellate cell activation, and hepatocyte injury occur, driving NAFLD progression. (Created with BioRender.com).

NATURAL POLYPHENOLS

Polyphenols (PPs) are plant-derived phytochemicals containing phenolic rings with two or more hydroxyl groups. They exhibit strong antioxidant and anti-inflammatory properties and offer therapeutic benefits in the treatment of metabolic disorders. Dietary polyphenols help alleviate features of metabolic syndrome, including obesity, dyslipidemia, atherosclerosis, hyper-glycemia, hypertension, and associated liver, cardiovascular, and neurodegenerative diseases. Polyphenols modulate inflammation and immune responses through pathways involving NF-κB, Toll-like receptors, NOD-like receptors, cytokines, chemokines, and inducible enzymes. Flavanol-rich foods such as green tea, cocoa, and grape seeds, along with compounds like epigallocatechin gallate, epicatechin, and procyanidins, have protective effects against obesity, diabetes, and metabolic syndrome by regulating oxidative stress, immune function, and the gut microbiota. Polyphenols are secondary plant metabolites found in fruits, vegetables, cereals, and beverages. They are classified mainly into phenolic acids and flavonoids. Phenolic acids include hydroxybenzoic and hydroxycinnamic acids, while flavonoids are divided into flavanols, flavones, flavanones, isoflavones, and anthocyanidins [11]. Flavonoids and phenolic acids exhibit strong antioxidant activity due to their hydroxyl groups and aromatic structures, and they show anti-inflammatory, cardioprotective, neuroprotective, anticancer and anti-aging effects by regulating reactive oxygen species (ROS) and cellular signalling pathways [12]. Medicinal plants such as milk thistle (Silybum marianum), which contains silymarin and berberis species, which contain berberine, have shown beneficial effects in metabolic disorders and NAFLD by improving lipid and glucose metabolism and reducing insulin resistance. Resveratrol shows potential metabolic benefits, but clinical results remain inconsistent, requiring further large-scale studies [13].

Quercetin

Quercetin is a dietary flavonoid polyphenol associated with improved glycolipid metabolism and insulin resistance. It is abundant in fruits and vegetables, such as blueberries and onions, and is used as a functional food for the treatment of metabolic disorders, including NAFLD. Oral administration) attenuates NAFLD by enhancing autophagy pathways. It modulates autophagy-related proteins, such as p62, LC3A, and LC3B, thereby improving autophagy flux, promoting lipid droplet degradation, and supporting liver homeostasis [14, 15].

Apigenin

Apigenin is a flavonoid found in tea, parsley, celery, onions, citrus fruits, chamomile, and thyme. It reduces oxidative stress and inflammation by decreasing CYP2E1, NF-κB, MDA, and TNF-α levels while increasing antioxidant enzymes (glutathione system enzymes). It improves lipid metabolism by regulating genes such as FAS, DGAT, SREBP-1c, PPARα, and CPT-1. Apigenin protects against liver injury by inhibiting NF-κB and restoring hepatic architecture damaged by toxins [16].

In NAFLD, apigenin primarily acts by activating Nrf2, enhancing antioxidant defense and regulating lipid metabolism. Nrf2 activation suppresses PPARγ-driven lipid synthesis, thereby improving metabolic abnormalities. Knockdown of Nrf2 reduces apigenin's protective effect, confirming its central role [17].

Naringin / naringenin

Naringin and its aglycone naringenin are flavonoids found in citrus fruits, bergamot, tomatoes, and other plants. They exhibit antioxidant, anti-inflammatory, neuroprotective, anticancer, antiviral, and cardio protective effects. Naringin improves oxidative balance by increasing glutathione levels and reducing free radical damage. Naringenin modulates multiple signaling pathways involved in metabolic syndrome, inflammation, and cardiovascular protection [18].

Ferulic acid

Ferulic acid is a phenolic acid present in cereals such as rice, wheat, barley, and rye. It has strong antioxidant, anti-inflammatory, and hepatoprotective effects. It prevents NAFLD progression by activating PPARα, enhancing fatty acid β-oxidation, ketone body synthesis, and energy expenditure, thereby reducing hepatic lipid accumulation. It is a potential functional food and therapeutic candidate for the treatment of metabolic diseases [19].

Baicalin

Baicalin is a flavonoid glycoside from Scutellaria baicalensis with strong antioxidant and anti-inflammatory properties. It shows hepatoprotective effects in NASH by suppressing inflammation, fibrosis, and lipid

dysregulation. It reduces hepatocyte injury by inhibiting NLRP3 inflammasome activation, ER stress, and GSDMD-mediated pyroptosis, suggesting strong therapeutic potential in NAFLD [20].

Luteolin

Luteolin (3′, 4′, 5, 7-tetrahydroxyflavone) is a type of natural flavonoid found in natural herbs, vegetables, and fruits. Previous studies showed that luteolin exhibits anti-inflammatory, antioxidant, and antitumor activity. Besides, it also regulates immune activity.

It was reported to have anti-obesity effects and has been shown to significantly improve NAFLD and obesity [21].

MOLECULAR TARGETS OF POLYPHENOLS IN NAFLD

The Keap1–Nrf2–ARE pathway is activated by oxidative and electrophilic stress and regulates antioxidant and detoxifying proteins in the cytosol, mitochondria, and ER, promoting cellular survival. This protection is supported by the unfolded protein response (UPR), which restores ER homeostasis, and autophagy, which removes damaged proteins and organelles. ER stress is closely linked to hepatic steatosis, as key lipogenic processes occur in the ER; disruption of UPR contributes to steatosis. During UPR, PERK-mediated phosphorylation promotes Nrf2 nuclear translocation and activation of target genes. Nrf2 is also activated via autophagy through p62–Keap1 interaction, where p62 accumulation stabilizes Nrf2 and enhances transcriptional activity. Basal p62–Nrf2 signalling maintains mitochondrial integrity, whereas Nrf2 deficiency causes mitochondrial dysfunction, reduced ATP production, and impaired fatty acid oxidation. NAFLD is a progressive disorder characterized by hepatic lipid accumulation, with about one-third of cases progressing to NASH, leading to inflammation and cirrhosis. ROS and electrophiles play a major role in NASH pathogenesis, making Nrf2 activation a promising therapeutic target. Nrf2 activation reduces oxidative stress and inhibits pathways such as JNK, improving NAFLD. Compounds like osteocalcin, scutellarin, and apigenin enhance antioxidant defenses (PPARγ, Nrf2, HO-1, GST, NQO1) and suppress NF-κB and Keap1. Scutellarin also shows preventive effects via Nrf2 activation in high-fat diet models. Nrf2 deficiency accelerates disease progression, whereas its activation maintains redox balance and reduces liver injury. Green tea extract and ezetimibe further enhance Nrf2-mediated protection against lipid accumulation and inflammation. However, clinical translation remains limited [22]. NRF2 is a key transcription factor regulating antioxidant defense. Impaired NRF2 signalling contributes to liver diseases and inflammation, making it a crucial therapeutic target in hepatic pathology [23]. Curcumin and Zn (II)-curcumin activate Nrf2 signalling, increasing HO-1, p62/SQSTM1, and Nrf2 while decreasing Keap1. This enhances antioxidant defense and reduces inflammation. Curcumin also improves insulin resistance by modulating Nrf2 and suppressing the expression of oxidative stress proteins. It increases glutathione synthesis by upregulating GCLM, thereby strengthening antioxidant capacity [24]. Although the Nrf2 system reduces oxidative stress, inflammation, and lipid accumulation in NAFLD, most evidence is preclinical. Its role in advanced fibrosis remains unclear. Limitations include poor bioavailability, safety concerns, and possible tumor-promoting effects. Curcumin also suppresses lipogenesis by inhibiting SREBP-1c, induces CYP enzymes, and modulates the Nrf2/FXR pathway, improving lipid metabolism and inflammation markers [25].

AMPK-RELATED PATHWAYS AND NAFLD

The two-hit hypothesis explains NAFLD: insulin resistance leads to hepatic lipid accumulation (first hit), followed by oxidative stress and inflammation (second hit), causing hepatocyte injury.

AMPK plays a central protective role by inhibiting lipogenesis (ACC1, SREBP-1, FAS), promoting fatty acid oxidation (PPARα), enhancing autophagy (Beclin1, mTOR, ULK1 regulation), improving insulin sensitivity and reducing oxidative stress and inflammation. AMPK activation is a key therapeutic strategy, and herbal compounds can modulate this pathway [26]. AMPK activation also regulates lipid metabolism by suppressing lipogenic genes (FAS, SREBP-1c, ACC, HMGCR) and increasing lipid oxidation genes (CPT1, PGC1, HSL, ATGL), thereby restoring lipid homeostasis in NAFLD and AFLD [27, 28, 29].

PPARs AND NAFLD

PPARs are therapeutic targets in metabolic diseases, including NAFLD. They regulate lipid metabolism, glucose homeostasis, inflammation, and hepatic stellate cell activation. They also mediate liver–extrahepatic tissue communication (adipose tissue, gut microbiota, muscle) [30]. PPAR-α enhances fatty acid oxidation, PPAR-δ regulates energy expenditure, and PPAR-γ controls adipogenesis and insulin sensitivity. Overall, PPAR activation improves lipid metabolism and reduces inflammation in NAFLD [31]. Dietary polyphenols from sources such as coffee, olives, berries, and rice modulate PPAR signalling, reducing adiposity and hepatic lipid accumulation and improving lipid metabolism. Their effects may vary due to gut microbial metabolism [32]. Polyphenols such as curcumin and resveratrol improve NAFLD by activating SIRT1. Curcumin increases SIRT1 and antioxidant enzymes (SOD1), reducing oxidative stress. Resveratrol activates SIRT1 and AMPK, enhancing fatty acid oxidation and suppressing NF-κB-mediated inflammation. It also regulates SREBP-1 and FOXO1 pathways [33].

Quercetin, resveratrol, curcumin, and fisetin improve NAFLD by modulating SIRT1-related signalling. Quercetin, an antioxidant, activates SIRT1/AMPK and improves insulin sensitivity, but its bioavailability is limited. resveratrol: activates SIRT1/AMPK, reduces steatosis and inflammation, curcumin: activates SIRT1, Nrf2, and AMPK; reduces oxidative stress and inflammation, fisetin: enhances SIRT1, regulates AMPK/PPAR, improves mitochondrial function. Overall, these polyphenols protect against NAFLD via SIRT1-centered metabolic regulation [34]. Polyphenols activate PPARγ or act as its agonists, reducing TNF-α and IL-6 while increasing adiponectin and insulin-related metabolic proteins, thereby improving insulin resistance. They also upregulate PPARα, enhancing fatty acid β-oxidation and NEFA transport, while inhibiting NF-κB–mediated inflammation and lowering CRP levels. However, the observed associations between polyphenol intake and reduced NAFLD risk are correlational, not causal. Higher lignin intake, mainly from flaxseed, whole grains, legumes, nuts, garlic, olive oil, and vegetables, is associated with lower NAFLD risk, and flaxseed supplementation has been shown to improve steatosis and inflammation in NAFLD patients [35].

FUTURE PRESPECTIVES

Future research on polyphenols in non-alcoholic fatty liver disease (NAFLD) should focus on improving clinical translation, bioavailability, and mechanistic understanding of their therapeutic effects. Although polyphenols such as curcumin, resveratrol, quercetin, and naringenin exhibit hepatoprotective activity by modulating oxidative stress, inflammation, and pathways involving AMPK, PPAR, and Nrf2, their clinical efficacy remains limited due to poor absorption and rapid metabolism [36]. Dietary polyphenols may improve liver enzymes, lipid metabolism, and inflammatory markers [37]. Oxidative stress caused by excess reactive oxygen species (ROS) plays a central role in NAFLD, which is now recognized as a redox-driven disease. Therefore, targeting oxidative stress–mediated pathways is essential for the development of therapy [38]. Polyphenols act through multiple molecular mechanisms, including inhibition of NF-κB–mediated inflammation, activation of PPAR-α to enhance β-oxidation, stimulation of AMPK, suppression of SREBP-1c–mediated lipogenesis, and activation of Nrf2-mediated antioxidant defense. They also promote autophagy and lipophagy, collectively reducing lipid accumulation and oxidative damage [39]. Plant phenolics are promising therapeutic agents due to their antioxidant, anti-inflammatory, hepatoprotective, and antidiabetic properties. However, their clinical use is limited by poor bioavailability, compositional variability, and incomplete mechanistic understanding. [40].

In addition, the bioavailability of flavonoids is relatively low; therefore, it is necessary to adopt emerging approaches, such as nanotechnology-based delivery systems, to enhance their bioavailability and anti-NAFLD efficacy. Moreover, it remains unclear which flavonoids are most effective or best suited for dietary or therapeutic applications; hence, further well-designed clinical trials are required [41].

CONCLUSION

Non-alcoholic fatty liver disease (NAFLD) is a progressive metabolic liver disorder ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). It is now one of the leading causes of chronic liver disease worldwide and an increasing indication for liver transplantation. Despite rising prevalence, no approved pharmacological therapy is available, and lifestyle modification remains the main treatment strategy. Oxidative stress plays a central role in NAFLD progression by increasing reactive oxygen species (ROS), causing mitochondrial dysfunction, lipid peroxidation, inflammation, and hepatocyte injury. These mechanisms further worsen insulin resistance and disease progression. Natural polyphenols have emerged as promising therapeutic agents due to their antioxidant and anti-inflammatory properties. They act through multiple molecular pathways, including activation of Nrf2, AMPK, PPARs, and SIRT1, while inhibiting NF-κB-mediated inflammation. Experimental studies show that polyphenols such as quercetin, curcumin, resveratrol, apigenin, and baicalin improve lipid metabolism, reduce oxidative stress, and attenuate hepatic steatosis.

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