Review Article

A review of the therapeutic effects of polyphenols on non-alcoholic fatty liver disease: Focus on oxidative stress

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ABSTRACT

A substantial body of research suggests that polyphenols may have health benefits, particularly in metabolic disorders associated with obesity, such as non-alcoholic fatty liver (NAFLD), type 2 diabetes, and cardiovascular disease. Given the importance of oxidative stress in the pathogenesis of metabolic disorders, significant emphasis has recently been placed on the characteristics of polyphenols in obesity-related problems. This narrative review summarizes the current knowledge on the inhibitory effects of polyphenols, including curcumin, resveratrol, baicalin, nobiletin, and quercetin, on oxidative stress, with a focus on the role of the Nrf2 pathway. This review compiles the data from articles showing that the aforementioned polyphenols improve health in metabolic diseases by regulating Nrf2 and its target proteins involved in reducing oxidative stress. However, due to the limitations of in vitro and in vivo investigations, as well as the lack of long-term human clinical trial studies, further high-quality research is required to definitively demonstrate the clinical usefulness of polyphenols for the prevention and management of NAFLD.

Keywords: Polyphenol, non-alcoholic fatty liver disease, oxidative stress, nuclear factor erythroid 2-related factor

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Introduction

In developed countries, nonalcoholic fatty liver disease (NAFLD) accounts for 20–40% of liver disease cases (1, 2). NAFLD is defined by the American Association for the Study of Liver Diseases as the presence of hepatic steatosis, assuming that the accumulation of secondary hepatic fat due to medication, hereditary disorders, or excessive alcohol consumption does not exist (3). NAFLD is a broad term for a multi-stage disease that includes several clinical comorbidities, such as insulin resistance, obesity, and dyslipidemia (4). NAFLD is diagnosed when lipid accumulation exceeds 5% of the hepatic volume (5). The majority of NAFLD patients have a benign disease state; however, in 10–20% of patients, an excess of lipid accumulation causes an inflammatory response, leading to hepatic injury (6, 7). Non-alcoholic steatohepatitis (NASH) is characterized by both hepatocellular steatosis and inflammation, as well as fibrosis. NASH may develop into cirrhosis and ultimately hepatocellular carcinoma (HCC), if patients

do not receive the proper treatment (8, 9). The terms steatohepatitis and NASH are used to describe the inflammatory metabolic state of the liver (9).

The mechanism of NAFLD progression was previously explained by the "two hits" hypothesis (10). According to early research, the "first hit" is insulin resistance and hepatic steatosis caused by an excess of fatty acids, while the "second hit" is hepatocyte damage, inflammation, fibrosis, and other pathological changes caused by oxidative stress and lipid peroxidation. Nowadays, it is commonly acknowledged that the "second hit" theory, which takes into account a number of variables like lipotoxicity, oxidative stress, and endoplasmic reticulum stress, forms the basis for the "multiple hit" theory (11, 12). This theory provides a better explanation for the pathophysiology of NAFLD.

Common pathogenic processes in NAFLD

The diagnosis of NAFLD histologically requires the presence of hepatic steatosis (13). Steatosis can result from multiple causes, such as: (1) increased supply of fat; (2) decreased export of fat in the form of triglycerides and very low-density lipoprotein; (3) decreased free fatty β-oxidation; and (4) increased de novo lipogenesis (DNL) (9, 13). Although the exact molecular mechanisms underlying the buildup of fat in the liver are unknown, certain cytokines originating from areas of inflammation, specifically extrahepatic adipose tissues, can initiate this process. Furthermore, it is thought that an increase in hepatic DNL is a special characteristic of steatosis. More crucially, many of the metabolic dysregulations of NAFLD appear to be primarily driven by insulin resistance. Currently, a variety of common pathogenic pathways, including lipotoxicity, oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress, have been postulated and characterized for the progression from basic steatosis to NASH.

The role of oxidative stress in the pathogenesis of NAFLD

Oxidative stress is characterized by an imbalance between the generation of free radical molecules such as reactive oxygen species (ROS) and nitrogen intermediates, and the cellular antioxidant defense system's capacity to scavenge or detoxify these harmful products (14). Long-term disturbance of lipid metabolism is intimately associated with alterations of the pro-oxidant/anti-oxidant balance in favor of pro-oxidants, which perturb multifunctional organelles involved in cellular metabolism, resulting in mitochondrial dysfunction, lipid peroxidation, cellular lipotoxicity, and sustained endoplasmic reticulum stress (15). Given that most oxidative reactions occur in the hepatocytes, the liver is considered the primary target organ for potential damage related to oxidative events (15). Elevated oxidative stress provokes deleterious interactions and cytotoxic pathways in hepatocytes, resulting in inflammatory and fibrotic responses, and ultimately contributes significantly to the development and progression of chronic liver disorders, including NAFLD and NASH (16). Superoxide anions ($O_2^{\bullet-}$), hydroxyl radicals (•OH), and hydrogen peroxide (H_2O_2), which are generated as by-products of the oxidative phosphorylation process, are major sources of oxidative stress in NAFLD. The metabolic activity of Cytochrome P450 isozymes in the endoplasmic reticulum or microsomes and elevated β-oxidation are considered other main sources of extremely reactive and unstable intermediates (15). During oxidative stress-induced liver damage, redox-sensing transcription factors, including nuclear factor kB (NF-κB), activator protein 1 (AP-1), and early growth response protein 1 (Egr-1), are activated. These factors are responsible for the harmful pro-oxidant effects (17).

An essential element of the antioxidant defense system is the oxidative stress-responsive transcription (18). Nuclear factor erythroid 2-related factor (Nrf2) is a pivotal transcription factor that serves as a cytoprotective agent and crucial regulator of cellular antioxidant response against oxidative stress-induced damages (19). Under healthy and basal status, Nrf2 is present in the cytosol bound to Kelch-like ECH-associated protein 1 (Keap1) and remains in an inactive form (20). Increased levels of reactive oxygen/nitrogen species (ROS/RNS) or electrophilic stress activate the Nrf2 signaling pathway, thereby inducing up-regulation of major intracellular detoxifying enzymes genes including superoxide dismutase (SOD), catalase (CAT), heme oxygenase-1 (HO-1), and glutathione peroxidase (GPx) by translocation of Nrf2 to the nucleus and binding to specific sequences located on DNA, called antioxidant response elements (ARE) (21). Importantly, Nrf2 expression seems to be regulated by numerous classes of endogenous and exogenous inducers. It has been shown that Nrf2 activation is critical for mitochondrial homeostasis, integrity, and lipid metabolism, thereby it may provide a beneficial role and hepatoprotective activity during the development of NAFLD and steatohepatitis (22). Overall, a variety of experimental models of NAFLD propose that Nrf2 activation acts as a protective antioxidant mechanism, and thus pharmacological or nutritional modification of the Nrf2-ARE pathway can be considered a novel promising strategy for alleviation or even treatment of NAFLD (22).

Polyphenols and NAFLD

Polyphenols are a diverse class of vegetable-derived chemicals that are hydrosoluble (23). They are abundant in fruits, tea, coffee, red wine, berries, and dark chocolate. They are also well-known antioxidant agents that have

been suggested as a possible treatment for a number of metabolic diseases (24). The most prevalent antioxidant molecules in the human diet are polyphenols, and their effects, along with those of vitamins, form the basis of the widely accepted benefit of fruits and vegetables in the treatment of various disorders (24, 25). Research has demonstrated that polyphenols can improve insulin resistance, enhance fatty acid β-oxidation, and prevent oxidative stress (26). Moreover, it has been suggested that these substances may influence the activity of lipogenic enzymes and enhance the production of lipolytic proteins, thus modulating the process of de novo lipogenesis (27).

Several researchers have attempted to assess the effect of polyphenols on metabolic diseases such as insulin resistance and NAFLD over the years (18, 20, 28, 29). The purpose of this review is to investigate the function of polyphenols in the treatment of NAFLD. Importantly, the main focus of this review is to discuss the role of oxidative stress and the Nrf2 signaling pathway in the beneficial effects of polyphenolic compounds against NAFLD.

Curcumin

Curcumin (also known as diferuloylmethane), a naturally occurring biphenolic bioactive compound categorized as curcuminoids, is primarily found in *Curcuma longa* (turmeric). It is utilized as a dietary and herbal supplement, cosmetics ingredient, and food flavoring agent. Given its numerous beneficial activities such as antioxidant properties, anti-inflammatory effects, antihyperlipidemic activity, preventive role in diabetes and obesity, and hepatoprotective features, this natural bioactive substance has received considerable attention in recent years (30-32). *In vivo* and *in vitro* studies have suggested that the induction of the Nrf2 signaling pathway and its downstream genes/proteins is one of the most important mechanisms contributing to curcumin's beneficial effects in alleviating NAFLD or steatohepatitis symptoms (32-34). In this regard, administration of curcumin improved liver injury parameters (liver enzymes and lipid profile) and rectified its structure (fibrotic and degenerative changes) in high-fat diet (HFD) fed rats via up-regulation of the Nrf2 expression (33). Moreover, curcumin treatment resulted in attenuation of hepatic steatosis and reversion of serum biochemical markers (increased levels of triglycerides, and total cholesterol) through the Nrf2-FXR-LXRα pathway in mice fed a high-fat, high-fructose diet (34). In another animal model, curcumin improved biochemical abnormalities in NASH by stimulating cellular self-preservation autophagy mechanism through elevating Beclin 1, up-regulating AMP-activated protein kinase (AMPK), and decreasing IL-6 amounts in the hepatocytes. It also retrieved oxidant/anti-oxidant balance as evident by attenuating malondialdehyde (MDA) synthesis and conservation of cytosolic antioxidants defense capacity via elevating glutathione (GSH) concentration, triggering Nrf2 signaling pathway, and superoxide dismutase (SOD) (35). Collectively, curcumin appears to be a useful therapeutic strategy for relieving oxidative stress-related injuries in the context of NAFLD.

Resveratrol

Resveratrol (RSV; 3,5,4′-trihydroxy-trans-stilbene), which belongs to the stilbene or non-flavonoid category of natural polyphenolic compounds, is mainly found in red grapes, berries, red wine, peanuts, and nuts (36). In recent decades, various studies have shown different pharmacological properties and multi-targeting action of resveratrol, including anti-tumor, anti-inflammation, anti-hyperlipidemia, anti-hyperglycemic, and hepatoprotective effects (37-40). In the context of liver disorders, particularly in NAFLD, resveratrol exerts its effect through modulating several signaling pathways, including AMPK/SIRT1, Keap1-Nrf2, ERK/p38, and PTEN/Akt, and also promoting cellular antioxidant defense by enhancing the ROS/RNS scavenging capability of detoxifying enzymes (41-43). As an example from animal model studies, resveratrol attenuated HFD-stimulated hepatic steatosis and insulin resistance via mitigating activation of SIRT1 induced by miR-34a in rats (44). Although the beneficial effects of resveratrol through activation of the Nrf2 pathway have been investigated in different diseases such as neurodegenerative, cardiovascular, renal, and various types of cancers, the hepatoprotective effects of resveratrol through the Nrf2 signaling have been conducted in a few studies (45). It was shown that resveratrol protected primary damage in hepatocytes by oxidative stress inducers such as tert-butyl hydroperoxide (tBHP), H_2O_2, and acrylamide through the Nrf2 activation that modulates the phase II detoxifying enzymes and antioxidant expression (46-48). Importantly, in the field of NAFLD, our previous findings from HFD-fed mice and also HepG2 cells treated with high glucose revealed that treatment with resveratrol attenuated lipid accumulation through up-regulation of the Nrf2 transcription factor (18). We found that resveratrol treatment activated the Nrf2 signaling pathway via decreasing the methylation of the Nrf2 promoter, and this effect was accompanied by a reduction in triglyceride level and a decrease in the expression of lipogenesis-related genes such as fatty acid synthase (FAS) and sterol regulatory element-binding protein-1c (SREBP-1c) (18). Taken together, the data from our and other studies suggest that Nrf2 signaling appears to be an important factor in the beneficial effects of resveratrol, particularly in the context of NAFLD.

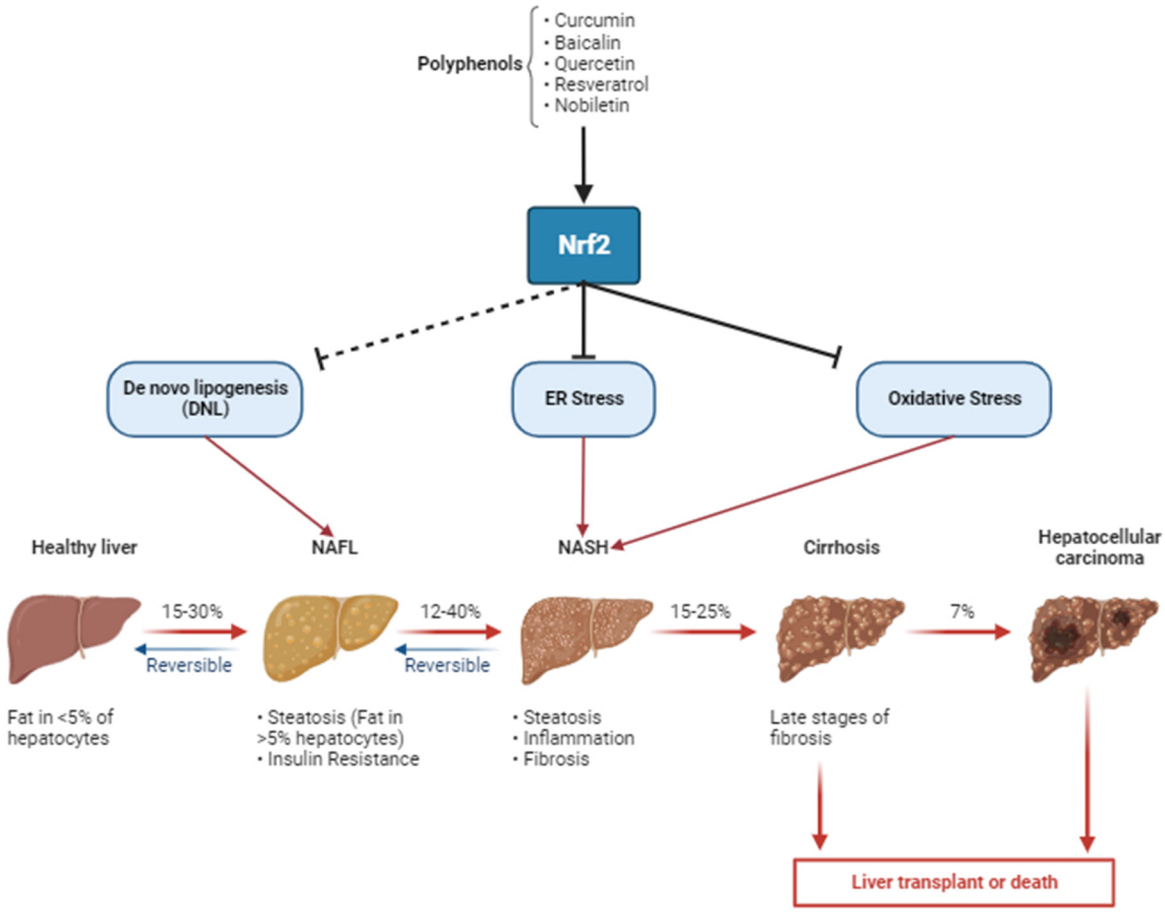

Figure 1: Overview of the pathogenesis of nonalcoholic fatty liver disease (NAFLD). The interplay between de novo lipogenesis (DNL), oxidative stress, endoplasmic reticulum stress, and inflammation plays a crucial role in the complex pathogenesis of NAFLD. Also, Nrf2 activators have the potential to improve and prevent the advanced stages of NAFLD. (Created in BioRender.com).

Baicalin

Baicalin, known by its chemical formula C21H18O11, is a flavonoid derived from the desiccated roots of Scutellaria baicalensis Georgi, a Chinese medicinal plant. Baicalin possesses various pharmacological properties, including anti-oxidative and anti-inflammatory attributes (49, 50). It has been reported that Baicalin has a therapeutic impact on NAFLD. Studies have shown that Baicalin hinders the oxidative stress in mice fed a high-fat diet (HFD). The supplementation of Baicalin not only reduced the levels of reactive oxygen species (ROS) and malondialdehyde (MDA), but also activated the Nrf2 pathway, which is closely linked to the activation of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione (GSH). The hepatoprotective efficacy of Baicalin is also associated with the induction of the AMPK signaling pathway (51). Another study reported that Baicalin markedly attenuated lipid accumulation in the liver of db/db mice. It was shown that Baicalin significantly reduced proinflammatory biomarkers and enhanced antioxidant enzymes, which appeared to be modulated by the upregulated Nrf2 signaling cascade (52). In addition, Baicalin was able to attenuate lipid accumulation and inflammation in the liver tissues of NASH mice via enhanced Nrf2/HO-1 expression and reduced NLRP3/Caspase1/GSDMD levels, the factors that are involved in the pyroptosis pathway (50). Collectively, the findings from the studies show that the beneficial functions of Baicalin in counteracting NAFLD might be via the regulation of the Nrf2 signaling pathway. This implies that Baicalin has the potential to be developed as a promising agent for treating NAFLD.

Nobiletin

Nobiletin (5,6,7,8,3′,4′-hexamethoxyflavone) is one of the polymethoxylated flavones (PMFs) found in citrus peel, and it has potent anti-inflammatory, anti-diabetic, and antioxidant properties (53). According to literature reports, nobiletin improved dyslipidemia in both LDL receptor-deficient (LDLR-/-) and C57BL/6 mice given a high-fat diet (HFD) (54, 55). Additional investigations have found that nobiletin supplementation reduced malondialdehyde (MDA) content and elevated

glutathione (GSH) activity in the liver tissues by up-regulating the expression levels of antioxidant factors of Nrf2 and its targeted factors such as heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and glutathione S-transferase alpha 2 (GSTA2), thereby alleviating the hepatic oxidative stress caused by the HFD (56). Nobiletin was used as an intervention in another study that used a methionine choline-deficient diet to induce NAFLD (57). The results showed that nobiletin dramatically reduced lipid accumulation, oxidative stress, and inflammation in both in vitro and *in vivo* models of NAFLD. It was suggested that the Nrf2, sterol regulatory element-binding protein 1c (SREBP-1c), and nuclear factor kappa B (NF-kB) signaling pathways are involved in its process. Furthermore, Nrf2 is not only a direct target for Nobiletin to reduce oxidative damage, but it is also engaged in lipid-lowering and anti-inflammatory mechanisms in NAFLD (57). All of this research shows that nobiletin improves NAFLD by modulating liver lipid metabolites, lipid-metabolism-related factors, and the hepatic Nrf2 pathway.

Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a potent antioxidant flavonoid, primarily found in various foods such as onions, berries, tea, broccoli, and citrus fruits. Several studies using in vitro and in vivo experimental models have shown the benefits of quercetin against liver steatosis and NAFLD (58-61). Importantly, one study reported that supplementation with quercetin in a diet-induced NAFLD rat model upregulated Nrf2 expression, leading to the activation of antioxidant response elements and subsequent upregulation of heme oxygenase-1 (HO-1). This, in turn, reduced oxidative stress (62). Quercetin could effectively ameliorate NAFLD by decreasing triglyceride accumulation, insulin resistance, inflammatory cytokine secretion, and increasing cellular antioxidants in oleic acid-induced hepatic steatosis in HepG2 cells (61). In addition, in one study, it was reported that activities of superoxide dismutase (SOD) and catalase (CAT), and glutathione (GSH) could be restored in the liver of db/db mice by quercetin treatment (60). Taken together, findings from these studies demonstrate that the hepatoprotective effects of quercetin might be achieved by scavenging reactive oxygen species (ROS) and increasing endogenous antioxidant levels by enhancing the nuclear activities of Nrf2.

Conclusion

In the context of chronic liver diseases, oxidative stress can be a powerful inducer of inflammation and fibrosis (15, 63). In recent years, the transcription factor Nrf2 has gained prominence as a potential therapeutic target for the treatment of liver diseases. The Nrf2 pathway promotes the production of antioxidant protection genes, which counteracts oxidative stress and reduces the development of liver damage in NAFLD (64, 65). Different antioxidative molecules such as curcumin, resveratrol, baicalin, nobiletin, and quercetin can modulate the Nrf2 pathway and have beneficial effects on ameliorating liver damage (Figure 1). There is currently no effective medication for treating the complicated pathophysiology of liver diseases. Thus, antioxidative substances such as polyphenols may be promising candidates for the therapy of liver diseases via regulating the NRF2 signaling pathway. In conclusion, Nrf2 mediates the crosstalk between lipid metabolism and antioxidant defense systems in NAFLD experimental models, and nutritional or pharmacological Nrf2 stimulation provides a promising prospective novel method for its prevention and treatment.

Conflict of Interests

The authors have nothing to declare.

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