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# Diet induces hepatocyte protection in fatty liver disease via modulation of PTEN signaling (Review)

YUKA IKEDA, MUTSUMI MURAKAMI, YUKIE NAKAGAWA, AI TSUJI, YASUKO KITAGISHI and SATORU MATSUDA

Department of Food Science and Nutrition, Nara Women's University, Nara 630-8506, Japan

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**Abstract.** Fatty liver disease (FLD) is characterized by accumulation of excess fat in the liver. The underlying molecular mechanism associated with the progression of the disease has been in elusive. Hepatocellular demise due to increased oxidative stress resulting in an inflammatory response may be a key feature in FLD. Recent advances in molecular biology have led to an improved understanding of the molecular pathogenesis, suggesting a critical association between the PI3K/AKT/PTEN signaling pathway and FLD. In particular, PTEN has been associated with regulating the pathogenesis of hepatocyte degeneration. Given the function of mitochondria in reactive oxygen species (ROS) generation and the initiation of oxidative stress, the mitochondrial antioxidant network is of interest. It is vital to balance the activity of intracellular key molecules to maintain a healthy liver. Consequently, onset of FLD may be delayed using dietary protective agents that alter PTEN signaling and reduce ROS levels. The advancement of research on dietary regulation with a focus on modulatory roles in ROS generation and PTEN associated signaling is summarized in the current study, supporting further preventive and therapeutic exploration.

*Correspondence to:* Professor Satoru Matsuda, Department of Food Science and Nutrition, Nara Women's University, Kita-Uoya Nishimachi, Nara 630-8506, Japan
E-mail: smatsuda@cc.nara-wu.ac.jp

*Abbreviations:* ALD, alcoholic liver disease; ASH, alcoholic steatohepatitis; DHA, docosahexaenoic acid; FLD, fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PIP3, phosphatidylinositol 3,4,5-triphosphate; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SOD, superoxide dismutase

*Key words:* PTEN, reactive oxygen species, fatty liver, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, alcoholic liver disease, alcoholic steatohepatitis, cell signaling

**Contents**



## 1. Introduction

The liver is an organ performing vital functions (1). Hepatic disorders can affect the physiological and biochemical functions of the body. Fatty liver disease (FLD) is the prevalent form of chronic liver diseases that constitutes a range of disorders, starting with steatosis progressing to advanced stages, such as steatohepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) (2). The origin of FLD involves non-alcoholic (NA) FLD and alcoholic liver disease (ALD (Fig. 1). In both cases, a complex process may cause the fatty liver in response to a variety of oxidative stress conditions (3). NAFLD is characterized by accumulation of excess fats in the liver of individuals unrelated to alcohol consumption; it is a progressive disease leading to irreversible liver injury (4). Non-alcoholic steatohepatitis (NASH) is an advanced stage of NAFLD, characterized by hepatic steatosis, ballooning injury and non-bacterial inflammation with or without fibrosis (5). The pathogenesis of the progression from NAFLD to NASH coincides with metabolic disorders that cause hepatosteatosis, and further progression to steatohepatitis is due to additional cellular processes, including mitochondrial injury, excess oxidative stress and inflammation (6). Genomic instability is one stage of hepatic carcinogenesis (7). Growing evidence suggests a key function of oxidative stress caused by the generation of reactive oxygen species (ROS) in the progression of FLD (Fig. 1) (8,9). An additional influence in the progression from steatosis to steatohepatitis is the sensitization of hepatocytes to oxidative stress and cell apoptosis (10). As mitochondria serve a central role in the control of ROS generation and modulate the sensitivity to the cell apoptosis signaling pathway, mitochondrial function may be a key regulator in the development of steatohepatitis (11). Under normal conditions, living cells maintain a balance between ROS formation and quenching (12).

An increasing incidence and prevalence worldwide mean that NAFLD has developed into a serious public health problem (13). As the underlying mechanism of FLD remains elusive and no effective therapeutic treatment has been established to date. It is suggested that excess uptake of free fatty acids from food leads to an early pathogenesis (14). Exercise is a simple therapeutic intervention; however, it was determined to be insufficient to relief symptoms (15). Type 2 diabetes, hypertriglyceridemia and obesity are frequently associated with NAFLD and NASH, while alcoholic steatohepatitis (ASH) is associated with alcohol abuse (16). ASH and NASH are intermediate stages of FLD, which can develop into cirrhosis or HCC. PTEN, a tumor suppressor, has been valuable in elucidating the pathways that regulate carcinogenesis in FLD (13). Progression of a fatty liver is accelerated by regulation of the liver PTEN signaling pathway (17). As with certain of other liver diseases, FLD increases the risk of liver cancer with poor outcomes and limited therapeutic options (13). Hence, a highly specific and effective drug treatment for FLD is required. The current review focuses on oxidative stress that contributes to the limited therapeutic effects in the treatment of FLD.

## 2. ROS involvement in the pathogenesis of fatty liver disease

Oxidative stress is considered as an imbalance between the generation of oxidants, such as ROS, and the activity of antioxidants, suggesting that the excess generation of free radicals and/or the modulation of antioxidant activity result in the accumulation of oxidative stress. Increased oxidative stress has harmful effects on cell functions that contribute to various diseases, including FLD (18). The imbalance in redox homeostasis is associated with the development of various tissue injuries, including brain, heart and bone (19). Cellular ROS increases via a certain pathways and mitochondrial damage. Mitochondria are the major intracellular site of oxygen consumption and are a source of ROS. Accordingly, alterations in mitochondrial function serve a significant role in the generation of ROS, which has been recognized to contribute to the development of ASH and NASH (11). Mitochondrial dysfunction is a contributor to ALD and this disease is linked to mitochondrial DNA fragmentation associated with active alcohol consumption (20). ROS are a group of oxygen-radical-containing molecules resulting from the metabolism of oxygen in the cells (21). Excessive concentrations of ROS result in macromolecular and genomic DNA damage, as well as cell death (22). In addition, elevated oxidative stress increases the risk of various cancer types (23). The formation of ROS during chronic inflammation is crucial to the progression of chronic liver diseases (24). ROS lead to a free radical chain-reaction in unsaturated fatty acids, a process called lipid peroxidation, generating toxic unsaturated aldehydes (25). The superoxide anion is the primary ROS generated in mitochondria and quenching of this compound is a critical step in preventing excessive oxidative stress. Additionally, ROS are physiologically important in signal transduction, cellular physiology, critical metabolic pathways and host defense (26,27).

ROS are abundant free radicals in nature, and ROS production and genomic stability are affected by lifestyle factors (28). Certain environment-associated lifestyle factors, including tobacco and alcohol consumption, ionizing radiation, infection, inflammation and the aging process, cause oxidative stress (29). High blood glucose and excessive insulin further cause elevated ROS production (30). Hyperglycemia exacerbates FLD by elevating apoptosis via generation of excessive ROS (31). In addition, obese patients have shown significantly higher serum levels oxidative stress compared with non-obese controls (32). Intensive aerobic and anaerobic exercise increases oxidative damage (33). Strenuous exercise disturbs the antioxidant equilibrium by increasing ROS levels. However, regular exercise upregulates endogenous antioxidant levels and reduces oxidative damage (34). As continued exposure to uncontrolled oxidative stress is an initiator of various chronic diseases and cancer, cells have developed a range of antioxidant strategies, including enzymatic and non-enzymatic antioxidants (35). Maintaining healthy ROS level is indispensable for the conservation of healthy cells and particularly in mitochondria a balance of antioxidants is necessary to avoid oxidative stress. Superoxide dismutases (SODs) have a strong antioxidant role characterized by scavenging ROS, through the reaction of superoxide to hydrogen peroxide (36). SODs are the primary defense against cellular damage by oxidative stress and the breakdown of mitochondrial superoxide is performed by manganese SOD (SOD2) (37). In addition to antioxidants, cells use distinct oxidative damage-repair mechanisms to eliminate DNA damage (38).

## 3. PTEN in the anti-oxidative machinery

ROS have been shown to modulate various physiological processes, including the regulation of growth factor signaling. One mechanism by which ROS exert cellular effects is through the regulation of target molecules, including PI3K/AKT/PTEN (39). The PI3K/AKT/PTEN signaling pathway protects against damaging effects originating from high levels of insulin (40). In addition, the PI3K/AKT/PTEN signaling pathway regulates factors involved in cell survival and proliferation (Fig. 2) (40). PTEN is a dual specificity phosphatase, processing lipids and proteins, and it is a member of the protein tyrosine phosphatase family of phosphatases (41,42). PTEN downregulates AKT activity through the conversion of phosphatidylinositol 3,4,5-triphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (43). Cells lacking PTEN have higher levels of PIP3, a critical second messenger mediating signals from various growth factors, including insulin (44). PTEN is a tumor suppressor and is involved in oxidative stress and genomic damage induction (45). Inactivation of PTEN leads to prolonged AKT activation, increased mitochondrial respiration and increased ROS in mouse models (40). Downregulation, inhibition or deactivation of PTEN results in an increase of mitochondrial ATP production (46). Furthermore, PTEN is associated with the activation of the proteolytic cell apoptosis cascade through decreased activity of PI3K/AKT signaling (47).

Deficiencies of PTEN have been shown to promote NASH development (48). A hepatocyte-specific deletion of the *PTEN* gene exhibited an age-dependent development of liver steatosis and HCC (49,50). In addition, animal models of PTEN haploinsufficiency exhibit hepatomegaly, increased liver lipogenic gene expression, including of peroxisome

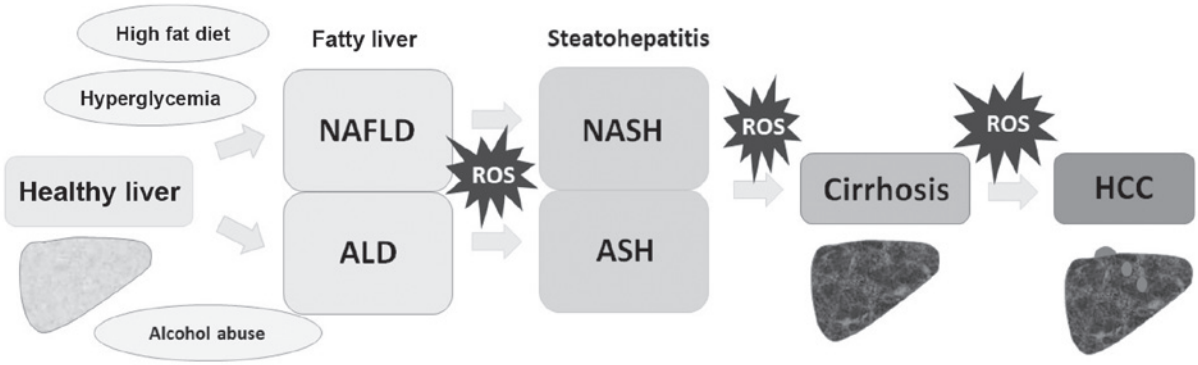


Figure 1. ROS affects the development in fatty liver diseases. Various roles of ROS in the development of steatohepatitis, including NASH and ASH, liver cirrhosis and HCC. Certain factors and stages were omitted for clarity. ROS, reactive oxygen species; HCC, hepatocellular carcinoma; ALD, alcoholic liver disease; ASH, alcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

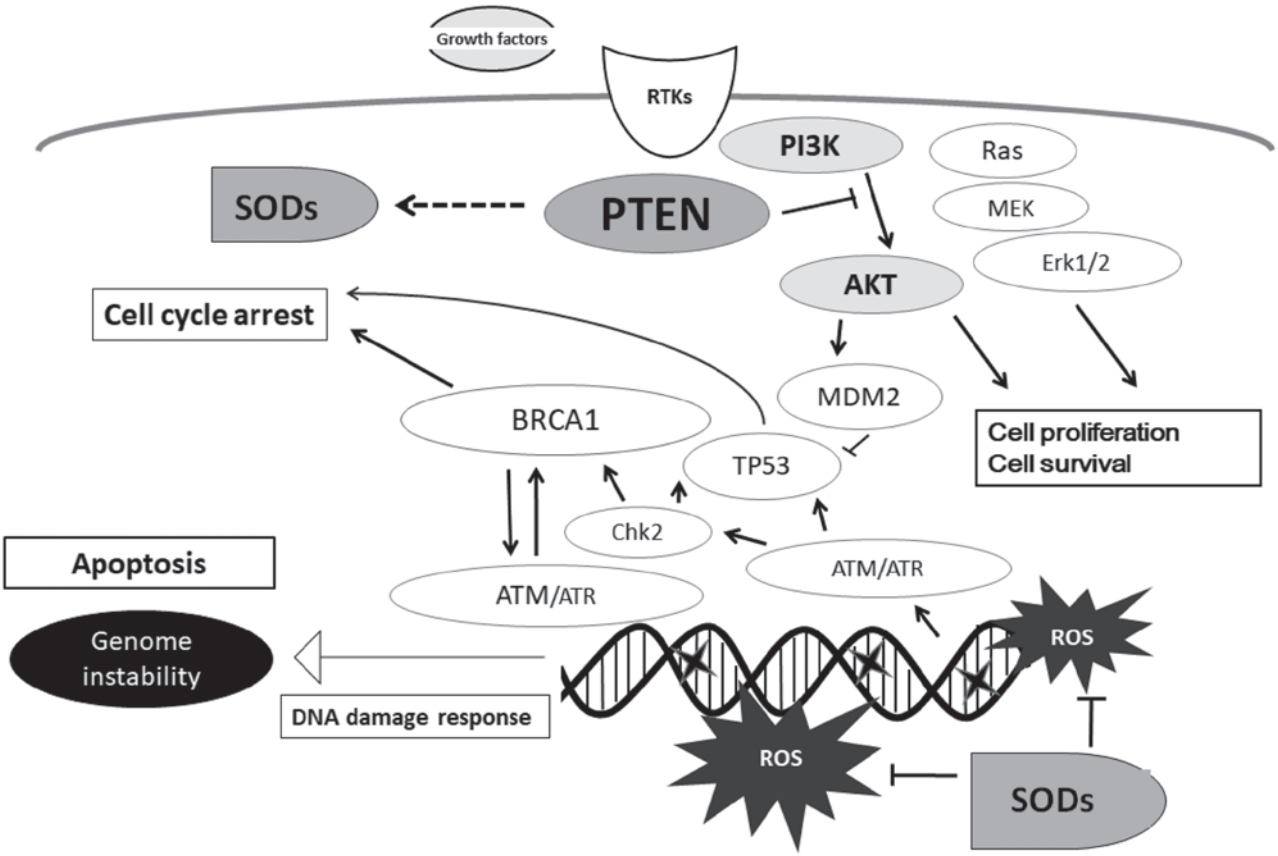


Figure 2. PTEN and oxidative DNA stress signaling pathways. Schematic representation of the regulatory pathways with exemplary molecules included; certain molecules were omitted for clarity. Solid arrows represent direct interaction; dashed arrows represent indirect interaction and the white head arrow refers to weak interaction. ROS, reactive oxygen species; SOD, superoxide dismutase; RTK, receptor tyrosine kinase.

proliferator-activated receptor (PPAR) γ and hepatic lesions, symptoms that are analogous to NAFLD (51). PTEN deficiency in hepatocytes induces upregulation of PI3K/AKT signaling, following increased lipogenesis and decreased lipolysis (52). Consistently, PTEN knockout mice exhibit insulin hypersensitivity, constitutive lipogenesis and hepatomegaly (53). In humans, PTEN mutations have been described in association with insulin hypersensitivity and obesity (54). In patients with FLD, reduced expression of PTEN and upregulation of AKT have been observed in liver biopsies (55). In addition, patients with NASH have shown decreased expression of PTEN compared with healthy patients (56). A marked increase of PTEN in hepatocellular steatosis progresses the disease to steatohepatitis and fibrosis, and in certain cases HCC (57). A previous study described PTEN and obesity-associated disorders as risk factors for HCC (13).

## 4. Diet and hepatocyte protection

Various disease-protective factors have been suggested in epidemiological studies (58,59). Dietary choices have been indicated to serve a role in liver protection (Fig. 3). Particularly,

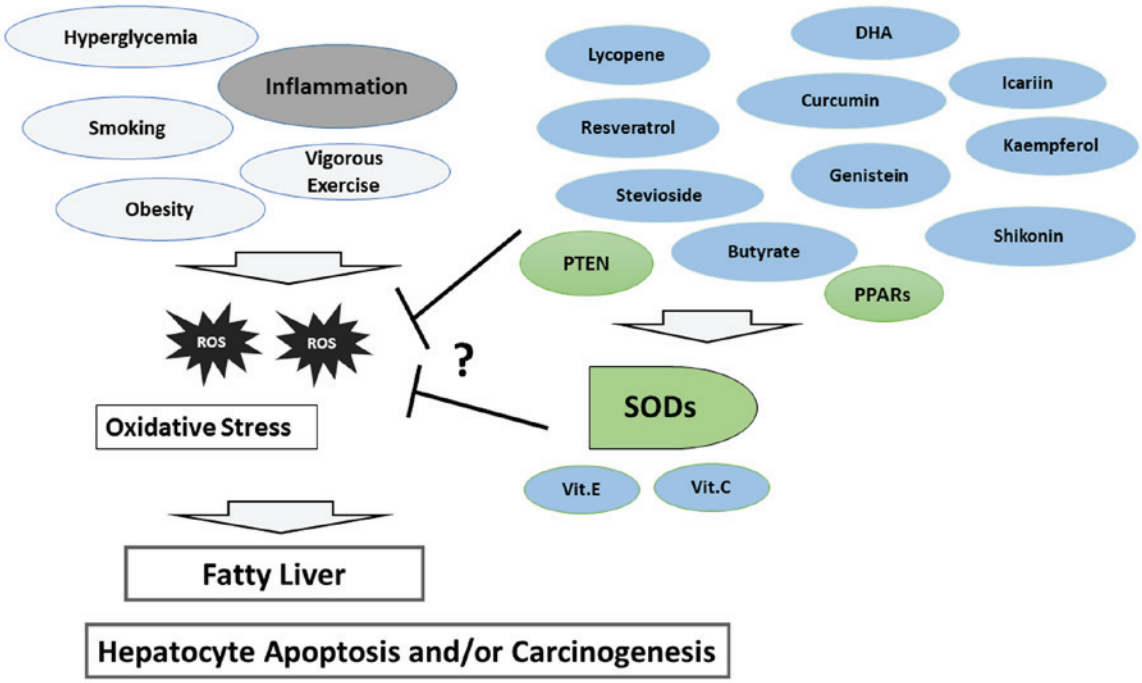


Figure 3. Lifestyle and diet affect oxidative stress levels. Certain food ingredients and dietary components contribute to the prevention of fatty liver diseases via the modulation of PTEN and SOD activities and lifestyle choices can impact liver health. PPAR, peroxisome proliferator-activated receptor; SOD, superoxide dismutase; ROS, reactive oxygen species; DHA, docosahexaenoic acid; Vit, vitamin.

dietary choices that modify the PI3K/AKT/PTEN signaling pathway may prevent FLD or decrease the rate of disease progression (60). Certain plants and fruits are promising targets (61-67).

Curcumin, an active ingredient derived from the root of *Curcuma longa* used as culinary turmeric, exhibits therapeutic potential for the treatment of diabetes and various types of cancer (62). Curcumin has strong antioxidant and anti-inflammatory effects and exhibits liver protective properties in an animal model (61). This protection is mediated by the PI3K/AKT/PTEN signaling pathway (63). Shikonin is a natural compound extracted from the roots of *Lithospermum erythrorhizon* (64) that was shown to prevent hepatotoxicity by upregulation of the PI3K/AKT/PTEN signaling pathway in an animal model (65). Kaempferol is a flavonol present in several plants, including grapefruits and edible berries, which was shown to inhibit hepatocyte apoptosis and prevent acute liver failure in an animal study (66). Icariin is a prenylated flavonol glycoside from *Epimedium koreanum*, which downregulates PTEN expression following AKT overexpression in an animal model (67). An antihepatotoxic activity of Icariin has been demonstrated in carbon tetrachloride-induced hepatocytes (68). In addition, in an animal model, rosemary (*Rosmarinus officinalis* L.) was shown to have liver protection activity at various stages of liver damage (69). Certain to-date unknown components of rosemary inhibit PTEN expression in K562 myeloid cells (70) and rosemary promotes liver regeneration in an experimental injury model (69). In contrast, levels of PTEN are increased when treated with Ginsenoside, a class of natural steroid glycosides, which exhibit hepatoprotective effects against acute hepatotoxicity in mice (71). Furthermore, certain types of diet rich in fat or carbohydrates contribute to hepatocyte protection (72). Further exploration is required to establish whether the protective characteristics are associated with the PI3K/AKT/PTEN signaling pathway.

*Antrodia camphorata* is a common mushroom found and used in Asia that protects against liver injury through reducing mitochondrial ROS (73). The active ingredient Genistein inhibits ROS production by enhancing SOD activities in an animal model (74). Genistein protects hepatocytes against toxicity due to creating a resistance to oxidative stress (75). Lycopene, an antioxidant found in red fruits such as tomatoes, inhibits hepatocyte apoptosis by reducing ROS levels and inhibiting mitochondrial dysfunction, and may have the ability to prevent FLD (76). It has been suggested that dietary intake of copper chloride and/or copper sulphate stabilizes SOD activity in an animal model, indicating a potential therapeutic benefit for FLD (77). Expression of SOD is associated with PPAR activity (78). The grape antioxidant resveratrol and its analogs increase SOD mRNA and protein expression levels *in vitro* (79). Furthermore, increased expression of SOD2 has been detected after administration of grape juice to an animal model (80). Commercially available grape juice reduces oxidative damage in the liver of experimental rats (81). Stevioside from Stevia leaves, a natural sweetener, increases the expression of various SODs, including SOD2, in mice experiments (82). The antioxidant potential of stevia extracts from Stevia leaves has been reported in an experimental liver damage model (83). Butyrate, a short-chain fatty acid which can be prepared from various vegetables, increases the expression of SODs (84), protecting mice from an early development of NAFLD (85). Blueberry juice protects liver function by reducing mitochondrial oxidative stress through elevating SOD and suppressing ROS activity in an animal model (86). Supplementation of antioxidants may protect

hepatocytes from oxidative damage. Antioxidant vitamins, including C and E, have also presented hepatocyte protective effects in an animal toxicity model (87). Enhanced protection of liver membranes has been described for animals fed with a coenzyme Q10 (88). Consumption of vitamin E has been linked to regeneration of SODs in an animal model (89). In addition, a long-term diet rich in polyunsaturated fatty acid (PUFA) and/or docosahexaenoic acid (DHA) leads to lower oxidative damage to proteins. DHA supplementation has been suggested as a preventive approach for patients with ALD based on findings of an animal model (90). *Perilla frutescens* is a source of PUFA, with high levels present compared with other edible plants, and PUFA can be converted to DHA in the animal liver (91).

It is suggested that SODs, as well as dietary antioxidants, may offer hepatocyte protection against the progression of FLD (Fig. 3). However, the association between nutrient consumption and hepatocyte protection is complex and requires further investigation. In addition, the complexity of the human diet makes it challenging to examine distinctive effects. As presented, certain food or dietary components provide hepatocyte protection through signaling pathway modifications via modulation of specific activities. Furthermore, the microbiome has been described as a hallmark of various liver diseases (92). It has been reported that probiotics, including *Lactobacillus*, restores gut microbiota and alleviates liver injury in animal models (93). The proportion of *Bacteroides* has been described as markedly higher in patients with liver fibrosis compared with healthy controls, which influences NAFLD progression (94). Furthermore, probiotic administration has been associated with improved levels of liver markers of hepatic inflammation in patients with NAFLD (95). Accordingly, modulation of the gut microbiome presents a new therapeutic target in NAFLD treatment due to the distinct changes in the composition of gut microbiota. In the future, dietary approaches restoring gut microbiota may emerge as a therapy fields for FLD.

## 5. Conclusions

The development FLD and co-morbidities has severe effects on the liver and associated functions. There are no approved therapies for the treatment of FLDs. Therapeutic progress is limited by the poor understanding of the initiating steps of fat accumulation in the liver. Accordingly, potential endogenous modulators of the pathogenesis may provide tools for therapeutic intervention. Any conceivable therapeutic strategy should build on the observation that there are changes in key processes required for the cellular function. Therefore, properties of food ingredients may have certain hepatocyte protective potentials, which are facilitated through reduction of ROS production. To maintain normal cellular function, cells are required to escape excessive oxidative stress. This represents a rational basis for the development of dietary treatments for FLD. However, despite the various experimental observations using food ingredients, the precise mechanisms remain elusive and are therefore not suitable for clinical use. Additional mechanistic studies are required to understand detailed molecular mechanisms and to clarify if certain dietary intake is associated with improved hepatocyte survival.

Liver steatosis is associated with mitochondrial dysfunction and excessive mitochondrial ROS production. Although mitochondria are key in the maintenance of cell functions, they are also the main source of ROS. The dual function of ROS, as apoptosis triggers and performers in cell survival signaling, may determine the role of mitochondrial function in disease progression. An instrumental role of PTEN in hepatic carcinogenesis has been suggested for obese patients highlighting potential antioxidant involvement. It is imperative to exploit benefits from treatment in combination with chemical and medical modulators associated with the function of ROS and PTEN. Long-term clinical studies are further required to clarify distinct effects in the management of FLD to address therapeutic potential.

In conclusion, ROS and PTEN are involved in a pathogenesis of FLD and certain diets associated with PTEN signaling may contribute to disease prevention or progression through hepatocyte protection from apoptosis induced by oxidative stress.

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## Availability of data and materials

Not applicable.

## Authors' contributions

YI and SM have contributed to the conception and design of the study. YI, MM, YN, AT, YK and SM participated in drafting and revising the article. All authors approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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