Role of Dietary Carotenoids in Different Etiologies of Chronic Liver Diseases

Uzma Latief and Riaz Ahmad

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.80650

Abstract

Carotenoids are tetraterpenoid organic pigments synthesized by a variety of plants and microorganisms. Dietary carotenoids, taken by animals through food, play an essential role in cell differentiation, morphogenesis, vision, prevention of cancer, atherosclerosis, and age-related macular degeneration in humans due to their potential to suppress oxidative stress. As reactive oxygen species and oxidative damage to biomolecules have been found to be involved in the causation and progression of chronic liver diseases (CLDs), including hepatocellular carcinoma (HCC), which is one of the major causes of morbidity and mortality worldwide. Therefore, dietary antioxidants, which inactivate reactive oxygen species and obstruct oxidative damage, are considered as vital prophylactic strategic molecules. Data from various epidemiological studies and clinical trials strongly validate the observation that adequate carotenoid supplementation may significantly reduce the risk of several liver disorders. This chapter, thus, provides a comprehensive account of dietary carotenoids and includes the recent information with respect to their role in prevention of liver diseases.

Keywords: β-carotene, lycopene, lutein, β-cryptoxanthin, oxidative stress, chronic liver diseases

1. Introduction

There are unambiguous evidences that regular consumption of vegetables and fruits decreases the prevalence of chronic liver disease (CLD) [1, 2]. One of the main reasons of the health organizations to increase the consumption of vegetables and fruits is that these are good sources of carotenoids and other biologically active phytochemicals. Carotenoids are naturally occurring tetraterpenoids and represented by approximately 700 different structural
variants, but only 50 have been reported to play an important role in human diet [3]. They are synthesized by plants, fungi, algae, and bacteria [4]. They are classified into two groups, carotenes containing only carbon and hydrogen atoms and xanthophylls containing at least one oxygen atom [5]. These carotenoids are further paired into two classes, provitamin A carotenoids (β-carotene and β-cryptoxanthin) and non-provitamin A carotenoids (lycopene and lutein) [6]. In animals and human beings, carotenoids particularly β-carotene, lycopene, lutein, and β-cryptoxanthin play an important role in protection against photooxidative damage by acting as singlet molecular oxygen and peroxyl radical scavenger [7, 8]. There are increasing evidences that an alteration of the cellular redox state involving production of reactive oxygen species (ROS) plays a central role in different steps that initiate and regulate the progression of various liver diseases irrespective of the cause. Liver damage caused by reactive oxygen species is induced by alcohol, alteration of lipid, viruses, carbohydrate metabolism, and xenobiotics [9]. In this context, provitamin A activity of these carotenoids [10, 11] has received considerable interest by researchers and health professionals to prevent chronic liver diseases.

Chronic liver diseases (CLDs) are the major concern throughout the world because of the increasing death rate due to them. CLDs such as alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), and viral hepatitis (B and C) progress to fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC) [12, 13]. HCC is the fifth most common type of cancer and third most common cause of cancer mortality throughout the world [14]. Globally, liver cancer is responsible for causing more than 700,000 deaths annually [15]. Oxidative stress resulting from various sources is a major mechanism for hepatic fibrosis and cirrhosis [16].

![Diagram of dietary carotenoids functions](image.png)
The major source of ROS in hepatocytes is the mitochondria. Hepatocytes contain many mitochondria and thus have high production of ROS. An imbalance between the production of ROS and antioxidant defense generates various pathophysiological alterations in the hepatic cells, such as activation of hepatic stellate cells (HSCs), initiation of collagen formation, and beginning of proliferative processes [17–21]. HSCs are responsible for storage of more than 90% of the body’s vitamin A content as retinyl esters in normal liver. Chronic liver injuries may cause these cells to undergo activation and lose their capacity to store vitamin A while acquiring pro-inflammatory and proliferative properties, responsible for fibrogenesis [22]. Fibrosis if not treated may lead to end stage of liver damage, that is, liver cancer (Figure 1) [15, 23, 24].

In this context, dietary carotenoids being an important part of antioxidant defense system and precursor of vitamin A play an important role in the prevention of chronic liver diseases. Nowadays, due emphasis is given on the search of alternative therapeutics or medicines as these have least side effects and are cost effective. In this context, this chapter focuses on the use of dietary carotenoids in chronic liver disease prevention which have been documented extensively in the recent literature.

2. β-Carotene and chronic liver diseases

β-Carotene is the major carotenoid present in human diet. It is mainly present in plant sources of human diet such as carrots, pumpkin, spinach, sweet potato, cantaloupe, papaya, and mangoes [25]. It is a potent quencher of singlet oxygen, scavenges peroxy radicals, reduces levels of reactive oxygen species, and augments the investigated antioxidant enzyme activities [26, 27]. It is also a precursor of vitamin A and is reportedly converted to vitamin A by the action of β-carotene 15,15′-monooxygenase [10].

Various studies have demonstrated the hepatoprotective potential of β-carotene carried out in animal models, cell lines, and human beings. Patel and Sail reported that β-carotene protects the physiological antioxidants against aflatoxin-B1-induced carcinogenesis in albino rats [28]. β-Carotene supplementation increases the levels of vitamin C, glutathione, and glutathione-related enzymes which function as free radical scavenger and, thus, reduces the toxicity of aflatoxin-B1 in rats. In another study, it was found that various antioxidants including β-carotene modulate the hepatotoxicity induced by aflatoxin-B1 [29]. Both HBV and HCV have been found to elevate inflammatory and oxidative conditions in hepatocytes. Moreover, in chronic liver diseases, hepatic stellate cells, which store almost 70–90% of vitamin A, become activated, lose their retinoid content, and produce extracellular matrix, which is responsible for liver fibrosis [30]. Hepatic fibrosis can lead to cirrhosis and in some cases hepatocellular carcinoma (HCC). Through its provitamin A activity and roles in inhibiting reactive oxygen species, β-carotene has been shown to ameliorate the development and progression of HBV- and HCV-induced HCC. In a human study, it was found that the oxidative stress increased in patients with chronic hepatitis C (CHC). Various antioxidants such as retinol, α- and γ-tocopherol, β-cryptoxanthin, lycopene, and α- and β-carotene were decreased in serum of CHC patients, and levels in liver tissue seem to reflect serum levels [31]. In Chinese patients,
it was observed in Chinese patients that the serum levels of retinoids are low in HBV-induced HCC [32, 33]. In another study, it was shown that a high percentage of patients have vitamin A deficiency in serum in chronic hepatitis C [34, 35]. This condition reflects no response to antiviral therapy, indicating that serum levels of vitamin A could regulate the responsiveness to interferon-based antiviral therapy [35].

The generation of very high levels of oxidative stress during the metabolism of alcohol may exceed the antioxidant defense ability of the body and cause the development of liver dysfunction. It has been reported that β-carotene exerts protective effect on chronic ethanol-fed rats [36]. It was shown that ethanol treatment causes increase in oxidative stress which could stimulate apoptosis in the liver, thus leading to liver injury. However, the lower dose of β-carotene supplementation (0.52 mg/kg BW/day), which acted as an antioxidant, decreased the ROS level by downregulating lipid peroxidation and CYP2E1 expression. Moreover, it prevented ethanol-induced liver damage by impeding hepatic apoptosis via inhibiting caspase-9 and caspase-3 expressions and increasing Bcl-xL expression in the liver. In addition, the higher dose of β-carotene supplementation (6.2 mg/kg BW/day) possibly halted ethanol-induced liver damage through inhibiting TNF-α secretion and lipid peroxidation in ethanol-fed rats. Literature revealed that β-carotene supplementation can prevent liver damage in rats with chronic alcohol consumption [37, 38]. β-carotene supplement is known to attenuate ethanol-induced liver damage, decreased oxidative stress and increased GSH concentrations in erythrocytes and the liver. β-Carotene may act as an antioxidant, scavenging lipophilic radicals produced by ethanol within the membranes [39]. In a human study, it was found that in alcoholic patients with liver damage, the plasma β-carotene level was found to be lowered than in control subjects [40]. ALD is also associated with depleted levels of hepatic vitamin A [41]. As β-carotene is the precursor of vitamin A, thus, the supplementation of this carotenoid tends to regain the hepatic vitamin A content, thus facilitating attenuation of the disease.

In a study, it was found that dietary intake of apricot reduced the risks of hepatic steatosis and damage induced by CCl₄ in Wistar rats [42]. Apricot is believed to have high content of carotenoids, especially β-carotene. Markers of oxidative stress such as malondialdehyde, total GSH levels, catalase, SOD, and GSH peroxidase activities were significantly altered by CCl₄, indicating increased oxidative stress. Hepatic damage and steatosis imposed by high concentration of ROS were ameliorated by β-carotene-rich apricot intake. Consumption of tomato juice which contains lycopene and β-carotene as the major components reduces plasmatic triglycerides, steatosis, and very low-density lipoproteins. Also, it elevates lipid metabolism by inducing the overexpression of genes involved in more efficient fatty acid oxidation in rats [43]. It is also shown that Campari tomato, which contains more β-carotene and lycopene than regular tomato, ameliorated diet-induced obesity, dyslipidemia, and hepatosteatosis via downregulation of gene expression related to lipogenesis in the zebra fish model. It decreased sterol regulatory element-binding transcription factor 1 (SREBF1) mRNA by increasing the forkhead box O1 (foxo1) gene expression. This may be due to high percentage of β-carotene in this strain of tomato which is responsible for downregulating the expression of SREBF1 [44]. In Chinese population greater levels of carotenoids such as β-carotene in serum have been correlated...
with low prevalence of NAFLD [45]. These carotenoids mediate the protective effects against NAFLD through antioxidant mechanism, enhancing gap junction communication, reducing inflammation, and modulation of gene expression. In another human study, it was found that NAFLD has reverse relationship with vitamin A nutritional status in individuals with class III obesity. Retinol and β-carotene serum levels were evaluated as biochemical indicators. The researchers observed low serum retinol and β-carotene serum levels in the patients with NAFLD [46].

In one study, β-carotene and vanadium inhibit the diethylnitrosamine (DEN)-induced hepatic carcinogenesis in rats [47]. It was observed that treatment of β-carotene and vanadium reduced the number and size of the hyperplastic nodules significantly, while the combination treatment proved as an additive effect, decreasing number and size of the hyperplastic nodules from 89 to 22%. Further, it significantly reduced the level of cytosolic glutathione and glutathione-S-transferase (GST) activity and stabilized the aerobic metabolism and hepatic architecture of the cells. In another study involving cell lines, it was found that acyclic retinoid (synthetic analog of retinoids) retards overexpression of Ras/Erk signaling system, thereby declining the progression of HCC [48]. In a human study, it was found that greater intake of retinol, total vitamin A, and carotenes decreases the risk of primary liver cancer at an intake of 1000 μg retinol equivalent (RE)/day or greater from food sources [49]. In another human study in the presence of hepatitis B virus, levels of dietary and serum vitamin A and β-carotene were significantly lower in HCC patients than in the control subjects [32].

3. Lycopene and chronic liver diseases

Lycopene, like other carotenoids, is a natural pigment mainly present in tomato and products of tomato. It is also present in watermelon, apricot, pink guava, pink grapefruit, and papaya [50]. It does not show provitamin A activity since it lacks the β-ionone ring structure which is characteristic in other carotenes that are precursors of vitamin A [50, 51]. Various studies showed that lycopene possesses antioxidant, anticancer, anti-cardiovascular disease, and detoxification abilities in many epidemiological and animal experiments with few side effects [52, 53, 54].

As a dietary phytochemicals, lycopene has been demonstrated to mitigate AFB1-induced adverse effects in vitro and in vivo. The carcinogenicity of aflatoxin B1 (AFB1) in HepG2 cells was prevented by lycopene through decreasing DNA damage and AFB1-N7-guanine (AFB1-N7-Gua) adduct formation [55]. In another study, it was found that lycopene, because of its high antioxidant activity and free radical scavenging capacity, has been shown to be effective against oxidative stress due to aflatoxin. Lycopene blocks phase 1 metabolic enzymes of AFB such as 3A4, 2A6, and 1A2 [56]. In another study, lycopene relieves AFB1-induced liver injury through enhancing hepatic antioxidation and detoxification potential with Nrf2 activation [57]. Lycopene, a nutritional antioxidant, has also been shown for its hepatoprotective potential in D-galactosamine/lipopolysaccharide (D-GalN/LPS)-induced...
hepatitis in rats [58, 59]. It is able to affect the lipoprotein metabolism by restoring the altered levels of lipid-metabolizing enzymes and stabilizing the arrangement of lipoprotein levels during experimentally induced hepatitis. Another study demonstrated that the regular use of our carotenoid-based functional food minimizes the severity of ribavirin-induced anemia in patients with CHC and improves tolerance to the full dose of antiviral therapy [60]. It was found that a mixture of various carotenoids particularly lycopene seems to be promising for the prevention of liver cancer in hepatitis virus-infected patients with cirrhosis [61, 62].

It is found that tomato powder which is rich in lycopene acts as a novel candidate for prevention against alcohol-related hepatic injury in rodents [63]. It provides protection against alcohol-induced liver injury by suppressing CYP450 2E1 induction. It has been reported that lycopene prevents nonalcoholic steatohepatitis induced by high-fat diet [64, 65, 66]. It can reduce high-fat diet-induced steatohepatitis by reducing oxidative stress to the cells. It has been also shown that incorporation of lycopene in balanced diet prevents NAFLD [67, 68]. Lycopene may be a useful functional compound for treating NAFLD by regulating hepatic lipid metabolism [69]. Lycopene inhibits the downregulation of miR-21, which led to the downregulation of fatty acid-binding protein 7 (FABP7) at both the transcriptional and translational levels, thus inhibiting hepatic steatosis induced by high-fat diet.

Lycopene also showed beneficial effects against hepatocellular carcinoma. It provides protection against HCC by modulation of cellular proliferation, glycolysis, and ultrastructure of hepatic cells [70]. Lycopene supplementation also prevents high-fat diet-induced HCC incidence in mice. It suppressed oncogenic signals, including methionine mRNA, β-catenin protein, and mammalian target of rapamycin (mTOR) complex 1 activation. These results provide novel experimental evidence that dietary lycopene and its metabolites can be used to prevent liver cancer and reduce cancer risk in patients with NAFLD [71].

4. Lutein and chronic liver diseases

Lutein is a non-provitamin A carotenoid that belongs to the oxycarotenoid family. It is present in dark green leafy vegetables, such as kale and spinach and eggs [72, 73]. It is commercially prepared from the marigold flower (Tagetes erecta L.) in which it occurs at 1.5–1.8%. It directly quenches free radicals, especially singlet oxygen species [74].

Lutein possesses an antiviral activity against hepatitis B. It exerts its antivirus effects through inhibition of hepatitis B virus transcription [75]. Because of its strong antioxidant potential, lutein has been shown to provide protection against ethanol-induced hepatic damage [76]. It increases levels of antioxidant enzymes, like superoxide dismutase, catalase, glutathione peroxidase, and glutathione, and decreases levels of hydroxyproline. Another study demonstrated that lutein attenuates alcohol-induced liver damage in rats by regulating inflammation and oxidative stress [77]. Its supplementation downregulated inflammatory proteins and cytokines with collateral upregulation of Nrf2 levels and antioxidant enzymatic activities.
Lutein decreases inflammation and oxidative stress in the liver and eyes of guinea pigs fed with hypercholesterolemic diet [78]. This carotenoid could prevent degenerative conditions of the liver by decreasing the free cholesterol pool and attenuating lipid peroxidation and pro-inflammatory cytokine production. Further, attenuated inflammatory state in the liver could be explained by decreased NF-κB DNA-binding activity. Another study demonstrated that lutein possesses ameliorative effect against NAFLD [79]. It suggests that lutein supplementation could protect against hepatic lipid accumulation and insulin resistance induced by high-fat diet, possibly via the activation of the expression of sirtuin 1 (SIRT1) and, subsequently, peroxisome proliferator activated receptor (PPAR)-α and other key factors in insulin signaling [80]. Sirtuin 1 is reported to have therapeutic potential in NAFLD and play a key role in insulin sensitivity. SIRT1 regulates the expression of PPAR-α, a key factor in the regulation of lipid metabolism [81, 82]. Lutein has also been found to have anticarcinogenic effects against NDEA-induced HCC in rats [83]. Inhibition of carcinogenesis by this carotenoid could be because of the combined effect of its antioxidant activity along with the inhibition of cytochrome P450 enzymes, inducing detoxifying enzymes such as glutathione-S-transferase and UDP glucuronyl transferase.

5. β-Cryptoxanthin and chronic liver diseases

β-Cryptoxanthin is an oxygenated carotenoid usually present in squash, pepper, papaya, sweet pickles, carrots, and orange juice [84]. It is a xanthophyll carotenoid specifically found in the Satsuma mandarin (Citrus unshiu Marc.). Similar to other carotenoids, β-cryptoxanthin has an antioxidant activity [85, 86]. β-Cryptoxanthin is readily absorbed and relatively abundant in human plasma, together with α-carotene, lycopene, lutein, and zeaxanthin [87].

It has been shown that β-cryptoxanthin ameliorates diet-induced nonalcoholic steatohepatitis by repressing inflammatory gene expression in mice [88]. β-Cryptoxanthin suppressed the expression of lipopolysaccharide (LPS)-inducible and TNFα-inducible genes in NASH. Elevated levels of the oxidative stress marker thiobarbituric acid-reactive substances (TBARS) were lowered by β-cryptoxanthin in NASH. Thus, it represses inflammation and the resulting fibrosis probably by primarily repressing the increase and activation of macrophages and other immune cells. Reducing reactive oxygen species is likely to be a major mechanism of inflammation and injury suppression in the livers of mice with NASH. Another study revealed that β-cryptoxanthin reversed steatosis, inflammation, and fibrosis progression in preexisting NASH in mice [89]. Thus, β-cryptoxanthin prevents and reverses insulin resistance and steatohepatitis through decreasing activation of macrophages or Kupffer cells in a lipotoxic model of NASH. It was found that plasma levels of carotenoids such as β-carotene, lycopene, lutein, and β-cryptoxanthin were decreased in patients with NASH [90]. This study suggests that antioxidant supplementation may be a rational option for the treatment of NASH. In patients of NAFLD, it was found that β-cryptoxanthin treatment inhibits its progression [91]. β-Cryptoxanthin supplementation is very effective in raising antioxidant and anti-inflammation activities in patients of NAFLD (Table 1).
| S. No. | Carotenoid investigated | Object of study       | Results                                                                                                                                  | References |
|-------|-------------------------|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------|
| 1     | β-Carotene              | Rat liver             | Liver antioxidant enzymes such as glutathione peroxidase, glutathione-S-transferase, catalase, and vitamin C were elevated            | [28]       |
| 2     | β-Carotene, vitamin E,  | Rat liver             | β-Carotene intake restored the levels of hepatic glutathione, RNA, and serum protein thiols relative to control animals             | [29]       |
|       | selenium, silymarin, and|                       |                                                                                                                                       |            |
|       | coenzyme Q₁₀           |                       |                                                                                                                                       |            |
| 3     | β-Carotene              | Rat liver             | Oxidative stress is decreased by CYP2E1 expression and lipid peroxidation. β-Carotene also inhibited hepatic apoptosis via inhibiting | [36]       |
|       |                         |                       | caspase-3 and caspase-9 and increasing Bcl-xL expression in the liver                                                                 |            |
| 4     | Retinol, α- and γ-      | Human liver and serum | Increased oxidative stress is present in patients with chronic hepatitis C. Antioxidants were severely depleted in serum and liver tissue | [31]       |
|       | tocopherol, lutein, β-  |                       |                                                                                                                                       |            |
|       | cryptoxanthin, lycopene |                       |                                                                                                                                       |            |
|       | and α- and β-carotene   |                       |                                                                                                                                       |            |
| 5     | β-Carotene              | Rat liver             | β-Carotene prevented ethanol-induced lipid peroxidation in hepatic tissues                                                             | [38]       |
| 6     | β-Carotene              | Rat liver             | Malondialdehyde, total glutathione levels and catalase, superoxide dismutase, and glutathione peroxidase activities were restored     | [42]       |
| 7     | α- and β-Carotene, lutein| Human serum          | Serum carotenoid levels were inversely associated with the risk of NAFLD                                                              | [45]       |
|       | and zeaxanthin          |                       |                                                                                                                                       |            |
| 8     | Dietary carotenes and   | Human liver           | Dietary consumption of retinol, carotenes, and total vitamin A decreases the risk of primary liver cancer risk                           | [49]       |
|       | vitamin A               |                       |                                                                                                                                       |            |
| 9     | β-Carotene, β-apo-8'-  | Rat liver             | Carotenoids exert protective effect against aflatoxin B1-induced liver preneoplastic foci and DNA damage                             | [55]       |
|       | carotenal, canthaxanthin|                       |                                                                                                                                       |            |
|       | , astaxanthin, and      |                       |                                                                                                                                       |            |
|       | lycopene                |                       |                                                                                                                                       |            |
| 10    | Lycopene                | Rat liver             | Enhanced hepatic antioxidant and detoxification potential                                                                              | [57]       |
| 11    | Lycopene                | Rat liver             | Liver function test enzymes, cholesterol, triglycerides, free fatty acids, and phospholipids in serum and liver were restored       | [58]       |
| 12    | Lycopene                | Rat liver             | It restored the increase in very-low-density lipoproteins, decrease in high-density lipoproteins, and lipid-metabolizing enzymes     | [59]       |
| 13    | Lycopene                | Rat and mouse liver   | Hepatic CYP2E1 protein levels, peroxisome proliferator-activated receptor-α, inflammatory gene expression, and reticulum stress markers were restored | [63]       |
| S. No. | Carotenoid investigated | Object of study | Results | References |
|-------|-------------------------|----------------|---------|------------|
| 14    | Lycopene                | Rat liver      | Supplementation with lycopene lowered serum malondialdehyde and tumor necrosis factor (TNF-α) levels and elevated liver GSH level | [64] |
| 15    | Lycopene                | Rat liver      | Lycopene treatment reverted changes in liver weight, serum low-density lipoproteins, total hepatic cholesterol, and activity of hepatic SOD, catalase, and glutathione peroxidase | [68] |
| 16    | Lycopene                | Rat liver      | Lycopene supplementation downregulated TNF-α and CYP2E1 expression and decreased infiltration of liver fats | [67] |
| 17    | Lycopene                | Rat liver      | Lycopene provides protection against NAFLD by alleviating amino acid depletion, recovery of the redox balance in liver, and incrementing L-carnitine levels | [65] |
| 18    | Lycopene                | Mouse liver    | It decreases the expression of cell proliferation-associated genes (PCNA, cyclin D1, and p21) and glycolytic enzymes | [70] |
| 19    | Lycopene                | Mouse liver    | Lycopene and its metabolites reduce cancer in NAFLD | [71] |
| 20    | Lutein                  | Human hepatoblastoma cells | Lutein inhibited the activity of HBV full-length promoter | [75] |
| 21    | Lutein                  | Rat liver      | SOD, catalase, glutathione peroxidase, glutathione, and hepatic hydroxyproline content were restored by lutein | [76] |
| 22    | Lutein                  | Rat liver      | Inflammatory proteins such as NF-κB, COX-2, and iNOS were downregulated along with the upregulation of Nrf2 levels and activities of antioxidant enzymes | [77] |
| 23    | Lutein                  | Rat liver      | Lutein administration decreased serum and hepatic cholesterol and triglyceride. It also increased the expression of key factors involved in hepatic insulin signaling | [79] |
| 24    | Lutein                  | Rat liver      | Lutein treatment inhibits cytochrome P450 enzymes and increases detoxifying enzymes such as glutathione-S-transferase and UDP glucuronyl transferase | [83] |
| 25    | β-Cryptoxanthin         | Mouse liver    | β-Cryptoxanthin reduced the levels of TBARS and suppressed the expression of lipopolysaccharide and TNF-α inducible gene. It further suppressed the activation of macrophages, T helper, and cytotoxic cells | [88] |
6. Other carotenoids and chronic liver diseases

Other carotenoids such as α-carotene, fucoxanthin, and zeaxanthin also show promising effects against chronic liver injury. It has been found that α-carotene has an inhibitory effect on spontaneous liver carcinogenesis in male mice [92]. α-Carotene significantly decreases the mean number of hepatomas per mouse. In another study, it was found that fucoxanthin promoted weight loss, reduced body and liver fat content, and improved liver function tests in obese nondiabetic women [93]. Zeaxanthin also shows protective effects against nonalcoholic steatohepatitis [94]. It significantly prevented NASH progression by decreasing oxidative stress and liver fibrosis. It has been found also that zeaxanthin showed therapeutic effects against alcoholic liver diseases [95]. Zeaxanthin show protective effects through the lower expression level of cytochrome P450 2E1 (CYP2E1), diminished activity of nuclear factor kappa B (NF-κB) through the restoration of its inhibitor kappa B alpha (IκBα), and the modulation of MAPK pathways including p38 MAPK, JNK, and ERK.

7. Conclusions and future directions

Various epidemiological studies investigate the effects of dietary carotenoids on various markers of oxidative stress and inflammation indicating their preventive role in chronic liver disease prevention. Oxidative stress is clearly associated with the etiology of chronic liver diseases. Thus, the use of carotenoid-rich fruits and vegetables should be the part of diet (Tables 2 and 3). Although several pathways related to inhibition of oxidative stress by carotenoids have been uncovered, many aspects remain poorly understood and warrant further research. As many carotenoids have been found to have provitamin A activity, the mechanism related to their regaining of vitamin A content by hepatic stellate cells and restoring their normal functions should be properly understood (Figure 2).

There is further need of long-term controlled trials in normal and diseased groups to study the dose response of each dietary carotenoid. Future research areas may include their bioavailability, metabolism, safety, and mechanism of action. Studies on the type of carotenoid and its metabolites which may act as a suitable regulator to alter pathways related to oxidative

| S. No. | Carotenoid investigated | Object of study | Results | References |
|--------|------------------------|-----------------|---------|------------|
| 26     | β-Cryptoxanthin         | Mouse liver     | β-Cryptoxanthin reduced total hepatic macrophage content | [89] |
| 27     | β-Cryptoxanthin         | Human liver     | β-Cryptoxanthin induced antioxidant and anti-inflammatory activities in NAFLD patients | [91] |
| 28     | Fucoxanthin            | Human liver     | It reduced liver and body fat content and improved liver function tests | [93] |

Table 1. Effects of carotenoids on chronic liver diseases in cell line, human, and animal models.
stress, inflammation, and carcinogenicity shall also be among the priority areas. However, studying the molecular targets of these dietary carotenoids cannot be ignored and be given full consideration.

Table 2. Dietary sources of major carotenoids (mg/100 g).

| S. no. | Carotenoid     | Recommended daily dose (mg) | References |
|-------|----------------|-----------------------------|------------|
| 1     | β-Carotene     | 7                           | [98]       |
| 2     | Lycopene       | 35                          | [99]       |
| 3     | Lutein         | 1–4                         | [100]      |
| 4     | β-Cryptoxanthin| 3                           | [91]       |

Table 3. Ingestion levels of dietary carotenoids to prevent liver diseases.

stress, inflammation, and carcinogenicity shall also be among the priority areas. However, studying the molecular targets of these dietary carotenoids cannot be ignored and be given full consideration.
Figure 2. Hypothesis of progression of chronic liver diseases and their prevention by dietary carotenoids.

Acknowledgements

The authors sincerely thank the Chairman of the Department of Zoology for necessary facilities. UL acknowledges the financial assistance from UGC-Maulana Azad National Fellowship.

Conflict of interest

The authors declare no potential conflict of interest and are responsible for the writing and content of the chapter.

Author details

Uzma Latief and Riaz Ahmad*
*Address all correspondence to: ahmadriaz2013@gmail.com
Section of Genetics, Department of Zoology, Aligarh Muslim University, Aligarh, UP, India
References

[1] Nishino H, Tokuda H, Murakoshi M, Satomi Y, Masuda M, Onozuka M, et al. Cancer prevention by natural carotenoids. BioFactors. 2000;13:89-94. DOI: 10.1002/biof.5520130115

[2] Coyne T, Ibiebele TI, Baade PD, Dobson A, McClintock C, Dunn S, et al. Diabetes mellitus and serum carotenoids: Findings of a population-based study in Queensland, Australia. The American Journal of Clinical Nutrition. 2005;82:685-693. DOI: 10.1093/ajcn/82.3.685

[3] Mueller L, Boehm V. Antioxidant activity of β-carotene compounds in different in vitro assays. Molecules. 2011;16:1055-1069. DOI: 10.3390/molecules16021055

[4] Bohn T. Bioavailability of non-provitamin A carotenoids. Current Nutrition & Food Science. 2008;4:240-258. DOI: 10.2174/157340108786263685

[5] Britton G. Structure and properties of carotenoids in relation to function. The FASEB Journal. 1995;9:1551-1558. DOI: 10.1096/fasebj.9.15.8529834

[6] Waris G, Ahsan H. Reactive oxygen species: Role in the development of cancer and various chronic conditions. Journal of Carcinogenesis. 2006;5:14. DOI: 10.1186/1477-3163-5-14

[7] Tapiero H, Townsend DM, Tew KD. The role of carotenoids in the prevention of human pathologies. Biomedicine & Pharmacotherapy. 2004;58:100-110. DOI: 10.1016/j.biopha.2003.12.006

[8] Stahl W, Sies H. Antioxidant activity of carotenoids. Molecular Aspects of Medicine. 2003;24:345-351. DOI: 10.1016/S0098-2997(03)00030-X

[9] Loguercio C, De Girolamo V, de Sio I, Tuccillo C, Ascione A, Baldi F, et al. Non-alcoholic fatty liver disease in an area of southern Italy: Main clinical, histological, and pathophysiological aspects. Journal of Hepatology. 2001;35:568-574. DOI: 10.1016/S0168-8278(01)00192-1

[10] Krinsky NI, Johnson EJ. Carotenoid actions and their relation to health and disease. Molecular Aspects of Medicine. 2005;26:459-516. DOI: 10.1016/j.mam.2005.10.001

[11] Burri BJ. Beta-cryptoxanthin as a source of vitamin A. Journal of the Science of Food and Agriculture. 2015;95:1786-1794. DOI: 10.1002/jsfa.6942

[12] Sanyal AJ, Yoon SK, Lencioni R. The etiology of hepatocellular carcinoma and consequences for treatment. The Oncologist. 2010;15:14-22. DOI: 10.1634/theoncologist.2010-54-14

[13] Gao B, Bataller R. Alcoholic liver disease: Pathogenesis and new therapeutic targets. Gastroenterology. 2011;141:1572-1585. DOI: 10.1053/j.gastro.2011.09.002

[14] HB E-S, Rudolph KL. Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. Gastroenterology. 2007;132:2557-2576. DOI: 10.1053/j.gastro.2007.04.061

[15] Affo S, Yu LX, Schwabe RF. The role of cancer-associated fibroblasts and fibrosis in liver cancer. Annual Review of Pathology: Mechanisms of Disease. 2017;12:153-186. DOI: 10.1146/annurev-pathol-052016-100322
[16] Ha HL, Shin HJ, Feitelson MA, Yu DY. Oxidative stress and antioxidants in hepatic pathogenesis. World Journal of Gastroenterology: WJG. 2010;16:6035-6043. DOI: 10.3748/wjg.v16.i48.6035

[17] Friedman SL. Liver fibrosis—from bench to bedside. Journal of Hepatology. 2003;38:38-53. DOI: 10.1016/S0168-8278(02)00429-4

[18] Ahmad R, Ahmed S, Khan NU, Hasnain A. Operculina turpethum attenuates N-nitrosodimethylamine induced toxic liver injury and clastogenicity in rats. Chemico-Biological Interactions. 2009;181:145-153. DOI: 10.1016/j.cbi.2009.06.021

[19] Ahmad A, Ahmad R. Understanding the mechanism of hepatic fibrosis and potential therapeutic approaches. Saudi Journal of Gastroenterology: Official Journal of the Saudi Gastroenterology Association. 2012;18:155-167. DOI: 10.4103/1319-3767.96445

[20] Latief U, Ahmad R. Herbal remedies for liver fibrosis: A review on the mode of action of fifty herbs. Journal of Traditional and Complementary Medicine. 2017;8:352-360 DOI: 10.1016/j.jtcme.2017.07.002

[21] Husain H, Ahmad R, Khan A, Asiri AM. Proteomic-genomic adjustments and their confluence for elucidation of pathways and networks during liver fibrosis. International Journal of Biological Macromolecules. 2018;111:379-392. DOI: 10.1016/j.ijbiomac.2017.12.168

[22] Senoo H, Yoshikawa K, Morii M, Miura M, Imai K, Mezaki Y. Hepatic stellate cell (vitamin A-storing cell) and its relative–past, present and future. Cell Biology International. 2010;34:1247-1272. DOI: 10.1042/CBI201000321

[23] Sakurai T, Kudo M. Molecular link between liver fibrosis and hepatocellular carcinoma. Liver Cancer. 2013;2:365-366. DOI: 10.1159/000343851

[24] Mukherjee D, Ahmad R. Dose-dependent effect of N'-Nitrosodiethylamine on hepatic architecture, RBC rheology and polypeptide repertoire in Wistar rats. Interdisciplinary Toxicology. 2015;8:1-7. DOI: 10.1515/intox-2015-0001

[25] Shete V, Quadro L. Mammalian metabolism of β-carotene: Gaps in knowledge. Nutrients. 2013;5:4849-4868. DOI: 10.3390/nu5124849

[26] Wang XD, Russell RM. Procarcinogenic and anticarcinogenic effects of β-carotene. Nutrition Reviews. 1999;57:263-272. DOI: 10.1111/j.1753-4887.1999.tb01809.x

[27] Vardi N, Parlakpinar H, Cetin A, Erdogan A, Cetin Ozturk I. Protective effect of β-carotene on methotrexate-induced oxidative liver damage. Toxicologic Pathology. 2010;38:592-597. DOI: 10.1177/0192623310367806

[28] Patel V, Sail S. β-Carotene protects the physiological antioxidants against aflatoxin-B1 induced carcinogenesis in albino rats. Pakistan Journal of Biological Sciences. 2006;9:1104-1111

[29] Kheir Eldin AA, Motawi TM, Sadik NA. Effect of some natural antioxidants on aflatoxin B1-induced hepatic toxicity. EXCLI Journal. 2008;7:119-131
[30] Lee YS, Jeong WI. Retinoic acids and hepatic stellate cells in liver disease. Journal of Gastroenterology and Hepatology. 2012;27:75-79. DOI: 10.1111/j.1440-1746.2011.07007.x

[31] Yadav D, Hertan HI, Schweitzer P, Norkus EP, Pitchumoni CS. Serum and liver micro-nutrient antioxidants and serum oxidative stress in patients with chronic hepatitis C. The American Journal of Gastroenterology. 2002;97:2634-2639. DOI: 10.1111/j.1572-0241.2002.06041.x

[32] Pan WH, Wang CY, Huang SM, Yeh SY, Lin WG, Lin DI, et al. Vitamin A, vitamin E or beta-carotene status and hepatitis B-related hepatocellular carcinoma. Annals of Epidemiology. 1993;3:217-224. DOI: 10.1016/1047-2797(93)90022-V

[33] Yuan JM, Gao YT, Ong CN, Ross RK, Yu MC. Prediagnostic level of serum retinol in relation to reduced risk of hepatocellular carcinoma. Journal of the National Cancer Institute. 2006;98:482-490. DOI: 10.1093/jnci/djj104

[34] Peres WA, Chaves GV, Gonçalves JC, Ramalho A, Coelho HS. Vitamin A deficiency in patients with hepatitis C virus-related chronic liver disease. The British Journal of Nutrition. 2011;106:1724-1731. DOI: 10.1017/S0007114511002145

[35] Bitetto D, Bortolotti N, Falleti E, Vescovo S, Fabris C, Fattovich G, et al. Vitamin A deficiency is associated with hepatitis C virus chronic infection and with unresponsiveness to interferon-based antiviral therapy. Hepatology. 2013;57:925-933. DOI: 10.1002/hep.26186

[36] Peng HC, Chen YL, Yang SY, Ho PY, Yang SS, Hu JT, et al. The antiapoptotic effects of different doses of β-carotene in chronic ethanol-fed rats. Hepatobiliary Surgery and Nutrition. 2013;2:132-141. DOI: 10.3978/j.issn.2304-3881.2013.06.08

[37] Lin WT, Huang CC, Lin TJ, Chen JR, Shieh MJ, Peng HC, et al. Effects of β-carotene on antioxidant status in rats with chronic alcohol consumption. Cell Biochemistry and Function. 2009;27:344-350. DOI: 10.1002/cbf.1579

[38] Werman MJ, Ben-Amotz A, Mokady S. Availability and antiperoxidative effects of β-carotene from Dunaliella bardawil in alcohol-drinking rats. The Journal of Nutritional Biochemistry. 1999;10:449-454. DOI: 10.1016/S0955-2863(99)00026-1

[39] Tsuchihashi H, Kigoshi M, Iwatsuki M, Niki E. Action of β-carotene as an antioxidant against lipid peroxidation. Archives of Biochemistry and Biophysics. 1995;32:137-147. DOI: 10.1006/abbi.1995.0019

[40] Stryker WS, Kaplan LA, Stein EA, Stampfer MJ, Sober A, Willett WC. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alphatocopherol levels. American Journal of Epidemiology. 1988;127:283-296. DOI: 10.1093/oxfordjournals.aje.a114804

[41] Leo MA, Sato M, Lieber CS. Effect of hepatic vitamin A depletion on the liver in humans and rats. Gastroenterology. 1983;84:562-572

[42] Ozturk F, Gul M, Ates B, Ozturk IC, Cetin A, Vardi N, et al. Protective effect of apricot (Prunus armeniaca L.) on hepatic steatosis and damage induced by carbon tetrachloride
in Wistar rats. The British Journal of Nutrition. 2009;102:1767-1775. DOI: 10.1017/S0007114509991322

[43] Martín-Pozuelo G, Navarro-González I, González-Barrio R, Santaella M, García-Alonso J, Hidalgo N, et al. The effect of tomato juice supplementation on biomarkers and gene expression related to lipid metabolism in rats with induced hepatic steatosis. European Journal of Nutrition. 2015;54:933-944. DOI: 10.1007/s00394-014-0770-4

[44] Tainaka T, Shimada Y, Kuroyanagi J, Zang L, Oka T, Nishimura Y, et al. Transcriptome analysis of anti-fatty liver action by Campari tomato using a zebrafish diet-induced obesity model. Nutrition and Metabolism. 2011;8:88. DOI: 10.1186/1743-7075-8-88

[45] Cao Y, Wang C, Liu J, Liu ZM, Ling WH, Chen YM. Greater serum carotenoid levels associated with lower prevalence of nonalcoholic fatty liver disease in Chinese adults. Scientific Reports. 2015;5:12951. DOI: 10.1038/srep12951

[46] Chaves GV, Pereira SE, Saboya CJ, Ramalho A. Non-alcoholic fatty liver disease and its relationship with the nutritional status of vitamin A in individuals with class III obesity. Obesity Surgery. 2008;18:378-385. DOI: 10.1007/s11695-007-9361-2

[47] Chattopadhyay MB, Kanna PS, Ray RS, Roy S, Chatterjee M. Combined supplementation of vanadium and beta-carotene suppresses placental glutathione S-transferase-positive foci and enhances antioxidant functions during the inhibition of diethylnitrosamine-induced rat liver carcinogenesis. Journal of Gastroenterology and Hepatology. 2004;19:683-693. DOI: 10.1111/j.1440-1746.2004.03378.x

[48] Matsushima-Nishiwaki R, Okuno M, Takano Y, Kojima S, Friedman SL, Moriwaki H. Molecular mechanism for growth suppression of human hepatocellular carcinoma cells by acyclic retinoid. Carcinogenesis. 2003;24:1353-1359. DOI: 10.1093/carcin/bgg090

[49] Lan QY, Zhang YJ, Liao GC, Zhou RF, Zhou ZG, Chen YM, et al. The association between dietary vitamin A and carotenoids and the risk of primary liver cancer: A case–control study. Nutrients. 2016;8:624. DOI: 10.3390/nu8100624

[50] Gerster H. The potential role of lycopene for human health. Journal of the American College of Nutrition. 1997;16:109-126. DOI: 10.1080/07315724.1997.10718661

[51] Rao AV, Rao LG. Carotenoids and human health. Pharmacological Research. 2007;55:207-216. DOI: 10.1016/j.phrs.2007.01.012

[52] Kavanaugh CJ, Trumbo PR, Ellwood KC. The US Food and Drug Administration’s evidence-based review for qualified health claims: Tomatoes, lycopene, and cancer. Journal of the National Cancer Institute. 2007;99:1074-1085. DOI: 10.1093/jnci/djm037

[53] Islamian JP, Mehrali H. Lycopene as a carotenoid provides radioprotectant and antioxidant effects by quenching radiation-induced free radical singlet oxygen: An overview. Cell Journal (Yakhteh). 2015;16:386-391. DOI: 10.22074/cellj.2015.485

[54] Müller L, Caris-Veyrat C, Lowe G, Böhm V. Lycopene and its antioxidant role in the prevention of cardiovascular diseases—A critical review. Critical Reviews in Food Science and Nutrition. 2016;56:1868-1879. DOI: 10.1080/10408398.2013.801827
[55] Gradelet S, Le Bon AM, Berges R, Suschetet M, Astorg P. Dietary carotenoids inhibit aflatoxin B1-induced liver preneoplastic foci and DNA damage in the rat: Role of the modulation of aflatoxin B1 metabolism. Carcinogenesis. 1998;19:403-411. DOI: 10.1093/carcin/19.3.403

[56] Yilmaz S, Kaya E, Kisacam MA. The Effect on Oxidative Stress of Aflatoxin and Protective Effect of Lycopene on Aflatoxin Damage. In: Aflatoxin-Control, Analysis, Detection and Health Risks. 2017. Pp. 67-90. DOI: 10.5772/intechopen.69321

[57] Xu F, Yu K, Yu H, Wang P, Song M, Xiu C, et al. Lycopene relieves AFB 1-induced liver injury through enhancing hepatic antioxidation and detoxification potential with Nrf2 activation. Journal of Functional Foods. 2017;39:215-224. DOI: 10.1016/j.jff.2017.10.027

[58] Shivashangari KS, Ravikumar V, Vinodkhumar R, Sheriff SA, Devaki T. Hepatoprotective potential of lycopene on D-galactosamine/lipopolysaccharide induced hepatitis in rats. Pharmacologyonline. 2006;2:151-170

[59] Sheriff SA, Devaki T. Lycopene stabilizes lipoprotein levels during D-galactosamine/lipopolysaccharide induced hepatitis in experimental rats. Asian Pacific Journal of Tropical Biomedicine. 2012;2:975-980. DOI: 10.1016/S2221-1691(13)60009-X

[60] Morisco F, Vitaglione P, Carbone A, Stingo S, Scarpati S, Ascione A, et al. Tomato-based functional food as interferon adjuvant in HCV eradication therapy. Journal of Clinical Gastroenterology. 2004;38:S118-S120. DOI: 10.1097/01.mcg.0000128935.48082.f9

[61] Nishino H. Prevention of hepatocellular carcinoma in chronic viral hepatitis patients with cirrhosis by carotenoid mixture. In: Cancer Prevention. Berlin, Heidelberg: Springer; 2007. pp. 67-71. DOI: 10.1007/978-3-540-37696-5_6

[62] Seren S, Mutchnick M, Hutchinson D, Harmanci O, Bayraktar Y, Mutchnick S, et al. Potential role of lycopene in the treatment of hepatitis C and prevention of hepatocellular carcinoma. Nutrition and Cancer. 2008;60:729-735. DOI: 10.1080/01635580802419772

[63] Stice CP, Liu C, Aizawa K, Greenberg AS, Ausman LM, Wang XD. Dietary tomato powder inhibits alcohol-induced hepatic injury by suppressing cytochrome p450 2E1 induction in rodent models. Archives of Biochemistry and Biophysics. 2015;572:81-88. DOI: 10.1016/j.abb.2015.01.004

[64] Bahcecioglu IH, Kuzu N, Metin K, Ozercan IH, Ustündag B, Sahin K, et al. Lycopene prevents development of steatohepatitis in experimental nonalcoholic steatohepatitis model induced by high-fat diet. Veterinary Medicine International. 2010; Article ID. 262179, 1-8. DOI: 10.4061/2010/262179

[65] Bernal C, Martín-Pozuelo G, Lozano AB, Sevilla Á, García-Alonso J, Canovas M, et al. Lipid biomarkers and metabolic effects of lycopene from tomato juice on liver of rats with induced hepatic steatosis. The Journal of Nutritional Biochemistry. 2013;24:1870-1881. DOI: 10.1016/j.jnutbio.2013.05.003

[66] Ip BC, Wang XD. Non-alcoholic steatohepatitis and hepatocellular carcinoma: Implications for lycopene intervention. Nutrients. 2013;6:124-162. DOI: 10.3390/nu6010124
[67] Jiang W, Guo MH, Hai X. Hepatoprotective and antioxidant effects of lycopene on non-alcoholic fatty liver disease in rat. World Journal of Gastroenterology. 2016;22:10180-10188. DOI: 10.3748/wjg.v22.i46.10180

[68] Piña-Zentella RM, Rosado JL, Gallegos-Corona MA, Madrigal-Pérez LA, García OP, Ramos-Gomez M. Lycopene improves diet-mediated recuperation in rat model of non-alcoholic fatty liver disease. Journal of Medicinal Food. 2016;19:607-614. DOI: 10.1089/jmf.2015.0123

[69] Ahn J, Lee H, Jung CH, Ha T. Lycopene inhibits hepatic steatosis via microRNA-21-induced downregulation of fatty acid-binding protein 7 in mice fed a high-fat diet. Molecular Nutrition & Food Research. 2012;56:1665-1674. DOI: 10.1002/mnfr.201200182

[70] Gupta P, Bhatia N, Bansal MP, Koul A. Lycopene modulates cellular proliferation, glycolysis and hepatic ultrastructure during hepatocellular carcinoma. World Journal of Hepatology. 2016;8:1222. DOI: 10.4254/wjh.v8.i29.1222-1233

[71] Ip BC, Liu C, Ausman LM, Von Lintig J, Wang XD. Lycopene attenuated hepatic tumorigenesis via differential mechanisms depending on carotenoid cleavage enzyme in mice. Cancer Prevention Research. 2014;7:1219-1227. DOI: 10.1158/1940-6207

[72] Mangels AR, Holden JM, Beecher GR, Forman MR, Lanza E. Carotenoid content of fruits and vegetables: An evaluation of analytic data. Journal of the American Dietetic Association. 1993;93:284-296. DOI: 10.1016/0002-8223(93)91553-3

[73] Perry A, Rasmussen H, Johnson EJ. Xanthophyll (lutein, zeaxanthin) content in fruits, vegetables and corn and egg products. Journal of Food Composition and Analysis. 2009;22:9-15. DOI: 10.1016/j.jfca.2008.07.006

[74] Landrum JT, Bone RA. Lutein, zeaxanthin, and the macular pigment. Archives of Biochemistry and Biophysics. 2001;385:28-40. DOI: 10.1006/abbi.2000.2171

[75] Pang R, Tao JY, Zhang SL, Zhao L, Yue X, Wang YF, et al. In vitro antiviral activity of lutein against hepatitis B virus. Phytotherapy Research. 2010;24:1627-1630. DOI: 10.1002/ptr.3155

[76] Sindhu ER, Firdous AP, Preethi KC, Kuttan R. Carotenoid lutein protects rats from paracetamol-, carbon tetrachloride-and ethanol-induced hepatic damage. The Journal of Pharmacy and Pharmacology. 2010;62:1054-1060. DOI: 10.1111/j.2042-7158.2010.01123.x

[77] Du SY, Zhang YL, Bai RX, Ai ZL, Xie BS, Yang HY. Lutein prevents alcohol-induced liver disease in rats by modulating oxidative stress and inflammation. International Journal of Clinical and Experimental Medicineis. 2015;8:8785-8793

[78] Kim JE, Clark RM, Park Y, Lee J, Fernandez ML. Lutein decreases oxidative stress and inflammation in liver and eyes of Guinea pigs fed a hypercholesterolemic diet. Nutrition Research and Practice. 2012;6:113-119. DOI: 10.4162/nrp.2012.6.2.113

[79] Qiu X, Gao DH, Xiang X, Xiong YF, Zhu TS, Liu LG, et al. Ameliorative effects of lutein on non-alcoholic fatty liver disease in rats. World Journal of Gastroenterology. 2015;21:8061-8072. DOI: 10.3748/wjg.v21.i26.8061
[80] Colak Y, Yesil A, Mutlu HH, Caklili OT, Ulasoglu C, Senates E, et al. A potential treatment of non-alcoholic fatty liver disease with SIRT1 activators. Journal of Gastrointestinal and Liver Diseases. 2014;23:311-319. DOI: 10.1543/jgld.2014.1121.233.yck

[81] Purushotham A, Schug TT, Xu Q, Surapureddi S, Guo X, Li X. Hepatocyte-specific deletion of SIRT1 alters fatty acid metabolism and results in hepatic steatosis and inflammation. Cell Metabolism. 2009;9:327-338. DOI: 10.1016/j.cmet.2009.02.006

[82] Ding X, Guo L, Zhang Y, Fan S, Gu M, Lu Y, et al. Extracts of pomelo peels prevent high-fat diet-induced metabolic disorders in c57bl/6 mice through activating the PPARα and GLUT4 pathway. PLoS One. 2013;8:e77915. DOI: 10.1371/journal.pone.0077915

[83] Sindhu ER, Firdous AP, Ramnath V, Kuttan R. Effect of carotenoid lutein on N-nitrosodiethylamine-induced hepatocellular carcinoma and its mechanism of action. European Journal of Cancer Prevention. 2013;22:320-327. DOI: 10.1097/CEJ.0b013e32835b69ff

[84] Maiani G, Periago Castón MJ, Catasta G, Toti E, Cambrodón IG, Bysted A, et al. Carotenoids: Actual knowledge on food sources, intakes, stability and bioavailability and their protective role in humans. Molecular Nutrition & Food Research. 2009;53:S194-S218. DOI: 10.1002/mnfr.200800053

[85] Lorenzo Y, Azqueta A, Luna L, Bonilla F, Domínguez G, Collins AR. The carotenoid β-cryptoxanthin stimulates the repair of DNA oxidation damage in addition to acting as an antioxidant in human cells. Carcinogenesis. 2008;30:308-314. DOI: 10.1093/carcin/bgn270

[86] Unno K, Sugiura M, Ogawa K, Takabayashi F, Toda M, Sakuma M, et al. Beta-cryptoxanthin, plentiful in Japanese mandarin orange, prevents age-related cognitive dysfunction and oxidative damage in senescence-accelerated mouse brain. Biological and Pharmaceutical Bulletin. 2011;34:311-317. DOI: 10.1248/bpb.34.311

[87] Sugiura M, Nakamura M, Ikoma Y, Yano M, Ogawa K, Matsumoto H, et al. High serum carotenoids are inversely associated with serum gamma-glutamyltransferase in alcohol drinkers within normal liver function. Journal of Epidemiology. 2005;15:180-186. DOI: 10.2188/jea.15.180

[88] Kobori M, Ni Y, Takahashi Y, Watanabe N, Sugiura M, Ogawa K, et al. β-Cryptoxanthin alleviates diet-induced nonalcoholic steatohepatitis by suppressing inflammatory gene expression in mice. PLoS One. 2014;9:e98294. DOI: 10.1371/journal.pone.0098294

[89] Ni Y, Nagashimada M, Zhan L, Nagata N, Kobori M, Sugiura M, et al. Prevention and reversal of lipotoxicity-induced hepatic insulin resistance and steatohepatitis in mice by an antioxidant carotenoid, β-cryptoxanthin. Endocrinology. 2015;156:987-999. DOI: 10.1210/en.2014-1776

[90] Erhardt A, Stahl W, Sies H, Lirussi F, Donner A, Häussinger D. Plasma levels of vitamin E and carotenoids are decreased in patients with nonalcoholic steatohepatitis (NASH). European Journal of Medical Research. 2011;16:76. DOI: 10.1186/2047-783X-16-2-76
[91] Matsuura B, Miyake T, Yamamoto S, Furukawa S, Hiasa Y. Usefulness of beta-crypto-xanthin for nonalcoholic fatty liver diseases. Journal of Food and Nutritional Disorders. 2016;5:3. DOI: 10.4172/2324-9323.1000196

[92] Murakoshi M, Nishino H, Satomi Y, Takayasu J, Hasegawa T, Tokuda H, et al. Potent preventive action of α-carotene against carcinogenesis: Spontaneous liver carcinogenesis and promoting stage of lung and skin carcinogenesis in mice are suppressed more effectively by α-carotene than by β-carotene. Cancer Research. 1992;52:6583-6587

[93] Abidov M, Ramazanov Z, Seifulla R, Grachev S. The effects of Xanthigen™ in the weight management of obese premenopausal women with non-alcoholic fatty liver disease and normal liver fat. Diabetes, Obesity & Metabolism. 2010;12:72-81. DOI: 10.1111/j.1463-1326.2009.01132.x

[94] Chamberlain SM, Hall JD, Patel J, Lee JR, Marcus DM, Sridhar S, et al. Protective effects of the carotenoid zeaxanthin in experimental nonalcoholic steatohepatitis. Digestive Diseases and Sciences. 2009;54:1460-1464. DOI: 10.1007/s10620-009-0824-2

[95] Xiao J, Wang J, Xing F, Han T, Jiao R, Liong EC, et al. Zeaxanthin dipalmitate therapeutically improves hepatic functions in an alcoholic fatty liver disease model through modulating MAPK pathway. PLoS One. 2014;9:e95214. DOI: 10.1371/journal.pone.0095214

[96] Arscott SA. Food sources of carotenoids. In: Carotenoids and Human Health. Totowa, NJ: Humana Press; 2013. pp. 3-19. DOI: 10.1007/978-1-62703-203-2_1

[97] Johnson EJ. The role of carotenoids in human health. Nutrition in Clinical Care. 2002;5:56-65. DOI: 10.1046/j.1523-5408.2002.00004.x

[98] Grune T, Lietz G, Palou A, Ross AC, Stahl W, Tang G, et al. β-Carotene is an important vitamin A source for humans-3. The Journal of Nutrition. 2010;140:2268S-2285S. DOI: 10.3945/jn.109.119024

[99] Rao AV, Agarwal S. Role of antioxidant lycopene in cancer and heart disease. Journal of the American College of Nutrition. 2000;19:563-569. DOI: 10.1080/07315724.2000.10718953

[100] Mares-Perlman JA, Millen AE, Ficek TL, Hankinson SE. The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease. Overview. The Journal of Nutrition. 2002;132:518S-524S. DOI: 10.1093/jn/132.3.518S