Chapter 18
Antioxidants in the Prevention and Treatment of Liver Diseases

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Abstract Oxidative stress is believed to play a role in the initiation and progression of liver diseases, leading to the proposal that antioxidant therapy has the potential to prevent and treat liver diseases that involve oxidative stress. This chapter reviews preclinical studies using animal models that evaluate the efficacy of various antioxidants including pure compounds and herbal medicines. Furthermore, therapeutic outcomes of antioxidants in patients with alcoholic liver disease and nonalcoholic liver disease are also summarized. Although a great deal of encouraging data on various antioxidants has been obtained in animal studies, the potential of application of antioxidants solely or as adjuvant therapy in human liver diseases is still controversial and challenging. On the one hand, this might be partly due to the fact that only the early phases of liver diseases are studied in most animal models, suggesting that antioxidants might have a greater role in less advanced hepatic diseases. On the other hand, translational research should also be further improved to realize the application of antioxidants in liver diseases. Factors such as the duration of treatment, dose to be used, bioavailability in human, and mode of administration should be carefully explored in future studies. Additionally, study design, clinical endpoints, and choice of patient population should also be critically considered in clinical trials. In summary, intensive efforts should be made to establish a role for antioxidant treatment of liver disease.

Keywords Antioxidants • Oxidative stress • Lipid peroxidation • Liver diseases

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18.1 Introduction

Free oxygen radicals and other reactive oxygen species (ROS) are generated during oxygen metabolism in biological systems. The liver is an important site of free radical production by hepatic enzymes. The mitochondria, endoplasmic reticulum, and peroxisomes of hepatic tissues generate ROS (Webb and Twedt 2008; Zhu et al. 2012). Under some conditions, free radicals are essential for signal transduction and gene expression and can have beneficial roles (Videla 2009). However, they become detrimental when the levels of superoxide production are increased by the activity of the electron transport chain. The imbalance between ROS production and antioxidants defenses induces oxidative/nitrosative stress in the body, which can initiate lipid peroxidation, trigger DNA injury, oxidize molecules in tissues, and more importantly, modulate cell signaling transduction processes; these changes lead to cellular and tissue damage (Li et al. 2015). Since the liver is particularly sensitive and susceptible to oxidative stress, ROS constitutes a crucial background of many hepatic disorders, and contributes to development of metabolic, inflammatory, and proliferative liver diseases. In fact, liver diseases are always characterized by augmented oxidative stress, which can also trigger hepatic injury (Horie et al. 2006). In addition to high levels of oxidative stress, multiple studies have shown that the extent of lipid peroxidation and oxidative protein always correlates with injury severity, which is further related to the progression of many liver diseases (Videla 2009).

Enzymatic and nonenzymatic systems control oxidative stress and are essential for maintaining cellular redox homeostasis under physiological conditions (Li et al. 2015) (Fig. 18.1). Antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase (GR), as well as nonenzymatic particles of electron acceptors such as glutathione (GSH), vitamin C, and vitamin E are of great importance in the cellular response to oxidative stress. In hepatic injury induced by metabolic disorders or hepatotoxins, the decreased activity of these antioxidant enzymes and a reduction of electron acceptors, such as GSH, occur frequently. Increases in oxidative stress regulate the activity of redox-sensitive transcription factors such as nuclear factor κ B (NF-κB), activator protein-1 (AP-1), and early growth response protein 1 (Egr-1). Importantly, a distinctive defense mechanism to eliminate ROS exists in the liver with the involvement of nuclear factor E2-related factor 2 (Nrf2). Increased oxidative stress activates cytoplasmic Nrf2, which then inhibits mitochondrial injury induced by oxidative stress by increasing the expression of antioxidant enzymes, maintaining the mitochondrial redox state, protecting against opening of mitochondrial permeability transition pore, and enhancing mitochondrial biogenesis (Wu et al. 2012; Li et al. 2015). However, when cellular protective defenses fail to remove ROS and reactive nitrogen species (RNS), the resultant increased oxidative stress alters mitochondrial function, modifies immune responses, regulates cytokine expression, and stimulates signaling cascades that result in apoptosis or cellular and tissue damage in the liver (Singal et al. 2011).

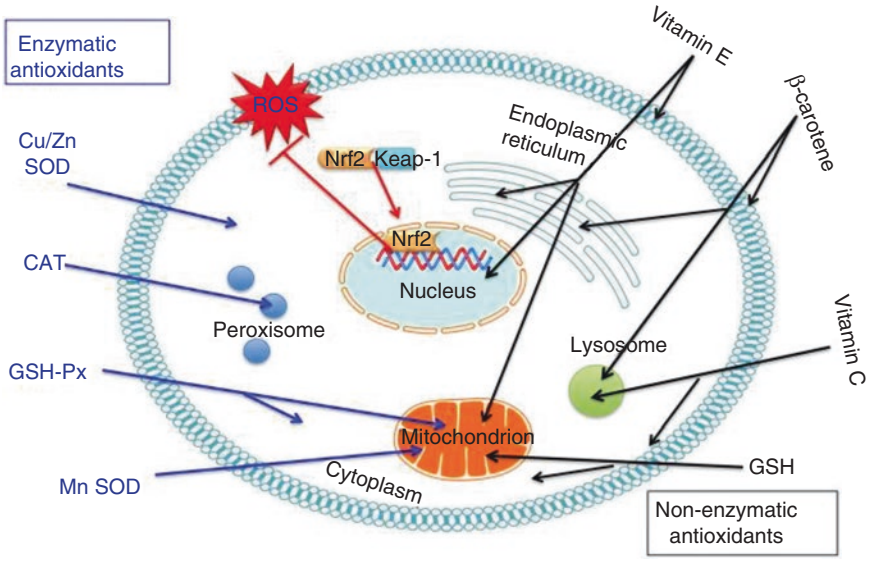

Fig. 18.1 Cellular antioxidant defenses including enzymatic and nonenzymatic systems and Nrf-2 activation

Antioxidants have been studied for the prevention and treatment of liver diseases. Generally, antioxidants are molecules that can donate electrons to free radicals (Fig. 18.2). However, substances that activate and/or enhance antioxidant defense in vivo are also sometimes regarded as antioxidants. Many compounds possessing outstanding antioxidative property have been used to prevent and treat liver diseases in experimental animal studies, including those from plant- or food-derived natural compounds (Li et al. 2007, 2013, 2014a; Guo et al. 2012). A beneficial role of natural or synthesized antioxidants in liver diseases in animal studies is likely to increase enthusiasm for use in patients with liver diseases. However, the therapeutic efficacy of antioxidants in various liver diseases is unclear in clinical trials (Singal et al. 2011). For example, vitamin E therapy in nonalcoholic steatohepatitis (NASH) shows some promising results as an antioxidant therapy for acute alcoholic hepatitis (Sanyal et al. 2010; Bell et al. 2012). In contrast, although oxidative stress is suggested to play a role in chronic viral hepatitis, there is as yet no convincing evidence showing that antioxidants are beneficial in the treatment of chronic patients with hepatitis C and hepatitis B (Acar et al. 2009, Gomez et al. 2010, Farias et al. 2012, Tasdelen Fisgin et al. 2012). Some explanations for this may be related to difficulty in understanding the detailed mechanisms of action of antioxidants and also challenges associated with the design and implementation of translational research and clinical trials. This chapter reviews the use of various antioxidants in a broad spectrum of liver diseases from data obtained from in vitro and in vivo studies and discusses the current status

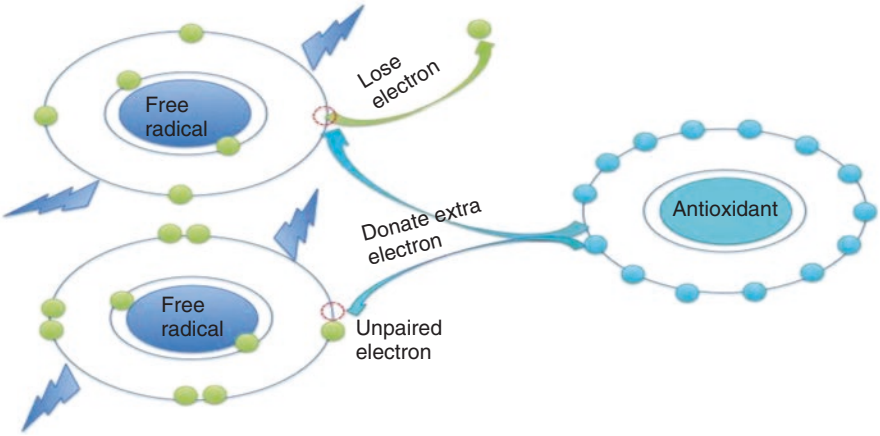

Fig. 18.2 Antioxidants scavenge free radicals by donating an extra electron

of antioxidant use in treating liver diseases including chronic viral hepatitis, alcoholic liver diseases, and NASH. Furthermore, drawbacks and challenges as well as perspective for the future use of antioxidants therapy in liver diseases are also discussed.

18.2 Antioxidants in the Prevention and Treatment of Liver Diseases

18.2.1 Alcoholic Liver Diseases

The common features of excessive alcohol exposure are often characterized by ROS production, mitochondrial damage, and hepatic steatosis. After alcohol exposure, increased ROS production and reduction of antioxidants activity occur in cytosol, mitochondria, and endoplasmic reticulum (Zima and Kalousova 2005). Dehydrogenase systems and microsomal ethanol-oxidizing systems (MEOS) are major enzymatic pathways responsible for ethanol metabolism. In the oxidation processes of alcohol with dehydrogenase and microsomal ethanol-oxidizing system (MEOS), substantial increases in nicotinamide adenine dinucleotide (NADH) or nicotinamide adenine dinucleotide phosphate (NADP+) occur, leading to the generation of ROS and oxidative stress (Panchenko et al. 2013; Wu and Cederbaum 2009; De Minicis and Brenner 2008). For impaired antioxidant defenses, GSH may be the most important nonenzymatic antioxidant that is affected in alcoholic liver diseases (De Minicis and Brenner 2008). Alcohol depletes GSH in mitochondria of centrilobular hepatocytes, and this precedes the development of mitochondrial injury and lipid alterations (García-Ruiz et al. 1994). Regarding antioxidant enzymes, a striking decrease in protein levels and activities of SOD, CAT, and GPX

have been detected in animals challenged with ethanol (Zima and Kalousova 2005). The alteration of enzyme activities and oxidative stress are positively correlated with the severity of lipid peroxidation and liver damage.

The underlying pathways of oxidative stress-caused alcoholic liver injury have been studied in some detail. Under peroxidative conditions, the mitogenactivating protein kinase (MAPK) pathway is stimulated by the activation of protein kinase C (PKC) or degradation of protein phosphatases (Bhalla et al. 2002; Kamata et al. 2005; Han et al. 2016). Disruption of this signaling network ultimately leads to steatosis and hepatic inflammation. On the one hand, activated MAPK leads to stimulation of the Bax/Bcl2 pathway, resulting in hepatocyte death. On the other hand, signaling by MAPK induces the protective activation of the Keap1-Nrf2 pathway, which then interacts with the antioxidant response element (ARE) to stimulate the expression of antioxidant enzymes such as SOD and CAT (Zima and Kalousova 2005; Li et al. 2015). Therefore, substances that normalize MAPK and/or activate Keap1-Nrf2 are potential candidates to prevent and treat alcoholic liver disease (ALD).

With better demonstration of the underlying mechanisms of oxidative stress in ALD, antioxidant therapy has been considered to prevent or treat ALD in in vitro and animal studies. Many foods and plants, such as fruits and medicinal plants rich in natural antioxidants, were used to eliminate ROS/RNS and to protect the liver from oxidative stress (Li et al. 2015). In recent years, a number of plant products have been used to alleviate liver injury induced by alcohol in animal models. For example, betaine, catechin, quercetin, and epigallocatechin gallate (EGCG) are protective against alcohol-caused oxidative stress in HepaG2 hepatic cells; these agents all downregulated GPX4 expression, while quercetin, catechin, and betaine prevented the formation of malondialdehyde (MDA)/4-hydroxynonenal (4HNE) induced by ethanol. In addition, catechin reduced the induction of CYP2E1, and betaine attenuated the upregulation of heat shock protein 70 by ethanol (Oliva et al. 2011).

The effect of Korean red ginseng in diminishing oxidative stress and steatosis induced by alcohol in a murine model and ethanol-treated hepatocytes has been investigated. The results indicated that RGE reduces the induction of cytochrome P4502E1, 4-HNE, and nitrotyrosine levels caused by alcohol. More importantly, red ginseng restores the phosphorylation of 5′-adenosine monophosphate-activated protein kinase (AMPK) that is decreased by alcohol. Additionally, RGE significantly inhibited fat accumulation in hepatocytes treated with alcohol by decreasing sterol regulatory element-binding protein-1 and increasing the expression of sirtuin 1 (Sirt 1) and peroxisome proliferator-activated receptor-α. This study suggested that RGE can potentially treat ALD by activating the AMPK/Sirt1 pathway (Han et al. 2015). Another study demonstrated that demethyleneberberine (DMB), a natural mitochondria-targeting antioxidant, penetrates mitochondrial membranes and accumulates in mitochondria, thus ameliorating oxidative stress induced by acute alcohol intake (Zhang et al. 2015). In chronic ethanol-treated mice, DMB ameliorated lipid peroxidation and macrosteatosis by suppression of CYP2E1 and normalization of Sirt 1/AMPK pathway-related fatty acid oxidation. Moreover, MitoQ, a synthetic mitochondria-targeted antioxidant, also has protective effects in a mouse model of ALD (Zhang et al. 2015). Green tea, which is rich

in water-soluble antioxidants, also has beneficial effects on the antioxidant defenses in the liver of rats chronically consuming ethanol (Augustyniak et al. 2005). Reductions of antioxidant levels, and increases in lipid peroxidation and protein modifications caused by ethanol are partially normalized by green tea. Epicatechin and epicatechin gallate are thought to be responsible for antioxidative activity of green tea.

In addition to polyphenol and flavonoids compounds, the antioxidant property of polysaccharide has also been investigated. Non-starch polysaccharide derived from peduncles of *Hovenia dulcis* has a protective effect in mice with acute alcoholic liver injury by enhancing the expression and activity of SOD as well as GPX (Wang et al. 2012a). Treatment of rats with polysaccharide from *Lycium barbarum* restored MDA levels and improved antioxidant defense in the liver, which effectively alleviated liver damage and prevented the progression of fatty liver (Cheng and Kong 2011). The effects of antioxidants (including natural products and synthesized compounds) on alcoholic liver injury are summarized in Table 18.1 (adopted from Li et al. 2015). As seen from Table 18.1, antioxidant therapy is a promising strategy for the prevention of alcoholic liver injury in animal studies. However, the active ingredients in natural plants that lead to reduced oxidative stress in these studies are thought to be flavonoids, and the underlying mechanisms have yet to be fully investigated.

18.2.2 Nonalcoholic Liver Diseases

Nonalcoholic fatty liver disease (NAFLD), an indicator of metabolic syndrome, is characterized by abnormal fatty acid deposition and is becoming increasingly prevalent (Li et al. 2015). NASH, a more advance form of NAFLD, is generally described by the occurrence of steatosis with severe inflammation and progressive fibrosis (Koek et al. 2011; Mitsuyoshi et al. 2006). Oxidative stress is considered to be a pivotal factor during the development of this disease. During free fatty acid metabolism in mitochondria, microsomes, and peroxisomes, ROS are generated in bulk. Unfortunately, antioxidant defenses are insufficient to combat the effects of excessive ROS production. An inflammatory cascade involving cytokines is triggered by oxidative stress (Koek et al. 2011; Takaki et al. 2013). When a free radical accepts an electron from an unsaturated fatty acid, lipid peroxidation is launched, and this then triggers a chain reaction creating lipid peroxides, resulting in membrane dysfunction and the generation of reactive metabolites such as MDA and 4-HNE (Koek et al. 2011). Oxidative stress affects hepatic lipid metabolism at multiple levels, ranging from simple lipid storage to inflammation, a process referred to as a "secondary hit." Necro-inflammation, resembling inflammation with rapid necrosis of tissue, is induced by nuclear and protein dysfunction as well as mitochondrial DNA damage in hepatocytes (Mitsuyoshi et al. 2006).

Antioxidants from medicinal plants and pure compounds have been intensively studied in NAFLD. As a preventive treatment of NAFLD, they are often used during

Table 18.1 The effects of natural products on alcoholic liver damage

Models (prevention/treatment)	Materials	Effect	Bioactive compounds	References
Mice treated with alcohol (treatment)	Freeze-dried, germinated, and fermented mung bean	↑ Antioxidant levels, NO		Mohd Ali et al. (2013)
Mice treated with alcohol (treatment)	Korean red ginseng	AMPK/Sirt1 activation	Ginsenoside components	Han et al. (2015)
Rats treated with ethanol diet (prevention)	Green tea	↑ Enzymes, nonenzymatic antioxidants; ↓ lipid and protein oxidation	Epicatechin, epicatechin gallate	Augustyniak et al. (2005)
Rats treated with ethanol (prevention)	*Ziziphus mauritiana* leaf	↓ ALT, AST, ALP, total bilirubin, CAT; ↑ GSH-Px, glutathione reductase, and SOD	Tannins, saponins, and phenolic compounds	Dahiru and Obidoa (2007)
Rats exposed to ethanol (prevention)	*Amaranthus hypochondriacus* seed	↓ MDA, NADPH; ↑ Cu, Zn-SOD	Total phenols	Lopez et al. (2011)
Rats treated with ethanol (prevention)	Methanolic extract from *Hammada scoparia* leaves	↓ Aminotransferase, glycogen synthase kinase-3 beta, lipid peroxidation; ↑ GSH-Px	Phenolic compounds	Bourogaa et al. (2013)
Mice chronically treated with alcohol (prevention)	Jujube honey	↓ Lipoprotein oxidation, AST, ALT, MAD, 8-hydroxy-2-deoxyguanosine; ↑ GSH-Px	Phenolic acids	Cheng et al. (2014)
Rats chronically treated with ethanol (prevention)	Virgin olive oil	↓ Transaminases levels, hepatic lipid peroxidation; ↑ GSH-Px, SOD, and CAT	Tocopherols, chlorophyll, total polyphenols	Kasdallah-Grissa et al. (2008)
Mice acutely treated with alcohol (prevention)	Peduncles of *Hovenia dulcis*	↓ ALT, AST, MDA; ↑ SOD, GSH-Px	Non-starch polysaccharide	Wang et al. (2012a)
Rats chronically treated with ethanol	*Lycium barbarum*	↓ ALT, AST; SOD, ↑ CAT, GSH-Px and GSH	Polysaccharide	Cheng and Kong (2011)

ALP alkaline phosphatase, ↑ means increase or enhance, ↓ means decrease

the early phases of the development of the disease. Both in vitro and animal studies using models of obesity, such as a high-fat diet or a methionine- and choline-deficient diet (MCDD), reveal that a variety of substances reduce oxidative stress and thus alleviate NAFLD. In in vitro models using free fatty acid-induced lipid overload and oxidative stress in hepatocytes and Kupffer cells, isoquercitrin (IQ), a flavonoid, weakened lipid overload and ROS production in hepatocytes via the AMPK pathway (Hassan et al. 2014). In models of NAFLD triggered by high-fat diet or obesity, a polyphenol extract from brown algae *Ecklonia cava* (a seaweed with a rich polyphenolic content) improved hepatic lipogenesis, oxidative stress, and inflammation via activation AMPK and Sirt 1 (Eo et al. 2015), and EGCG diminishes oxidative stress, inflammation, and fibrosis via pathways such as transforming growth factor-β (TGF-β)/SMAD and NF-κB (Xiao et al. 2014). Liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, has antioxidant and hepatoprotective properties, which might be regulated by the elevation of adiponectin levels and the inactivation of Jun N-terminal kinase-signaling (JNK) (Gao et al. 2015). Garlic essential oil, choline, and fructooligosaccharide (FOS, used as a sweetener) also protect against NAFLD through regulation of lipid metabolism and oxidative stress (Lai et al. 2014; Xiao et al. 2014).

In models of NASH induced by MCDD diet, antioxidants, such as indole-derived NecroX-7 (a mitochondrial-specific ROS inhibitor), alpha-lipoic acid, and 6-gingerol (active constituent of fresh ginger), also showed beneficial effects via suppression of oxidative stress and inflammatory response. Specifically, indole-derived NecroX-7 suppressed whole-cell ROS/RNS (Chung et al. 2015); alpha-lipoic acid improved antioxidative capacity of liver by increasing SOD activity and GSH levels (Stanković et al. 2014); 6-gingerol downregulated cytochrome CYP2E1 and JNK (Tzeng et al. 2015). Additionally, retinoic acid-related orphan receptor alpha (ROR alpha) can regulate diverse genes related to lipid metabolism and which have been found to have reduced expression in the livers of patients with NASH. It also induces the expression of SOD2 and GSX and thus protects mice from NASH induced by MCDD (Han et al. 2014). Studies using high-fat diets or streptozotocin-induced diabetic model to investigate the efficacy of antioxidant substances in NAFLD are summarized in Table 18.2 (adopted from Li et al. 2015). In Table 18.2, most of these compounds or plants show both antioxidant and hepatoprotective effects. Regarding the streptozotocin-induced diabetic model, many antioxidants displayed positive roles not only for the prevention but also for the treatment of hyperglycemia, further implying a promising potential role for antioxidants.

18.2.3 Liver Diseases Induced by Pharmaceuticals and Pollutants

Since the liver is a central organ for detoxification and metabolism, it is vulnerable to damage by pharmaceuticals and pollutants (Li et al. 2015), including paracetamol, D-galactosamine, lipopolysaccharide (LPS), heavy metals, microcystin, and carbon tetrachloride (CCl_4). The production of ROS/RNS and the reduction of antioxidant

Table 18.2 The effects of some antioxidants/plants on NAFLD in animal studies

Models (prevention/treatment)	Antioxidant/plants	Effects	References
Streptozotocin-induced diabetic rats (treatment)	Stobadine		Cumaoglu et al. (2007)
Mice fed with high-fat diet (prevention and treatment)	*Moringa oleifera* leaves; haw pectic oligosaccharide; *Thymbra spicata*	↑ GSH; ↓ ALT, AST, ALP, lipid peroxidation	Li et al. (2014b); Akkol et al. (2009); Das et al. (2012)
Streptozotocin-induced diabetic rats (treatment)	Berberine; N-acetylcysteine; *Oroxylum indicum* stem bark; maslinic acid; resveratrol	Antioxidation	Zhou and Zhou (2011)
Diabetic rats fed on a high-fat thermolyzed diet (prevention)	Omega-3 polyunsaturated fatty acids	↑ SOD, CAT; ↓ triglycerides, non-esterified fatty acid, lipoperoxidation	de Assis et al. (2012)
Liver damage in diet-induced atherosclerotic rats (prevention)	*Tulbaghia violacea* rhizomes	↓ LDH, AST, ALT, ALP, bilirubin antioxidation	Olorunnisola et al. (2012)
Rabbits with high-fat diet (prevention)	Apolipoprotein A-I	↑ SOD, GSH-Px; ↓ iNOS, MDA	Wang et al. (2013)
Rats fed a high-fat diet (prevention)	Black cabbage sprout	↑ SOD, CAT, NADPH, GSH-Px, GRD GST	Melega et al. (2013)
Streptozotocin-induced diabetic aged rats (prevention)	Vitamins C and E	Antioxidation, hepatoprotection	Naziroglu et al. (2011)
Streptozotocin-induced diabetic rats (prevention)	Acai; *Herba bidenti*; (−)-epicatechin; *Stevia rebaudiana*; *Aloe vera* leaves	Antioxidation, hepatoprotection	Guerra et al. (2011)
Streptozotocin-induced diabetic mice (prevention)	*Terminalia glaucescens* leaves	Antioxidation	Njomen et al. (2008)

LDH lactate dehydrogenase, *NADPH* nicotinamide adenine dinucleotide phosphate-oxidase, *iNOS* inducible nitric oxide synthase (iNOS), *GRD* glutathione reductase, *GST* glutathione S-transferase, ↑ means increase or enhance, ↓ means decrease

defenses have been suggested as indicators of the hepatotoxic potential of these substances (Videla 2009). Elevated markers of oxidative stress and lipid peroxidation and reduction of antioxidants in the liver occur after administration of many pharmaceuticals. For example, sulfasalazine, a drug used to treat inflammatory bowel diseases, is thought to cause liver damage via oxidative stress (Linares et al. 2009). Hepatic disorders induced by paracetamol are related to increases in MDA and significant decreases of SOD activity (Mladenovic et al. 2009). Mercury chloride causes liver damage in rats with simultaneous decreases in SOD activity and reduced activities of CAT, GPX, GR, and glucose-6-phosphate dehydrogenase (G6PD) (Bando et al. 2005).

A variety of antioxidants relieve liver damage induced by hepatotoxic substances and are summarized in Table 18.3 (adopted from Li et al. 2015). Animals treated with CCl_4, a CC chemokine, have been extensively used to study the role of antioxidants in hepatotoxicity. Exposure to CCl_4 increases oxidative stress and leads to lipid peroxidation and damages hepatocellular membranes. This is followed by secretion of pro-inflammatory cytokines that ultimately results in hepatic injury. A number of natural products, especially herbal plants, have been used to treat liver dysfunction caused by CCl_4. For example, *Coptidis rhizome* and its bioactive compound berberine, a medicinal plant widely used in Chinese Medicine, exert beneficial effects on CCl_4-induced hepatotoxicity in rats partly by reducing phosphorylation of extracellular-signal-regulated kinases (Erk1/2) expression (Ye et al. 2009; Feng et al. 2011; Wang et al. 2012b). In addition, substances, such as anthocyanins, present in all tissues of higher plants like the root of Radix Platycodi activate Nrf2 to protect cells from oxidative stress through upregulation of antioxidant gene expression in dimethylnitrosamine- or cadmium-induced hepatic injury models (Niture et al. 2009). While many natural products act as antioxidant and hepatoprotective agents (see Table 18.3), their mechanisms are still unknown and need further exploration.

18.2.4 Liver Cancer

There is much evidence that ROS induces protein alterations and DNA injury and thus can act to initiate or promote carcinogenesis (Li et al. 2015; Wang and Feng 2015). For example, the progression of hepatosteatosis to liver cancer by cytoglobin deficiency occurs by the oxidative stress pathway; oxidative stress production by the core protein of hepatitis C virus (HCV) may also partly contribute to the development of hepatocellular carcinoma (Koike 2007). Antioxidants are an important defense system in suppressing tumor initiation and progression and so represent an attractive target in the prevention and treatment of liver cancer. Antioxidant extracts from potatoes inhibits the proliferation of human liver cancer cells (Wang et al. 2011). The antioxidant property of the unicellular green microalgae *Chlorella vulgaris* has antitumor effects against liver cancer, likely by increasing expression of p53, caspase-3, and pro-apoptotic proteins. Our previous studies demonstrated that *Coptidis rhizome* and berberine are potential drugs for the treatment of liver cancer due to their striking hepatoprotective and antioxidant abilities (Tan et al. 2014; Wang et al. 2014). Furthermore, the combination of chemotherapeutic drugs and antioxidants has been reported to lower drug resistance and to sensitize liver cancer cells to chemotherapeutic agents (Xu et al. 2014). Importantly, the effects of antioxidants on liver cancer have primarily been investigated in in vitro studies, and detailed animal experiment and clinical trials are yet to be undertaken.

Table 18.3 The effects of natural products or compounds on liver injury induced by toxins

Models (prevention/treatment)	Materials	Effects	References
Paracetamol-induced liver toxicity in mice (prevention)	Gallic acid; sauchinone; genistein; *Phyllanthus niruri*; *Polyalthia longifolia* leaves	Antioxidation, hepatoprotection	Rasool et al. (2010)
Paracetamol-induced liver damage in rats (prevention)	*Boerhaavia diffusa* leaves; saponarin from *Gypsophila trichotoma*	Antioxidation, hepatoprotection	Olaleye et al. (2010)
Lipopolysaccharide-induced liver injury in rats (prevention)	Carnosic acid	Antioxidation, hepatoprotection	Xiang et al. (2013)
D-Galactosamine-induced liver injury in rats (prevention)	Combination of selenium, ascorbic acid, beta-carotene, and alpha-tocopherol; *Leucasaspera*; swertiamarin from *Enicostemma axillare*	Antioxidation, hepatoprotection	Catal and Bolkent (2008)
Lipopolysaccharide/D-galactosamine-induced liver injury in rats (prevention)	Curcumin; betulinic acid; *Tridax procumbens*	Antioxidation, hepatoprotection	Cerný et al. (2011)
Doxorubicin-induced liver injury in rats (prevention)	N-Acetylcysteine	Antioxidation, hepatoprotection	Kockar et al. (2010)
Cisplatin-induced liver injury in rats (prevention)	Tomato juice	Antioxidation, hepatoprotection	Avci et al. (2008)
Tert-butyl hydroperoxide-induced liver injury in rats (prevention)	Propolis	Antioxidation, hepatoprotection	Wang et al. (2006)
Tamoxifen-induced liver injury in mice (prevention)	Catechin	Antioxidation	Tabassum et al. (2007)
Hepatic steatosis stimulated with tunicamycin (treatment)	Melatonin	↓ ER stress, expression of miR-23a	Kim et al. (2015)
Ethionine-induced liver injury in mice (prevention)	Melatonin	Antioxidation, hepatoprotection	Ferraro and Lopez-Ortega (2008)
CCl_4-induced liver damage in rats (prevention)	*Coptidis rhizome* and berberine	↑ SOD;↓ ALT, AST, Erk1/2	Feng et al. (2011)
CCl_4-induced liver damage in rats (prevention)	Friedelin isolated from *Azima tetracantha* leaves	↑ SOD, CAT, GSH, GPx; ↓ ALT, AST, LDH	Adegbesan and Adenuga (2007)
CCl_4-induced liver damage in rats (treatment)	n-Butanol fraction of *Actinidias deliciosa* roots	↑ GSH; ↓ALT, AST, MDA	Bai et al. (2007)
CCl_4-induced liver damage in rats (prevention)	*Dioclea reflexa* seeds	↑ SOD, CAT; ↓ Transaminases, MDA	Iliemene and Atawodi (2014)

(continued)

Table 18.3 (continued)

Models (prevention/treatment)	Materials	Effects	References
CCl_4-induced liver damage in rats (prevention)	*Pleurotus ostreatus* (oyster mushroom)	↑ GSH, CAT, SOD, GSH- Px; ↓ ALT, AST, ALP, MDA	Jayakumar et al. (2006)
CCl_4-induced liver damage in rats (prevention)	*Cytisus scoparius*	↑ GSH, CAT, SOD, GSH- Px, GST, GRD; ↓ ALT, AST, LDH	Raja et al. (2007)
CCl_4-induced liver damage in rats (prevention)	Ethanol extract of *Phellinus merrillii*	↑ CAT, SOD, GSH-Px; ↓ ALT, AST	Chang et al. (2007)
CCl_4-induced liver damage in rats (prevention)	*Ginkgo biloba*	↑ GSH, SOD, CAT, GSH-Px, GRD, albumin; hepatoprotection	Naik and Panda (2008)
CCl_4-induced liver damage in mice (prevention)	Protein isolate from *Phyllanthus niruri*	↑SOD, CAT; ↓ALT, ALP; lipid peroxidation	Bhattacharjee and Sil (2007)
CCl_4-induced liver damage in mice (prevention)	Kahweol and cafestol *(Coffee)*	↓ALT, AST, cytochrome P450 2E1, lipid peroxidation	Lee et al. (2007)
CCl_4-induced liver damage in rats (prevention)	*Cirsium setidens*	↑ GSH-Px; SOD; hepatoprotection	Lee et al. (2008)
CCl_4-induced liver damage in rats (prevention)	Curcumin and saikosaponin A	↑SOD, GSH; ↓MDA; hepatoprotection	Wu et al. (2008)
CCl_4-induced liver damage in rats (prevention)	Ethanolic extract of *Momordica tuberosa* tubers	Antioxidation, hepatoprotection	Kumar and Deval (2008)
CCl_4-induced liver damage in rats (prevention)	Oregano and rosemary	↓AST, ALT, ALP; antioxidation	Botsoglou et al. (2009)
CCl_4-induced liver damage in rats (prevention)	*Ficus carica* leaves and fruits, *Morus alba* root barks	↑CAT, SOD, GSH; ↓ MDA, AST, ALT, ALP	Singab et al. (2010)
CCl_4-induced liver damage in rats (prevention)	*Podophyllum hexandrum*	↑ GSH, GSH-Px, GRD, SOD, GST; ↓ AST, ALT, LDH	Ganie et al. (2011)
CCl_4-induced liver damage in rats (prevention)	*Ficus religiosa* roots	↑ CAT, GSH-Px, GRD, SOD, GST; ↓ lipid peroxidation; hepatoprotection	Gupta et al. (2011)
CCl_4-induced liver damage in rats (prevention)	Dehydroabietylamine, *Carthamus tinctorious*	↓ AST, ALT, ALP; antioxidation	Paramesha et al. (2011)
CCl_4-induced liver damage in rats (prevention)	Artemetin, *Vitex glabrata*	↑SOD, CAT, GSH-Px; ↓ AST, ALT, ALP, lipid peroxidation, total bilirubin	Sridevi et al. (2012)

Table 18.3 (continued)

Models (prevention/treatment)	Materials	Effects	References
CCl_4-induced liver damage in mice (prevention)	Blueberry anthocyanins	↑ SOD, CAT, GRD, glycogen; ↓ AST, ALT, MDA	(Chen et al. 2012)
CCl_4-induced liver damage in rats (prevention)	*Matricaria chamomilla*	↑SOD, CAT, GSH-Px, GSH; ↓AST, ALT, MDA	Aksoy and Sozbilir (2012)
CCl_4-induced liver damage in mice (prevention)	*Lysimachia clethroides*	↑ SOD; ↓ AST, ALT, MDA	(Wei et al. 2012)
CCl_4-induced liver damage in rats (prevention)	*Garcinia indica* fruit rind	↑ SOD, CAT, GRD, GSH-Px, GSH; ↓ AST, ALT, MDA	Panda and Ashar (2012)
CCl_4-induced liver damage in rats (prevention)	*Agaricus blazei*	↑GSH, GRD; ↓ AST, ALT, MDA	Al-Dbass et al. (2012)
CCl_4-induced liver damage in rats (prevention)	*Nerium oleander* flowers	↑SOD; ↓ AST, ALT, ALP, MDA	Singhal and Das Gupta (2012)
CCl_4-induced liver damage in rats (prevention)	*Hybanthus enneaspermus*	↓ AST, ALT, ALP, total bilirubin; antioxidation	Vuda et al. (2012)
CCl_4-induced liver damage in mice (treatment)	Anthocyanins in black rice bran	↑SOD, GSH-Px; hepatoprotection	Hou et al. (2013)
CCl_4-induced liver damage in rats (prevention)	*Rourea induta*	↑ SOD, CAT, GSH, GSH-Px; ↓ AST, ALT, total bilirubin;	Kalegari et al. (2014)
CCl_4-induced liver damage in rats (prevention)	Proanthocyanidins extracted from grape seeds	↑ SOD, GSH, GSH-Px, CAT; ↓ lipid accumulation, liver injury, DNA damage	Dai et al. (2014)
CCl_4-induced liver damage in mice (prevention)	*Veronica ciliata*	↑ SOD, GSH; ↓ ALT, AST, ALP	Yin et al. (2014)
CCl_4-induced liver damage in rats (prevention)	*Suberea mollis*	↑ SOD, GSH, GSH-Px, CAT; ↓ ALT, AST, ALP, MDA	Abbas et al. (2014)
CCl_4-induced liver damage in rats (prevention)	*Solanum xanthocarpum* leaves	↑ SOD, CAT, GSH, GST; ↓ ALT, AST, ALP, LDH	Jalali Ghassam et al. (2014)
Methidathion-induced liver injury in rats (prevention)	Vitamins C and E	↓ AST, ALT, ALP, MDA;	Sutcu et al. (2006)
Pesticide (chlorpyrifos and cypermethrin)-induced hepatic damage in mice (prevention)	Black tea	↑ SOD, GSH, GSH-Px, CAT, GRD, GST; ↓ AST, ALT, ALP	Khan (2006)
Polychlorinated biphenyl-induced hepatic damage in rats (prevention)	Alpha-tocopherol	Antioxidation	Banudevi et al. (2006)

(continued)

Table 18.3 (continued)

Models (prevention/treatment)	Materials	Effects	References
Aflatoxin-induced hepatic injury in rats (prevention)	*Urtica dioica* seed	↑ SOD, GSH-Px, CAT, GRD, GST; ↓ lipid peroxides, hydroxyl radical, and hydrogen peroxides	Yener et al. (2009)
Thioacetamide-induced hepatic damage in rats (prevention)	Eugenol	↑ COX-2;↓ AST, ALT, ALP, bilirubin, CYP2E1, lipid peroxidation; antioxidation	Yogalakshmi et al. (2010)
Lead-induced liver damage in rats (prevention)	Ginger	↑ SOD, CAT; ↓ MDA,	Khaki and Khaki (2010)
Dimethylnitrosamine-induced hepatic damage in rats (prevention)	Anthocyanins from purple sweet potato	↑ Nrf2, NADPH, GSH, GST; ↓ yclooxygenase-2, MDA	Hwang et al. (2011)
Cadmium-induced hepatic injury in rats (prevention)	Heated garlic juice, ascorbic acid	↑ Nrf2, SOD, CAT; ↓ MDA	Lawal et al. (2011)
Potassium bromate-induced hepatotoxicity of rat (prevention)	*Launaea procumbens*	↑ SOD, CAT, GSH, GSH-Px, GRD, GST	Khan et al. (2012)
Dimethylnitrosamine-induced liver fibrosis in rats (prevention)	*Platycodi radix* root	↑ Nrf2, heme oxygenase-1, NADPH, NQO1, GST; ↓ ALT, AST; anti-fibrotic action	Choi et al. (2013)
As_2O_3-induced hepatotoxicity in cat (prevention)	Resveratrol	↑ GSH; ↓ ROS, MDA	Zhang et al. (2014)
Sodium arsenite-induced liver damage in rats (prevention)	*Emblica officinalis*	Antioxidation	Maiti et al. (2014)
Trichloroacetic acid-induced liver injury in rats (prevention)	Date palm fruit	↑ SOD, CAT, GSH-Px; ↓ MDA	El Arem et al. (2014)

↑ means increase or enhance, ↓ means decrease

18.3 Clinical Trials of Antioxidants in Selected Liver Diseases

18.3.1 Viral Hepatitis

Oxidative stress increases oxidized proteins, impairs nucleic acid and reduces antioxidant defenses in the early stages of viral hepatitis (Ko et al. 2005; Saeki et al. 2006). Concentrations of MDA in chronic hepatitis B (HBV) patients are significantly increased (Tasdelen Fisgin et al. 2012). The level of oxidative stress correlates with the severity of HCV in patients, and there are increases in GSH levels and

reduced activities of antioxidant enzymes such as SOD and GPX (Fujita et al. 2007). Furthermore, oxidative stress is regarded as a risk factor for the development of hepatocellular carcinoma (HCC) in patients with hepatitis. After viral depletion, oxidative stress is normalized, which provides evidence that the virus itself generates oxidative stress (Fujita et al. 2007). In in vitro studies, mitochondrial impairment and oxidative stress induced by hepatitis C virus is calcium dependent and can be inhibited by calcium chelating agents (Wang et al. 2010). However, the absence of a suitable animal model for HCV makes it difficult to undertake preclinical studies of antioxidants for viral hepatitis.

Some clinical trials have evaluated the role of antioxidants therapy in patients with viral hepatitis. Supplementation with Vitamin E in patients with hepatitis C has been assessed in several studies. Although some beneficial effects such as decreased MDA and alanine transaminase (ALT) levels were observed, the clinical significance of these results is uncertain. Subsequently, therapy with a combination of antioxidants was attempted in other studies (Melhem et al. 2005; Gabbay et al. 2007). For example, 50 patients with hepatitis C were treated with several antioxidants including vitamin E. After 20-weeks of treatment, levels of ALT were normalized in 48% of patients and HCV ribonucleic acid (RNA) was negative in 25% of patients, and quality of life was improved in 58% of patients. These results appeared to be promising at first, but in another placebo-controlled randomized study to assess the effect of combination treatment with vitamin C, vitamin E, and selenium for 6 months in 23 hepatitis C patients, the antioxidants failed to improve ALT, HCV RNA, or histology (Singal et al. 2011). Agents such as MitoQ and N-acetylcysteine (NAC) have also been tested in patients with hepatitis C, but with unclear the clinical significance (Farias et al. 2012). The role of agents such as zinc and silymarin in the treatment of hepatitis C patients has also been studied; zinc supplementation improves ALT normalization and could reduce the risk of HCC in patients with zinc deficiency, while silymarin had some positive effects on hepatitis C in several studies, which needs to be confirmed in randomized controlled trials with larger sample sizes (Singal et al. 2011). In summary, although some beneficial outcomes have been reported, there is a lack of studies using randomized, double-blinded clinical trials on the possible merits of antioxidant treatments for patients with hepatitis C.

18.3.2 Alcoholic Hepatitis and Alcoholic Cirrhosis

Markers of oxidative stress and lipid peroxidation are amplified in patients with alcohol-related liver disease. The pro-oxidant and antioxidant levels in patients with chronic alcohol consumption show increases in MDA, and decreases in vitamins E and C were correlated with the severity of the disease in ALD patients (Zima and Kalousova 2005). Significant decreases of GSH levels in liver and blood of patients with ALD were detected; however, the change of SOD and CAT was uncertain, depending on the manner of alcohol intake (Wu and Cederbaum 2009). Enhanced expression of antioxidants enzymes could be a compensatory response to heightened oxidative stress (Li et al. 2015).

Therapy with antioxidant supplements to improve outcomes in patients with alcoholic liver diseases was studied on 20 chronic alcoholic patients; polydatin, a hydroxystilbene derived from the rhizome of *Polygonum cuspidatum* with antioxidant properties, reduced elevated plasma aspartate aminotransferase (AST) and ALT levels in patients while also significantly decreasing lipid peroxidation levels (Pace et al. 2015). The effects of vitamin E supplementation on alcoholic hepatitis and alcoholic cirrhosis were assessed in several randomized double-blind clinical trials. However, vitamin E failed to improve liver function or survival rates in patients. A well-known antioxidant, NAC, has been assessed to treat alcoholic hepatitis in some clinical trials (Singal et al. 2011). In one such study, patients receiving steroids and NAC had lower mortality and lower complication rates when compared to patients treated with steroids alone. The promising therapeutic effects of NAC as an adjuvant treatment on alcoholic hepatitis have yet to be confirmed in a study with a larger population size. Treatment with polyenylphosphatidylcholine improves liver function (as reflected by reduced liver enzymes and serum bilirubin levels) in patients with alcoholic cirrhosis and with HCV infection. Some studies have reported that silymarin has beneficial effects in alcoholic cirrhosis patients. Patients receiving silymarin (420 mg/day) had improved histological results such as inflammatory lesion and necrosis and biochemical findings such as ALT and AST. Another study reported that treatment with silymarin (520 mg/day) improved 4-year survival rates when compared with placebo-treated patients (Singal et al. 2011). But in several other studies, silymarin treatment did not provide any biochemical, histological, or survival benefits. Additionally, a meta-analysis on the use of silymarin in patients with alcoholic cirrhosis concluded that it has no beneficial effect (Singal et al. 2011). This could be due to difficulties in controlling alcohol intake and abstinence rates in many of the studies. In summary, the therapeutic effect of antioxidants on alcoholic hepatitis and alcoholic cirrhosis is unproven.

18.3.3 Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Increased serum markers of oxidative stress and lower antioxidant levels occur in NAFLD patients (Singal et al. 2011). Oxidative stress, as a secondary contributor to the progression from NAFLD to NASH, positively correlates with disease progression (Madan et al. 2006). The role of oxidative stress in this disease has not been fully explored with well-designed clinical trials evaluating the effects of antioxidant supplements. Vitamin E has been studied to patients with NAFLD and NASH (Singal et al. 2011). The results of improved oxidative stress without significant clinical efficacy in patients with NASH have limited enthusiasm for this approach, especially since there were no striking improvements in biochemical and histological parameters in these studies (Singal et al. 2011). However, more promising data

for the use of vitamin E was achieved when treatment lasted longer. In a double-blinded placebo-controlled trial with nondiabetic NASH, patients were treated for 96 weeks with either pioglitazone (30 mg/day), vitamin E (800 IU/day), or placebo. Patients treated with vitamin E (but not pioglitazone) had significant improvements in liver biopsy results and improvements in NASH activity scores, while both vitamin E and pioglitazone improved liver enzymes and reduced hepatic steatosis and lobular inflammation (Sanyal et al. 2010).

Other antioxidant agents such as NAC, coenzyme Q10, vitamin D, and betaine have also been evaluated in patients with nonalcoholic liver diseases. An open-label prospective trial of 20 patients treated for 12 months with NASH, NAC (1.2 g/day), and metformin (500 mg/day) improves liver enzymes, insulin resistance, body mass index, steatosis, and fibrosis (de Oliveira et al. 2008). In a randomized double-blinded placebo-controlled trial that enrolled 44 NAFLD patients, waist circumference and AST levels of patients were significantly decreased after 4 weeks of treatment with coQ10 treatment (100 mg/day), suggesting a potential for coQ10 therapy in NAFLD management (Farhangi et al. 2014). In another study of patients with NAFLD receiving vitamin D supplementation, the median of serum 25(OH) D-3 levels significantly increased along with significant decreases in serum MDA, indicating that vitamin D might be effective as an adjunctive therapy to NAFLD patients (Sharifi et al. 2014). Several studies have evaluated the efficacy of betaine in NASH patients. Although some encouraging results were obtained in these studies, it was suggested that the primary underlying mechanism of betaine was as a methyl donor rather than as an antioxidant (Federico et al. 2014).

18.4 Conclusions

This chapter provides an overview of our current understanding of oxidative stress and the actions of antioxidants in liver diseases. On the one hand, the pivotal role of oxidative stress in a broad spectrum of liver diseases has been well documented, and promising data were obtained with antioxidants in animal studies. The underlying mechanisms of action of endogenous and exogenous antioxidants in hepatoprotective effects are unclear. On the other hand, clinical trials studying the potential application of antioxidants alone or in combination therapy in liver diseases are challenging. This might be partly due to the fact that most of the animal studies reflect an early stage of liver disease, where antioxidants might have more satisfactory effects on less advanced liver diseases. In this regard, translational research should be better refined so that the role of antioxidants in more advanced stages of liver diseases can be studied more fully. Variables such as duration of treatment, as well as dose to be used, bioavailability in humans, and mode of administration of antioxidants should be carefully explored. In addition, it would also be important to critically evaluate the study design, clinical endpoints, and patient populations in such clinical trials.

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