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TOPIC HIGHLIGHT

2016 Alcoholic Liver Disease: Global view

Relationships among alcoholic liver disease, antioxidants, and antioxidant enzymes

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Abstract

Excessive consumption of alcoholic beverages is a serious cause of liver disease worldwide. The metabolism of ethanol generates reactive oxygen species, which play a significant role in the deterioration of alcoholic liver disease (ALD). Antioxidant phytochemicals, such as polyphenols, regulate the expression of ALD-associated proteins and peptides, namely, catalase, superoxide dismutase, glutathione, glutathione peroxidase, and glutathione reductase. These plant antioxidants have electrophilic activity and may induce antioxidant enzymes *via* the Kelch-like ECH-associated protein 1-NF-E2-related factor-2 pathway and antioxidant responsive elements. Furthermore, these antioxidants are reported to alleviate cell injury caused by oxidants or inflammatory cytokines. These phenomena are likely induced *via* the regulation of mitogen-activating protein kinase (MAPK) pathways by plant antioxidants, similar to preconditioning in ischemia-reperfusion models. Although the relationship between plant antioxidants and ALD has not been adequately investigated, plant antioxidants may be preventive for ALD because of their electrophilic and regulatory activities in the MAPK pathway.

Key words: Electrophile; Mitogen-activating protein kinase; Plant antioxidants; Reactive oxygen species; Preconditioning

Core tip: The metabolic process of ethanol generates reactive oxygen species, which play a significant role in the deterioration of alcoholic liver disease (ALD). Antioxidant phytochemicals, such as polyphenols, upregulate the expression of antioxidant enzymes and peptides *via* the Kelch-like ECH-associated protein

1-NF-E2-related factor-2 pathway, which leads to antioxidant responsive elements in animal models. Furthermore, these antioxidants alleviate cell injury caused by oxidants or inflammatory cytokines *via* impairment of hyperactivation of mitogen-activating protein kinase pathways, similar to preconditioning in ischemia-reperfusion models. Although the relationship between plant antioxidants and ALD has not been adequately investigated, plant antioxidants may be preventive for ALD.

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INTRODUCTION

Humans are surrounded by many chemicals, including nutrients, phytochemicals, food additives, pharmaceuticals, and drugs. Although the intestine and liver absorb and metabolize many types of chemicals[1] for utilization or detoxification[2], some become more toxic once metabolized[3]. Ethanol, which is a component of alcoholic beverages, is one of the most common and abundant chemicals in daily life. Consuming ethanol can be relaxing and provides other benefits, but excessive drinking can be harmful physically and mentally and may decrease quality of life. Moderate consumption of alcohol has been shown to reduce the risks of cardiovascular disease[4] and non-alcohol fatty liver disease[5]. With moderate intake, most ethanol is oxidized by alcohol dehydrogenase and catabolized to acetaldehyde, which is subsequently catabolized to acetate *via* aldehyde dehydrogenase in the mitochondria. However, with binge drinking, ethanol is predominately metabolized to acetaldehyde *via* cytochrome P450, family 2, subfamily E, polypeptide 1 (CYP2E1), which comprises a microsomal ethanol-oxidizing system[6] that is involved in the generation of reactive oxygen species (ROS)[7-9]. Despite much evidence demonstrating a role for CYP2E1 in alcoholic liver disease (ALD), several of our studies have demonstrated that consumption of ethanol-containing diets significantly increased hepatic CYP2E1 levels without significantly affecting plasma alanine aminotransferase (ALT) activity (unpublished data). These findings support the existence of a potent endogenous antioxidant system that can prevent potential damage *via* the excessive expression of CYP2E1[10].

Binge drinking may cause liver injury, as demonstrated by increased blood levels of ALT, aspartate aminotransferase (AST), and/or lactate dehydrogenase (LDH)[11-14] and lipid accumulation in the liver-alcoholic fatty liver[12,13,15,16]. Hepatic functions are gradually lost with the progression of ALD[11], which is one of the most critical causes of cirrhosis[11,17]. Three mechanisms have been proposed to cause alcoholic liver injury: (1) acetaldehyde toxicity[18]; (2) metabolic generation of ROS or exposure to oxidative stress[10,19-21]; and (3) provocation of an immune response that causes oxidative stress in hepatocytes[13,22-24]. ALD patients appear to exhibit oxidative stress[11]; thus, increasing defense activities against this stress is important in the prevention of ALD.

In mammals, ROS is scavenged by antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, and antioxidant substances, such as vitamins and glutathione (GSH) in collaboration with glutathione peroxidase (GPx) and glutathione reductase (GR)[25]. In previous studies, the induction and/or restoration of these substances and enzymes, which are reduced by ethanol administration, appeared to ameliorate ALD[12,13,23,26]. Some vitamins exhibit antioxidant activity and are reduced in the ALD model[27-29]. They are also deficient in ALD patients, although if present in sufficient quantities, may contribute to the prevention of oxidative stress[30]. Vitamin E is not only a lipophilic antioxidant but also may improve lipid metabolism *via* interaction with lipid accumulation-related proteins, namely patatin-like phospholipase domain containing 3 (PNPLA3) and microsomal triglyceride transfer protein[31]. However, several clinical studies have identified only partial effects of vitamin E in ALD[32,33]. Therefore, the induction of antioxidant enzymes may be more effective than vitamin supplementation in the prevention of ALD.

A trend in gastronomic culture is the exclusion of low molecular weight phytochemicals during plant breeding or processing because of their toxicity, taste, or deteriorating color. However, phytochemicals have recently received attention for their physiological activities in mammals. Many types of phytochemicals abundant in fruit and vegetables are known to have antioxidant activity. Although research efforts have focused on phenolic compounds due to their direct scavenging activity of ROS[34,35], their direct activity towards endogenous ROS appears limited in mammals because of their relatively low concentrations in the bloodstream[2,36,37]. However, many types of polyphenols, non-phenolic phytochemicals, and antioxidant-rich plant fractions have recently been reported to elicit an antioxidant defense system against liver damage induced by ethanol[34,35,38,39], other chemicals[40-43], or abnormal metabolism[21,44] to reduce oxidative stress and cell death[34,42,43,45] and to improve lipid metabolism[12,16,44,46] in various organs. In addition, some phytochemicals change both phase Ⅰ and phase Ⅱ enzymes of drug metabolism, including CYP2E1[7,13,16,47]. Recent reports indicated that some polyphenols can improve epithelial cell junctions[48-51], indicating a role for the hepatic immune response. These findings

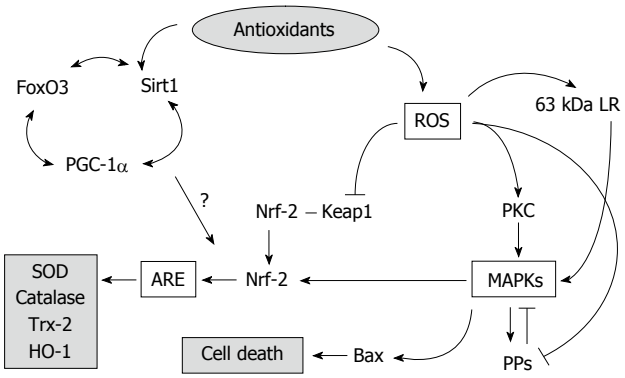

Figure 1 Oxidative stress-stimulating signaling pathways. The oval with the gray indicates the start point; gray boxes indicate consequences; other boxes indicate key substances. ARE: Antioxidant responsive element; FoxO3: Forkhead winged-helix box class O3 transcription factor; HO-1: Heme oxygenase-1; Keap1: Kelch-like ECH-associated protein 1; LR: Laminin receptor; MAPK: Mitogen-activating protein kinase; Nrf2: NF-E2-related factor-2; PGC-1α: Peroxisome proliferator-activated responsive element γ coactivator-1α; PKC: Protein kinase C; PP: Protein phosphatase; ROS: Reactive oxygen species; Sirt1: Sirtuin 1; SOD: Superoxide dismutase; Trx: Thioredoxin.

suggest that phytochemicals could potentially have a comprehensive preventive effect on ALD. However, the physiological activities of phytochemicals in the prevention of ALD have not been well recognized.

In this review, we discuss the physiological activities of phytochemicals and the mechanisms for cell injury, the regulation of antioxidant and pro-oxidant enzyme expression, and concomitant intestinal permeability. Herein, "antioxidants" are defined as the phytochemicals that elicit or enhance the antioxidant defense system, regardless of their radical scavenging activity. Because information regarding the effects of antioxidants in ALD patients or animal models is insufficient for discussion, various oxidative stress models in animals and cells are included. In particular, the mechanisms of non-alcoholic fatty liver disease (NAFLD) may comprise, in part, the mechanisms of ALD because these two diseases likely share many common pathways[31].

MECHANISMS OF LIVER INJURY FROM ALCOHOL CONSUMPTION

As a cause of oxidative stress, ROS are generated by pro-oxidant enzymes, such as CYP2E1 in hepatocytes[7,52,53] and NADPH oxidase (NOX) in Kupffer cells (liver-dwelling macrophages)[25]. In addition, populations of intestinal bacteria that comprise the intestinal environment have been suggested to be involved in ALD *via* stimulation of the immune system. For example, lipopolysaccharides (LPS) derived from intestinal bacteria[15,24,54] activate NOXs and produce inflammatory cytokines[55-58] in macrophages. Acetaldehyde increases the permeability of LPS between intestinal epithelial cells[15,59,60], which is also involved in the deterioration of ALD. Dietary polyunsaturated fatty acids are also thought to enhance oxidative stress[15,29] and are a source of prostaglandins[61]. In a previous study, ethanol administration increased the plasma prostaglandin E_2 level[62], and some prostaglandins are thought to cause inflammation in NAFLD[61,63]. These data suggest that prostaglandins enhance deterioration of ALD; however, the influence of antioxidants on prostaglandins will not be detailed here.

As shown in Figure 1, oxidative stress stimulates intracellular events *via* the mitogen-activating protein kinase (MAPK)[64] pathway, as initiated by the activation of protein kinase C (PKC)[30,65,66] or the degradation of protein phosphatases (PPs)[67]. These signals activate the Kelch-like ECH-associated protein 1 (Keap1)-NF-E2-related factor-2 (Nrf2) pathway, which leads to antioxidant responsive element (ARE)[45,68-70]. However, MAPK hyperactivation also leads to cell death *via* activation of the Bax/Bcl-2 pathway[71,72]. In addition, antioxidant enzymes have been reported to be induced *via* several intracellular pathways, such as the Keap1-Nrf2-ARE pathway[45,69,70,73] and the Sirt1 (sirtuin-1)-FoxO3 (forkhead winged-helix box class O3 transcription factor)-PGC-1a (PPARγ coactivator-1a) pathway[45,68]. The regulation of Sirt1 and Nrf2 levels has also been reported[45], which implies cross-talk between both pathways, whereas the activation of Sirt1 and resveratrol, an activator of Sirt1, have been reported to inhibit the DNA-binding activity of Nrf2 *via* deacetylation *in vitro*[74]. Taken together, substances that deactivate or normalize MAPKs and/or activate ARE or Sirt1[45,75] are potential candidates for the prevention of ALD, but the mechanisms are unknown.

Antioxidant enzymes and peptides

In mammals, SOD generates hydrogen peroxide, which is catabolized to a hydroxyl radical by catalase and detoxified by GSH in collaboration with GPx[25]. The oxidized glutathione form is recruited to GSH by GR with NAD(P)H[76]. Heme oxygenase-1 (HO-1) contributes to the antioxidant system because of the production of bilirubin as a redox substance.

It has been suggested that the hepatic catalase level is negatively associated with the severity of alcoholic liver injury[10] and that SODs scavenge hydroxyl peroxides generated in the cytosol and mitochondria, thereby terminating autoxidation. Thus, catalase and SODs are essential for the antioxidant system. There are three isozymes of SOD in the cytosol, mitochondria, and extracellular matrix: CuZn-SOD, Mn-SOD, and extracellular SOD. SOD levels have been shown to be regulated by MAPK activity[77]. GSH is not an enzyme but a redox tripeptide that acts as a proton donor. GSH levels, GPx content, and/or GR content were reduced in rats fed ethanol diets and, in some cases, ALD animals[16,23,62] or under other oxidative conditions[3,78]. The FoxO transcriptional factor is involved in GPx and Sirt1 protein expression[79]. These findings indicate that in addition to catalase and SOD, GSH is essential for

reducing hepatic oxidative stress.

Under oxidative conditions, HO-1 appears to be rapidly induced *via* the Keap1-Nrf2 pathway[45,69,80,81]. This enzyme may also be involved in the immune response[55]. Furthermore, in ALD model animals, HO-1 levels have been reported to be reduced[13,16,82]. Adiponectin has received recent attention because of its anti-inflammatory functions *via* Sirt1 activation, HO-1 induction, and NOX suppression in Kupffer cells[55]. However, the blood concentration of this adipokine was higher in ALD patients compared with controls[83] or equal to the controls in ALD animals[84], which suggests that adiponectin may be less effective against ALD than antioxidants.

Thioredoxin (Trx) is a ubiquitous scavenger of oxidative species. Endogenous Trx is reported to be reduced by ethanol ingestion; however, the levels can be restored by supplementation with exogenous Trx, which has been demonstrated to ameliorate the symptoms of ALD[84]. Because Trx is a peptide, it must be digested in the digestive system, indicating that it is difficult for exogenous Trx to directly scavenge hepatic ROS.

Pro-oxidant enzymes

In microsomes, CYP2E1 is a phase Ⅰ enzyme of drug metabolism that adds a hydroxyl residue to chemicals to increase hydrophilia and may generate ROS[7-9]. Chronic ingestion of ethanol and other small chemicals increase hepatic CYP2E1. CYP2E1 induction has also been demonstrated in animals with NAFLD[52,85] and hepatic insufficiency. Insulin signaling may suppress CYP2E1 expression[53] *via* the Akt pathway but not the MAPK pathway[86], with subsequent expression of certain microRNAs[87].

Macrophage-like cells, including Kupffer cells, express NOXs and generate ROS with the consumption of NAD(P)H[24] to eliminate xenobiotics[25]. Many isoforms of NOXs have been identified, and NOX-2 is uniquely expressed in phagocytes. NOX expression was regulated *via* the Keap1-Nrf2 pathway in a mouse glial-neural co-cultured system[88] in which NOX-2 predominantly caused oxidative stress. In ALD animals, NOX-2 in Kupffer cells was activated by LPS[55]. In addition, Kupffer cells produce inflammatory cytokines[13,24,55], such as tumor necrosis factor alpha (TNF-α) and interleukin-6. Thus, the reduction of NOXs and inflammatory cytokines are important for ALD.

Given the gut-liver axis in ALD, intestinal conditions play a considerable role in ALD severity, particularly conditions mediated by LPS[15,60]. In the large intestine in humans (or the cecum in animals), an enormous number of intestinal bacteria live and ferment undigested food matter, flaked epithelial cells, and digestive fluid[25]; some of these species generate LPS, which provokes the host's immune system[15]. Small amounts of LPS can pass through gaps in the epithelial cells into the intestine. Ethanol or its metabolites are reported to widen this gap[15,59]. Therefore, improving intercellular junctions or reducing LPS-producing bacteria may have a partial preventive effect on ALD[15].

PLANT ANTIOXIDANTS

Classification of plant antioxidants

Figure 2 shows the structures of representative antioxidants abundant in fruit and vegetables. Polyphenol is a generic name for compounds that have a mono- or polycyclic structure with hydroxyl residues. Flavonoids, including anthocyanins, catechins, and flavonols, form one of the largest groups of polyphenols. Anthocyanins have a red, purple, or blue color in grapes[42], berries[34], seed coats[89], and root crops[37,77]. Catechins include epicatechin, epigallocatechin, and epigallocatechin galate (EGCG) and are sometimes referred to as "tannins"[35]. Proanthocyanidins are polymers of catechins (but not anthocyanin despite the similarity in names); they are categorized as catechins and are widely abundant in crops, particularly tea[27,90], apples[91], and grapes[92]. Quercetin, kaempferol, and isorhamnetin belong to the flavonol group and are ubiquitous in plants. Narirutin and hesperidin belong to the flavanone group and are abundant in the albedo of citrus peel[14,23]. Resveratrol is categorized as a stilbenoid, a phytoalexin, and is present in wine[93] and grapes[42]; it has recently received substantial attention for its physiological functions. Chlorogenic acid is a caffeic acid derivative and one of the most widely consumed polyphenols because of its abundance in coffee and other plants. Alkaloids, such as berberine[46], are also included in the polyphenol group. Curcumin, a curcuminoid present in turmeric, has a yellow color and also belongs to polyphenols.

Lignans, a terpenoid whose metabolites exert estrogenic activity in the lumen, as well as isoflavones and coumestans possess antioxidant activity. Sulfide and thiocyanate compounds are present in garlic[12,82], onions[47], and *Brassicaceae* plants[16] and are reported to be chemopreventive.

PROVOCATION OF THE ANTIOXIDANT SYSTEM BY PLANT ANTIOXIDANTS AND PLANT EXTRACTS

Flavonoids

In animal models, quercetin ameliorated lipid metabolism and ethanol-induced liver damage by inducing antioxidant enzymes, increasing GSH levels, and reducing CYP2E1 activity[20,39]. Quercetin also inhibited the activity and expression of CYP2E1 in human hepatocytes[20,94], which was consistent with *in vivo* findings. In non-alcoholic steatohepatitis animals, quercetin ingestion increased hepatic catalase, SOD, GPx, and GR activities and the GSH level[21] and reduced hepatic lipid accumulation and CYP2E1

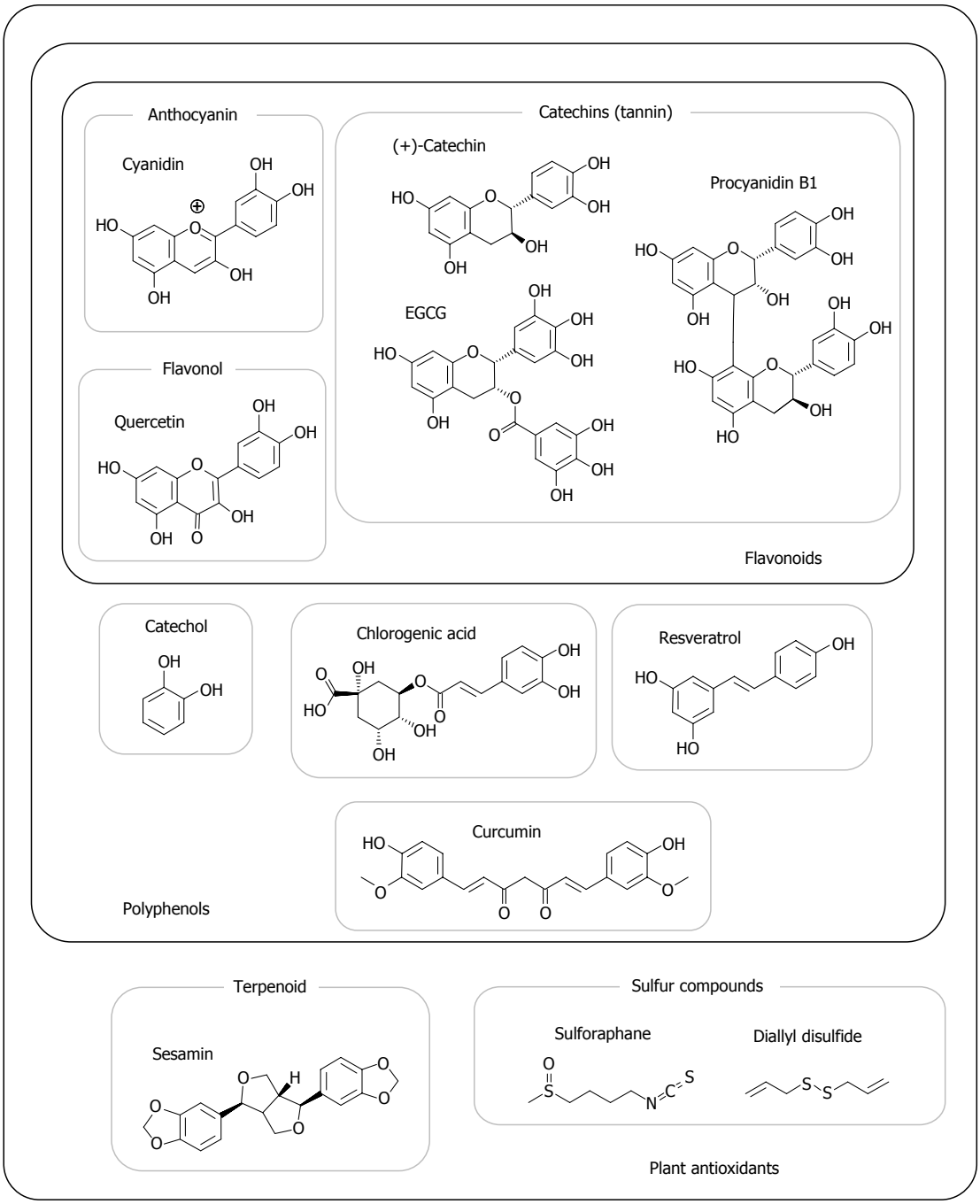

Figure 2 Structures of representative plant antioxidants and their classification.

expression[21,85]. A computer simulation predicted the involvement of quercetin in PGC1a and PNPLA3[31]. Furthermore, hyperoside (quercetin-3-O-galactoside) has been reported to increase cell viability and HO-1 activity *via* MAPKs and ARE[95] in L-02 cells.

Pigments from grapes[42], colored potatoes[77], and black soybean seed coats[89] that contain abundant anthocyanin have been reported to induce antioxidant enzymes *via* the alteration of MAPK activities in cells in other oxidative conditions. An anthocyanin fraction from bilberries appears effective in improving lipid metabolism *via* the AMP-activated protein kinase pathway[96]; however, its involvement in ALD has not been assessed. Alcohol-free red wine increased the blood antioxidant capacity in a human study[97], which suggests a preventive function of the polyphenol fraction in red wine against ALD. However, other studies have demonstrated that alcohol-free red wine worked with ochratoxin A to increase the intercellular permeability in Caco-2/TC7 cells[98], and alcohol-containing red wine increased hepatic and renal CYP2E1 expression in rats, whereas ethanol did not[99]. Malvidin, an anthocyanin in red wine, has been reported to attenuate MAPK activity, which was

promoted by LPS[64], and to enhance PP activity in RAW 264.7 macrophage cells. An anthocyanin-rich extract from colored potato increased Mn-SOD expression *via* extracellular signal regulated kinase (ERK) activation in HepG2 cells[77]. It has also been reported that an ethanol-induced acute gastric lesion was prevented by the ingestion of strawberry extract rich in anthocyanin prior to ethanol treatment *via* the induction of gastric antioxidant enzymes[34].

In animal studies, catechin- and tannin-rich extracts from pecan nut shells improved ALD symptoms by restoring antioxidant enzymes[35,38]. A tea extract rich in catechins reduced CYP2E1 expression and hepatic lesion *via* paracetamol injection[92], and a diet that contained EGCG improved hepatic injury; although there was no reduction in hepatic CYP2E1 levels[100]. In a clinical study, EGCG-rich green tea and its extract also increased the blood GSH level[90]. The ingestion of green tea extract also restored antioxidant activity in the brain that had been decreased by ethanol and aging[28]. Furthermore, catechins have been reported to suppress the expression of NOX and inflammatory cytokines in macrophages[56], dendrocytes[57], and human cerebral microvascular endothelial cells (hCMEC)[101] as well as restore antioxidant enzymes in human neuroblastoma cells[102]. Catechins have both antioxidant and pro-oxidant activities. They have recently been reported to stimulate the 63 kDa laminin receptor[56,57,101,103], which ROS may initiate[104], and consequently to calm over-activation of the immune system *via* the inactivation of the Toll-like receptor (TLR) 2 and 4 pathways. TLR 4, in particular, plays a central role in Kupffer cell stimulation with LPS and the induction of ALD deterioration[57]. Dietary catechins may thus contribute to the impairment of ROS generation *via* LPS and the prevention of ALD.

Citrus flavonoids, narirutin, and glycosylated citrus flavonoids also improved ALD and reduced inflammatory cytokine levels[14,23].

Other phenolic antioxidants and non-phenolic antioxidants

Resveratrol (Figure 2) restores or induces antioxidant enzymes in ALD model rats[93], lung fibroblasts[105], and rats with spontaneous hypertension[75] and diabetes[44,73] *via* the activation of sirtuins in some cases. *In vitro*, resveratrol stimulated HO-1 induction *via* the MAPK-Nrf2 pathway in PC12 cells[81]. Thus, red wine consumption is likely to be superior to other alcoholic beverages in the prevention of ALD. Resveratrol concentrations in wine may be insufficient to prevent ALD; however, it may be responsible for the "French paradox"[106]. Resveratrol has been reported to activate monocytes and produce inflammatory cytokines *in vitro*, which indicates that provoking the immune system with resveratrol may not prevent the deterioration of ALD[107]. Thus, excessive red wine consumption should not be recommended. Polydatin, a resveratrol glycoside, stimulates Sirt1 and Nrf2 and induces antioxidant enzymes in glomerular cells[45].

Chlorogenic acid (Figure 2) and caffeic acid restored the hepatic activity of SOD and GPx and hepatic injuries promoted by methamphetamine injection for 7 d[43].

Honokiol, identified in *Magnolia officinalis*[19], improved ALD, restored the hepatic GSH content and SOD activity, and reduced inflammatory cytokine levels in an ALD animal model[19].

Hispidin, a fungal polyphenol with PKC-inhibitory activity, increased HO-1 and catalase activities in H9c2 cardiomyoblast cells[65].

Berberine is a benzyl isoquinoline alkaloid in the *Coptis* genus that has been reported to reduce ALD symptoms, increase levels of GSH and PGC1a, and normalize CYP2E1 expression in the livers of animals fed an alcohol-containing diet[46].

The sulfur-containing compounds (Figure 2) diallyl disulfide and garlic oil have been reported to improve alcoholic hepatic injury[12] by increasing HO-1 levels *via* the Nrf2 pathway and increasing the GSH level *in vivo*[82] and *in vitro*[94]. A similar preventive effect has also been identified in diallyl sulfide treatment in astrocytes[30]. Sulforaphane has been reported to act as an inducer of HO-1[16], which suggests that these compounds may be useful in the treatment of ALD. In addition to restoring HO-1 levels, sulforaphane improved hepatic lipid accumulation in ALD animals[16]. The consumption of onion powder, which is rich in sulfide compounds and flavonols, has also been reported to reduce hepatic CYP2E1 levels in normal rats[47].

Oleanolic acid, a triterpenoid, restored antioxidant enzymes and increased nucleic Nrf2 levels and improved ALD[13]. Sesamin (Figure 2) is a well-characterized terpenoid in sesame seeds that may contribute to the reduction of fatty liver by promoting β-oxidation of fatty acids and inducing hepatic aldehyde dehydrogenase[108,109]. Maslinic acid, a triterpenoid rich in basil, brown mustard, and other plants, has been reported to protect hepatic injury *via* acute ethanol toxicity[62]. These data suggest that some types of terpenoids may improve the symptoms of ALD.

Curcumin (Figure 2), but not resveratrol, has been reported to restore hepatic antioxidant enzymes reduced by aflatoxin in rats[110]. Curcumin also increased antioxidant enzymes as well as Nrf2 and HO-1 levels in quails under heat stress[111].

Mangiferin, identified in mango[112], is a xanthine derivative that has been reported to restore pulmonic and hepatic antioxidant enzyme levels reduced by benzo(a)pyrene in mice[3].

Plant extracts that contain significant amounts of antioxidants also prevent oxidative damage in various other organs. An extract from black tea[27] improved ALD symptoms in rats. The extracts from apples[91], *Amorphophallus commutatus*[40], cinnamon[113], and hibiscus[22,41] partially normalized hepatic oxidative

stress induced by chemical toxins.

Improvement of fatty acid accumulation

Alcoholic fatty liver is a predictive symptom of ALD, and hepatic inflammation is also present in non-alcohol steatohepatitic animals[21,41,52]. Moreover, a computer simulation predicted many common pathways between alcoholic fatty liver and NAFLD that were associated with inflammation, lipid metabolism, and some immunity[31]. These data suggest that a reduction in lipids in the liver may lead to an improvement in liver injuries[16,19,100]. In addition to the induction of antioxidant enzymes, some plant antioxidants have recently been reported to improve lipid metabolism and reduce hepatic lipid accumulation[19,39,46], which may also contribute to the amelioration of ALD.

Improvement of intestinal permeability by plant antioxidants and plant extracts

Antioxidants, such as quercetin, resveratrol, EGCG, and naringenin, prevent the downregulation of junction proteins, namely, Zo-1 and/or Occludins, and consequently enhance intercellular barrier functions *in vitro*[49] and *in vivo*[50]. In contrast, EGCG has been reported to disturb the barrier function of hepatic epithelial cells[114] because of ROS-induced ERK activation. In addition to intestinal cell models, cocoa polyphenol extract improved barrier functions disturbed by a high glucose condition in retinal pigment epithelium cells[51]. Cocoa polyphenol extract and resveratrol also attenuated the permeability of renal cell junctions *in vitro*[48,115], and EGCG increased the adhesion of hCMEC[101]. The tightness of cellular junctions regulated by antioxidants may be involved in the severity of ALD and should be elucidated.

Mechanisms for ALD prevention via plant antioxidants

Cellular oxidative stress is caused by many factors, such as exposure to humoral factors[22,75], enzymatic generation of ROS[7-9,24], metabolites of chemicals[41,91,102,116], or the mitochondrial respiratory chain[39]. Two major mechanisms may be proposed for hepatic injury prevention *via* oxidation: (1) the impairment of oxidative signaling that leads to cell death; and (2) the activation of the Keap1-Nrf2 pathway, which results in the induction of antioxidant enzymes.

As a leading mechanism, "preconditioning" in ischemia-reperfusion models has been proposed to alleviate tissue damage. In ischemia-reperfusion models, excessive ROS are present following reperfusion, whereas slight ischemic-reperfusion pretreatment to tissues or cells alters MAPK activities and interferes with cellular damage[117-119]. It has been reported that ROS stimulate PKC, MAPKs, and subsequent events that lead to cell death[89] or induce an antioxidant system (Figure 1). MAPKs appear to activate both PPs[66,120] and Nrf2[69]. Once activated, PPs may deactivate not only MAPKs but also other phosphorylated proteins related to the MAPK signaling pathways[66], which may lead to a comprehensive impairment of MAPK signaling. Despite their antioxidant activity, polyphenols also have a slight pro-oxidant activity[72,121]. This impact may increase MAPK and PP activity[103] or PP stability[120] prior to crucial oxidative stress by ROS. At minimum, PPs activated by antioxidants may partially inhibit MAPK pathway activation. Following pretreatment with plant antioxidants, the hyperactivation of MAPKs by injuring stimuli appears to decrease[22,41,48,64]. These findings may support the preconditioning hypothesis[1]. Taken together, ROS and/or MAPK are key regulators of both cell injury and antioxidant enzyme induction.

In addition, this mechanism can explain the effects of antioxidants on the barrier functions of epithelial cells. Junction proteins and the intercellular barrier function are disturbed by oxidative stress[48,114]. Antioxidants have been reported to exhibit minimal activity to generate ROS[114,121] and subsequently activate MAPKs, which disturbs barrier function *in vitro*[114]. However, antioxidant pretreatment may diminish excessive oxidative stress, as previously discussed, which leads to the protection of barrier function[49,50].

It has been suggested that ROS (and electrophilic reagents) directly activate the Keap1-Nrf2 pathway. Keap1 is a sensor of intracellular oxidative stress and couples with Nrf2[122]. Once Keap1 is oxidized, Nrf2 is released, moves to the nuclei, and activates ARE. Regarding the relationship between chemical structures and antioxidant activities, it has been suggested that electrophilic compounds, such as flavonoids, curcumin, and thiocyanate-related compounds, stimulate the Keap1-Nrf2 pathway[122]. Satoh *et al*[123] proposed the importance of ortho- or para-positions of hydroxyl residues in the benzene structure, which result in hydroquinone and catechol, respectively (Figure 2), because of their electrophilic residue. Some flavonoid compounds have a catechol structure (Figure 2), which indicates an interaction between flavonoids and Keap1. These results may support the hypothesis proposed by Satoh *et al*[123].

This hypothesis suggests that antioxidants directly activate Keap1. However, some antioxidants appear to induce antioxidant enzymes *via* MAPK activation despite the upper proteins of Keap1 (Figure 1), as demonstrated with specific inhibitors of MAPKs that diminished the induction[77] or activation of Nrf2[81]. Antioxidants may contribute to the induction of antioxidant enzymes *via* MAPK pathways rather than through direct activation of Keap1. Moreover, resveratrol has a resorcinol structure rather than a catechol structure. Resorcinol has less electrophilic activity than catechol[123]; however, it appears to stimulate Nrf2[122]. This mechanism must also be elucidated.

In *in vivo* studies, the ingestion of antioxidants induces (or tends to induce) antioxidant enzymes in the lung[3], thymus[124], brain[28,125], and kidney[45], despite very low concentrations in the bloodstream[2,36,37].

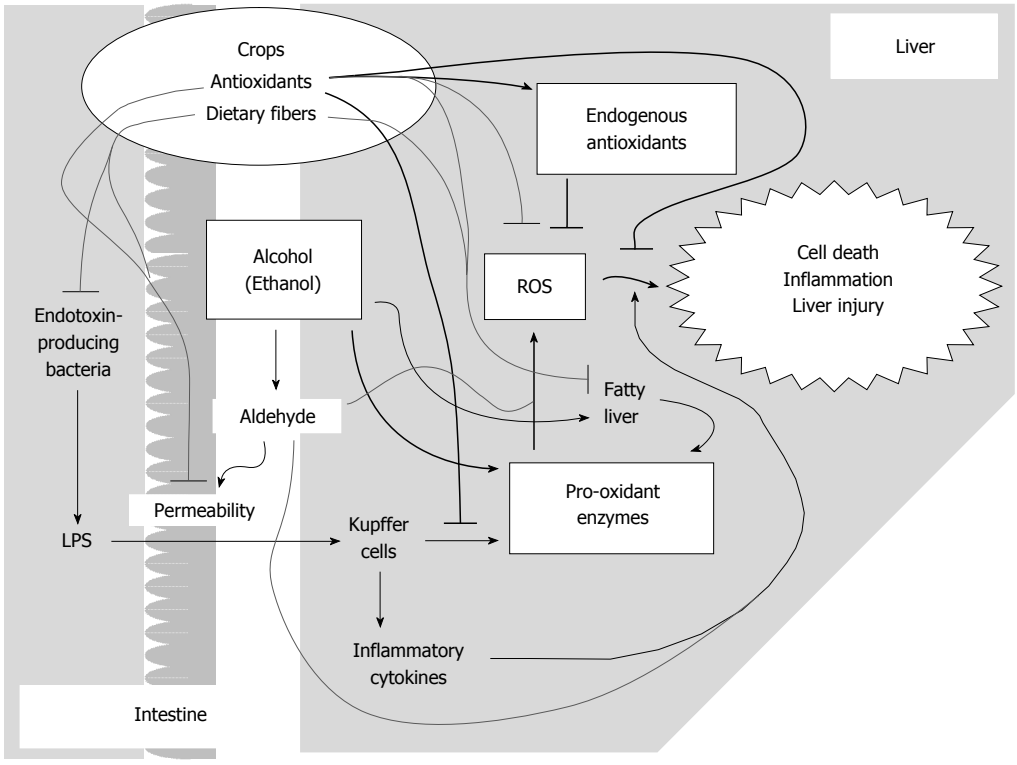

Figure 3 Potential multiple effects of crop components on alcoholic liver disease. LPS: Lipopolysaccharide; ROS: Reactive oxygen species.

These reports imply that there is an intermediate signal by polyphenols, such as nerve and/or humoral pathways, rather than direct stimulation of cells or organs; they may also be explained by remote ischemic preconditioning[117]. This preconditioning suggests that some types of stimuli can regulate MAPK activities in remote organs.

PERSPECTIVE

Even ubiquitous plant antioxidants, such as anthocyanins and flavonols, appear to have many physiological activities, indicating that botanical substances can provoke the antioxidant system. Apart from oxidative stress *via* lipid accumulation, lipids also appear to be a central cause of ALD. For example, prostaglandins, which are initiated by phospholipase (PL) A_2 and activated by cyclooxygenases[61], are involved in inflammatory events, and PNPLA3 has been suggested to have PLA_2 activity and to regulate hepatic lipid accumulation[63]. Therefore, the regulation of prostaglandins and/or expression of their related proteins may be critical for the improvement of ALD.

Fruits and vegetables are great sources of antioxidants as well as dietary fibers (DFs)[126], which were once considered to be unwanted materials or non-nutrients. It is now well established that the ingestion of DFs improves lipid metabolism and reduces hepatic lipids[127,128]. Some types of DFs, particularly water-soluble fibers, promote the excretion of lipids into feces and the synthesis of short-chain fatty acids (SCFA) in the intestine[126,129], which are proposed as prebiotics. Oral ingestion of butyrate, a type of SCFA produced from DF, promotes junction protein expression and an increase in intestinal barrier function[130]. These findings also suggest the potential of DFs in the prevention of ALD. Thus, intact fruits and vegetables, including both antioxidants and DF, are worthy of consideration for ALD prevention.

Mammals often intrinsically treat plant chemicals as xenobiotics and have developed metabolic systems against phytochemicals[1]. The human body evolved with environmental factors, including phytochemicals and DFs. The data reviewed here imply the necessity for the unwanted materials to elicit an accomplished defense system, a barrier function in the intestine and a chemical metabolizing system in the intestine, and liver against xenobiotic substances.

However, most of these data are derived from animal and cell studies. In these studies, antioxidants may, in some cases, be overdosed[75], which makes it difficult to justify their effectiveness in humans, particularly ALD patients who may have impaired liver functions[11]. As previously reported, vitamin E supplementation only partially improved ALD[32,33] despite its effectiveness in cell studies. Thus, it is important for future studies to accumulate clinical data regarding the relationships among ALD, antioxidants, and antioxidant enzymes.

In conclusion, plants have a potential role in the prevention of ALD (Figure 3). Although most individuals are aware that abstinence from alcohol is the most

effective way to prevent ALD, it is recognized that this is not easy. Therefore, it is important to improve our defense system against ALD. Many types of plant antioxidants with electrophilic activity may activate antioxidant enzymes or peptides under oxidative conditions and alleviate ALD, which may occur *via* a mechanism that is somewhat similar to preconditioning in ischemia-reperfusion models[117-119]. The antioxidants reviewed here are common in vegetables and fruits, which can be easily consumed. Moreover, plants contain abundant amounts of DF and vitamins. Vitamins are wasted by binge drinking[27,28], and DFs can improve lipid metabolism and intestinal conditions[127,128] in mammals. Therefore, non-processed food materials may have considerable intrinsic potential. Clearly, ALD patients should be administered appropriate medications to facilitate recovery from crucial damage. However, fresh vegetables and fruits may be more effective than processed foods in comprehensively preventing hepatic damage induced by alcohol. Antioxidants commonly taste bitter, and DFs appear to exhibit a bad texture; thus, they have been eliminated from foods over centuries. However, humans have evolved alongside phytochemicals and DFs to overcome these issues. Thus, an approach that elicits the intrinsic potential of the human body to prevent ALD and other lifestyle-related disorders should be reconsidered.

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