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**Relationship among alcoholic liver disease, antioxidants, and antioxidant enzymes**

Han KH *et al*. ALD and antioxidants

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**Abstract**

Alcoholic beverages are a serious cause of liver disease in many countries. The ethanol metabolic process generates reactive oxygen species, considered to 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 Keap1-Nrf2 pathway and antioxidant responsive elements. Furthermore, these antioxidants are reported to alleviate cell injury caused by oxidants or inflammatory cytokines. These phenomena are likely exerted *via* regulation of mitogen-activating protein kinase (MAPK) pathways by plant antioxidants, similar to preconditioning in ischemia-reperfusion models. Although the relationship of plant antioxidants with ALD patients is not well studied, plant antioxidants may be preventive for ALD because of their electrophilic and regulating activities of the MAPK pathway.

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

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**Core tip:** The ethanol metabolic process generates reactive oxygen species, which are considered to play a significant role in the deterioration of alcoholic liver disease (ALD). Antioxidant phytochemicals such as polyphenols often up-regulate the expression of antioxidant enzymes and peptides *via* the Keap1-Nrf2 pathway, leading to antioxidant responsive elements in animal models. Furthermore, these antioxidants are reported to alleviate cell injury caused by oxidants or inflammatory cytokines by impairment of hyperactivation of mitogen-activating protein kinase pathways, similar to preconditioning in ischemia-reperfusion models. Although the relationship between plant antioxidants and ALD is not well studied, plant antioxidants may be preventive for ALD.

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**INTRODUCTION**

We are surrounded by many chemicals, including nutrients, phytochemicals, food additives, pharmaceuticals, and drugs. The intestine and liver absorb and metabolize many kinds of chemicals[1] for utilization or detoxification[2]; however, some become more toxic after metabolism[3]. Ethanol, found in alcoholic beverages, is one of the commonest and most abundant chemicals in daily life. Ethanol can bring relaxation and some other benefits, but over-consumption may harm drinkers’ bodies, minds, and even lives. Moderate consumption of alcohol may reduce risks of cardiovascular disease[4] and even non-alcohol fatty liver disease[5]; and with moderate intake, most of the ethanol is oxidized by alcohol dehydrogenase and catabolized to acetaldehyde, which is then catabolized to acetate by aldehyde dehydrogenase in the mitochondria. However, with binge drinking, ethanol will largely be metabolized to acetaldehyde by cytochrome P450, family 2, subfamily E, polypeptide 1 (CYP2E1), the microsomal ethanol-oxidizing system[6] that is reported to be involved in the generation of reactive oxygen species (ROS)[7-9]. Despite much evidence of the involvement of CYP2E1 in alcoholic liver disease (ALD), some of our studies have shown that hepatic CYP2E1 levels were significantly induced by feeding ethanol-containing diets without an increase in plasma alanine aminotransferase (ALT) activity (unpublished data). These results suggest the existence of a potent endogenous antioxidant system that can prevent potential damage by excessive expression of CYP2E1[10].

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

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

As a trend in gastronomic culture, low molecular weight phytochemicals have been excluded during plant breeding or processing because of their toxicity, taste, or deteriorating color. Recently, however, phytochemicals have received attention for their physiological activities in mammals. Many kinds of phytochemicals abundant in fruit and vegetables are known to have antioxidant activity. Although there has been a focus on phenolic compounds for 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]. On the other hand, many kinds 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 sometimes to improve lipid metabolism[12,16,44,46] in various organs. In addition, some of phytochemicals change both phase I and phase II enzymes of drug metabolism including CYP2E1[7,13,16,47]. Recent reports show that some polyphenols can also improve epithelial cell junctions[48-51], suggesting involvement in the hepatic immune response. These findings suggest a possibility that phytochemicals could potentially have a comprehensive preventive effect on ALD. However, such physiological activities of phytochemicals against ALD appear to be little recognized.

In this review, therefore, we will discuss in particular the physiological activities of phytochemicals and the mechanisms for cell injury, the regulation of expression of antioxidant and pro-oxidant enzymes, and concomitant intestinal permeability. In this review, “antioxidants” are defined as the phytochemicals that elicit or enhance antioxidant defense system, regardless of their radical scavenging activity. Because the information on the effects of antioxidants on ALD patients or animal models is not sufficient to discuss, various oxidative stress models of animals and cells will be also covered. In particular, mechanisms of non-alcoholic fatty liver disease (NAFLD) may be partly available to those of ALD because of prediction of many common pathways between them[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, intestinal environments including populations of intestinal bacteria have also been suggested to be involved in ALD through stimulating the immune system, as lipopolysaccharides (LPS) derived from intestinal bacteria[15,24,54] activate NOXs and produce inflammatory cytokines[55-58] in macrophages. Acetaldehyde can increase 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 believed to enhance oxidative stress[15,29] and are source of prostaglandins[61]. In a previous study, administration of ethanol increased plasma prostaglandin E2 level[62], and some prostaglandins are believed to cause inflammation in NAFLD[61,63]. These data suggest deterioration of ALD by some prostaglandins, although 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 initiated by the activation of protein kinase C (PKC)[30,65,66] or by degradation of protein phosphatases (PPs)[67], and the signals further activate the Keap1 (Kelch-like ECH-associated protein 1)-Nrf2 (NF-E2-related factor-2) pathway leading to antioxidant responsive element (ARE)[45,68-70]. However, hyperactivations of MAPKs also lead 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 levels along with Nrf2 levels has been also reported[45], implying cross-talk between both pathways, whereas activation of Sirt1 and resveratrol, an activator of Sirt1, have been reported to inhibit the DNA-binding activity of Nrf2 by deacetylation *in vitro*[74]. Taken together, substances deactivating or normalizing MAPKs and/or activating ARE or Sirt1[45,75] are possible candidates for the prevention of ALD with uncertain mechanism.

***Antioxidant enzymes and peptides***

In mammals, SOD generates hydrogen peroxide, which is catabolized to 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) appears to contribute to the antioxidant system because of production of bilirubin as a redox substance.

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

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

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

***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 induce hepatic CYP2E1. Induction of CYP2E1 has also been observed in animals with NAFLD[52,85] with hepatic insufficiency. Insulin signaling may suppress CYP2E1 expression[53] *via* the Akt pathway but not the MAPK pathway[86], with consequent 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. The expression of NOXs was regulated *via* the Keap1-Nrf2 pathway in a mouse glial-neural co-cultured system[88] in which NOX-2 predominantly appeared to cause 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-α (TNF-α) and interleukin-6. Thus, reduction of NOXs and inflammatory cytokines are important for ALD.

Given the gut–liver axis in ALD, intestinal conditions have considerable involvement in ALD severity, particularly 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], and some of those 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 the gap[15,59]. Therefore, improving intercellular junctions or reducing the LPS-producing bacteria may have a partial preventive effect on ALD[15].

**PLANT ANTIOXIDANTS**

***Classification of plant antioxidants***

Figure 2 shows structures of representative antioxidants abundant in fruit and vegetables. Polyphenol is a generic name for compounds that have a mono- or polycyclic structure with some hydroxyl residues. Flavonoids, including anthocyanins, catechins, and flavonols, form one of the largest groups of polyphenols. Anthocyanins have red, purple, or even a 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 too 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 flavanone group, and are abundant in the albedo of citrus peel[14,23]. Resveratrol is categorized as a stilbenoid, a phytoalexin, and is found in wine[93] and grapes[42]; recently, it has received much attention for its physiological functions. Chlorogenic acid is a caffeic acid derivative and one of the most widely consumed polyphenols because it is abundant in coffee and in other plants. Some alkaloids such as berberine[46] are also included in the polyphenol group. Curcumin, a curcuminoid found in turmeric with a yellow color, and also belongs to polyphenols.

Lignans, a terpenoid, the metabolites of which exert estrogenic activity in the lumen as well as isoflavones and coumestans, possess antioxidant activity. Sulfide and thiocyanate compounds are found in garlics[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 and GSH levels and reducing CYP2E1 activity[20,39]. Quercetin also inhibited the activity and expression of CYP2E1 in human hepatocytes[20,94], which supported *in vivo* studies. In non-alcoholic steatohepatitis animals, ingestion of quercetin induced activities of hepatic catalase, SOD, GPx, and GR and GSH level[21] and reduced hepatic lipid accumulation and CYP2E1 expression[21,85]. A computer simulation predicted involvement of quercetin in PGC1a and PNPLA3[31]. Hyperoside (quercetin-3-O-galactoside) was reported to increase cell viability and to induce 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] containing abundant anthocyanin have been reported to induce antioxidant enzymes *via* the alteration of MAPK activities in cells under 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 blood antioxidant capacity in a human study[97], suggesting a preventive activity of polyphenol fraction in red wine against ALD. However, other studies have shown that alcohol-free red wine worked with ochratoxin A to increase in intercellular permeability in Caco-2/TC7 cells[98] and that alcohol-containing red wine increased hepatic and renal CYP2E1 expression in rats, although ethanol itself did not[99]. Malvidin, an anthocyanin in red wine, was 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 induced Mn-SOD by activating ERK in HepG2 cells[77]. It has also been reported that an ethanol-induced acute gastric lesion was prevented by ingestion of strawberry extract rich in anthocyanin prior to ethanol treatment, by the induction of gastric antioxidant enzymes[34].

In animal studies, catechin- and tannin-rich extracts from pecan nut shells improved ALD symptoms with the restoration of antioxidant enzymes[35, 38]. A tea extract, rich in catechins, reduced CYP2E1 expression and hepatic lesion by paracetamol injection[92], and a diet containing EGCG improved hepatic injury, but without a reduction of hepatic CYP2E1 levels[100]. In a clinical study, EGCG-rich green tea and its extract also increased blood GSH level[90]. Ingestion of green tea extract even recovered antioxidant abilities in the brain that had been lowered by ethanol and aging[28]. In addition, catechins are reported to suppress the expression of NOX and inflammatory cytokines in macrophages[56], dendrocytes[57], and human cerebral microvascular endothelial cells (hCMEC)[101], and to restore antioxidant enzymes in human neuroblastoma cells[102]. Catechins have not only antioxidant but also pro-oxidant activity. 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* inactivation of Toll-like receptor (TLR) 2 and 4 pathways. TLR 4, in particular, plays a central role in stimulating Kupffer cells with LPS and in causing a deterioration in ALD[57]. Dietary catechins may thus contribute to impairing ROS generation by LPS and to preventing 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***

It is suggested that resveratrol (Figure 2) restores or induces antioxidant enzymes in ALD model rats[93], lung fibroblasts[105], and rats with spontaneous hypertension[75] or diabetes[44,73], in some cases *via* activation of sirtuins. *In vitro*, resveratrol stimulated HO-1 induction *via* the MAPK-Nrf2 pathway in PC12 cells[81]. Thus, red wine consumption is possibly better than other alcoholic beverages at preventing ALD. Resveratrol concentrations in wine may be insufficient to prevent ALD, although it may be responsible for the “French paradox”[106]. However, resveratrol reportedly activates monocytes and production of inflammatory cytokines *in vitro*, which means 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 restore hepatic activity of SOD and GPx and hepatic injuries promoted by injection of methamphetamine for 7 d[43].

Honokiol, identified in Magnolia officinalis[19], improved ALD in an animal model, and restored 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, induced activities of HO-1 and catalase in H9c2 cardiomyoblast cells[65].

Berberine is a benzyl isoquinoline alkaloid in the *Coptis* genus and was reported to reduce ALD symptoms, to induce the GSH level and PGC1a, and to normalize CYP2E1 expression in the liver in animals fed with an alcohol-containing diet[46].

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

Oleanolic acid, a triterpenoid, restored antioxidant enzymes and increased nucleic Nrf2 levels with improvement in 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 by acute ethanol toxicity[62]. These data suggest that some kinds of terpenoids also improve symptoms of ALD.

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

Mangiferin, identified in mango[112], is a xanthin derivative and was 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 symptoms of ALD in rats; and 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 predicted symptom of ALD, and hepatic inflammation is also observed in non-alcohol steatohepatitic animals[21,41,52]. Moreover, a computer simulation predicted many common pathways between alcoholic fatty liver and NAFLD, associated with inflammation, lipid metabolism, and some immunity[31]. These data suggest that a reduction in lipids in the liver may lead to improvement in liver injuries[16,19,100]. In addition to 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 additionally contribute to amelioration of ALD.

***Improvement of intestinal permeability by plant antioxidants and plant extracts***

Some antioxidants, such as quercetin, resveratrol, EGCG, and naringenin, prevent down-regulation of junction proteins, namely Zo-1 and/or Occludins, and consequently enhance intercellular barrier functions *in vitro*[49] and *in vivo*[50]; whereas EGCG has been reported to disturb the barrier function of hepatic epithelial cells[114] because of ERK activation by its ROS-generating activity. 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 adhesion of hCMEC[101]. The tightness of cellular junctions regulated by antioxidants may be involved in the severity of ALD; this should be elucidated.

***Mechanisms for prevention of ALD by 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 preventing hepatic injury by oxidation: (1) impairment of oxidative signaling that leads to cell death; and (2) activation of the Keap1-Nrf2 pathway resulting 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 is observed after reperfusion, whereas slight ischemic-reperfusion pretreatment to tissues or cells can alter MAPK activities and interfere with cellular damage[117-119]. It has been reported that ROS stimulates PKC, MAPKs, and subsequent events that lead to cell death[89] or to induce an antioxidant system (Figure 1). MAPKs appear to activate both PPs[66,120] and Nrf2[69]. Once activated, PPs may deactivate not only the MAPKs themselves but also other phosphorylated proteins related to MAPK signaling pathways[66], which may lead to comprehensive impairment of MAPK signaling. Despite their antioxidant activity, polyphenols also have a slight pro-oxidant activity[72,121]. Such an impact may increase the activity of MAPKs and PPs[103] or the stability of PPs[120] prior to crucial oxidative stress by ROS. At the least, PPs activated by antioxidants probably partially break the activation of MAPK pathways. In facts, after pretreatment with plant antioxidants, hyperactivation of MAPKs by injuring stimuli appears to decline[22,41,48,64]. These results may support hypothesis[1]. Taken together, ROS and/or MAPK appear key regulators of both cell injury and the induction of antioxidant enzymes.

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 reported to be disturbed by oxidative stress[48,114]. Antioxidants are reported to have slight activity to generate ROS[114,121] and subsequently to activate MAPKs, disturbing the barrier function *in vitro*[114]. However, pretreatment of antioxidants may diminish excessive oxidative stress as explained above, leading to protection of the 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 is 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, resulting in hydroquinone and catechol, respectively (Figure 2), because of their electrophilic residue. Some flavonoid compounds have a catechol structure (Figure 2), suggesting an interaction between flavonoids and Keap1. These results may support hypothesis.

This hypothesis suggests direct activation of Keap1 by antioxidants. However, some antioxidants appear to induce antioxidant enzymes *via* activation of MAPKs despite the upper proteins of Keap1 (Figure 1), because specific inhibitors for MAPKs 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], but it appears to stimulate Nrf2[122]. This mechanism also needs to be elucidated.

Even in *in vivo* studies, ingestion of antioxidants induces (or tends to) antioxidant enzymes in the lung[3], thymus[124], brain[28,125], and kidney[45], despite very low concentrations in the bloodstream[2,36,37]. These reports imply that there is an intermediate signal by polyphenols, such as *via* nerve and/or humoral pathways, rather than direct stimulation into cells or organs; they may be also explained by remote ischemic preconditioning[117]. The preconditioning suggests that some kinds of stimuli can regulate MAPK activities in remote organs.

**PERSPECTIVE**

As described, even ubiquitous plant antioxidants, anthocyanins and flavonols, appear to have many physiological activities, such that at least botanical substances can provoke the antioxidant system. Apart from oxidative stress by lipid accumulation, lipids themselves also appear to be central cause of ALD. For instance, prostaglandins, which are initiated by phospholipase (PL) A2 and activated by cyclooxigenases[61], are involved in inflammatory events, and PNPLA3 is suggested to have PLA2 activity and to regulate hepatic lipid accumulation[63]. Therefore, regulation of prostaglandins and/or expression of their related proteins may be critical for improvement of ALD.

Fruit and vegetables are great sources not only of antioxidants but also of dietary fibers (DFs)[126], once considered to be unwanted materials or non-nutrients. It is now well established that ingestion of DFs improves lipid metabolism with a reduction in hepatic lipids[127,128]. Some kinds 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], proposed as prebiotics. Oral ingestion of butyrate, a type of SCFA made from DF, promotes the expression of junction proteins and increase in intestinal barrier function[130]. These findings also suggest the potential of DFs in preventing ALD. Thus, intact fruits and vegetables, including both antioxidants and DF, are worthy of consideration for preventing ALD.

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

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

In conclusion, plants have a potential role in preventing ALD (Figure 3). Although most people know that abstinence from alcohol is the most effective way to prevent ALD, it is recognized that this is not easy. It is therefore important to improve our defense system against ALD. Many kinds of plant antioxidants with electrophilic activity may exert antioxidant enzymes or peptides under oxidative conditions and alleviate ALD, which mechanism may be similar in some ways 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 metabolisms and intestinal conditions[127,128] in mammals. Therefore, non-processed food materials may have considerable intrinsic potential. Of course, ALD patients should be administered appropriate medications to help recover from crucial damage. However, fresh vegetables and fruit may be more effective than processed foods in comprehensively preventing hepatic damage by alcohol. Since antioxidants commonly taste bitter and DFs appear to give a bad texture, they have been eliminated from foods over centuries. However, humans have evolved alongside phytochemicals and DFs to overcome such problems. 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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**Figure 1 Oxidative stress-stimulating signaling pathways.** The oval with the shadow indicates the start point; boxes with shadows 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.



**Figure 2 Structures of representative plant antioxidants and their classification.**



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