

# Advances in Compounds that Accelerate Alcohol Metabolism

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**Abstract.** Ethanol is a popular beverage ingredient worldwide and plays an important role in everyday life. The use of ethanol drinks can make a person feel happy, reduce anxiety, and at the same time have a certain addictive nature. However, with the increasing use of ethanol, a series of chronic diseases caused by ethanol, such as ethanol poisoning, have gradually become the focus of attention. The frequency of diseases of the digestive system, nervous system and cardiovascular organisms caused by ethanol and its metabolites acetaldehyde and reactive oxygen species (ROS) is also increasing. Currently, many potential compounds that accelerate alcohol metabolism are still under development, anti-alcohol drugs are rare, and the mechanism of action remains controversial. This article first introduces the metabolic process and distribution of ethanol in the human body, including a small number of gastric first-pass metabolism and major liver metabolism. The roles of alcohol dehydrogenase, catalase and cytochrome P450, the three main oxidative metabolic enzymes, in ethanol metabolism are briefly introduced. Some mechanisms of action of alcoholism and related diseases are expounded, and then the types and pathways of polyphenols, polysaccharides, flavonoids, amino acids and other compounds to promote ethanol metabolism and protect ethanol damage were summarized according to these mechanisms. It is hoped that this paper can provide references for subsequent research.

**Keywords:** Alcohol metabolism, Alcohol injury, Alcohol dehydrogenase, Aldehyde dehydrogenase.

## 1. Introduction

As an important beverage, ethanol is popular all over the world. Whether when having guests or drinking alone, it has been fully integrated into human lives and even into the traditional culture of some countries. Ethanol oxidative metabolism is not regulated but depends only on ethanol catalase and local ethanol concentration. This process reduces nicotinamide adenine dinucleotide (NAD<sup>+</sup>) in cytoplasmic mitochondria, stimulates dopamine neurons to increase the release of dopamine, makes people feel euphoric and happy, inhibits the anxiety and anxiety released by glutamine active activity. However, alcohol has a certain degree of addiction and excessive use of ethanol can cause some adverse effects. Alcohol and its metabolites cannot only directly cause irreversible damage to the human body, but also cause violent crimes, traffic accidents, and increase the burden on society. According to a report by the World Health Organization in May 2022, harmful use of alcohol causes 3 million deaths worldwide each year. In particular, approximately 13.5% of deaths in people aged 20 to 39 years can be attributed to harmful use of alcohol [1].

Ethanol is a small molecule that easily diffuses through biofilms, peaking in the blood within 30–90 minutes of ingestion. 20% of this is absorbed in the stomach and 80% in the upper part of the small intestine. 5-10% of ethanol first undergoes first-pass metabolism in the stomach through alcohol dehydrogenase 7 (ADH7), and the rest enters the liver through the portal vein, and a large part of it enters the blood without being metabolized by the liver, spreads to the whole body, and even passes through the blood-brain barrier, causing various degrees of damage to all organs, and finally circulates back and is mainly (90%) metabolized in the liver [2]. In addition to the toxicity of ethanol itself, acetaldehyde and free radicals produced during its metabolism can also cause more damage to the body.

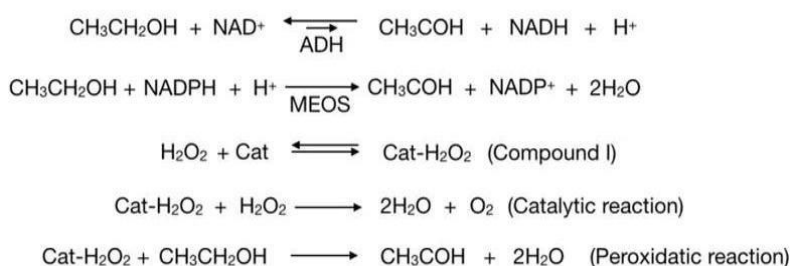
Ethanol poisoning is generally classified into acute and chronic ethanol poisoning. Acute ethanol poisoning usually occurs during a single episode of drinking and is characterized by an initial euphoric phase, flushing or pale face, easy agitation, nausea and vomiting. Then there is the ataxia phase, which is characterized by clumsy movements, unsteady walking, and slurred speech. Finally,

there is the drowsiness period, which is accompanied by paleness, moist skin, blue lips, slowed breathing, and finally death. Chronic ethanol poisoning refers to a series of cardiovascular diseases in the digestive tract, nervous system, and blood systems caused by long-term alcohol exposure. Fatty liver, cirrhosis, addiction, optic neuropathy, memory loss, cognitive confusion, coronary heart disease, stroke, heart failure, and a range of cancers, blood disorders, and reproductive disorders are common [3, 4].

This article will first introduce the main metabolic pathways of ethanol, such as alcohol dehydrogenase pathway, catalase pathway and cytochrome pathway, then briefly introduce the damage mechanism of ethanol and its metabolites to the digestive system, nervous system and cardiovascular system, and finally summarize some compounds that alleviate alcoholism and protect ethanol damage in recent years, such as polyphenols, polysaccharides, branched-chain amino acids, flavonoids, etc.

## 2. Ethanol Metabolism

Most (92-95%) of ethanol metabolism is oxidized, and a small part is non-oxidized. In the first stage of ethanol oxidative metabolism, ethanol is metabolized by alcohol dehydrogenase (ADH), catalase and cytochrome P450 CYP2E1 (also known as MEOS). The metabolic response is shown in Figure 1 [5].



**Figure 1.** Enzymatic-mediated ethanol oxidation [5]

Among them, NAD is often used as a cofactor, but NAD regenerated by NADH needs to be transported through the mitochondrial electron transport chain, so the decrease in NAD/NADH ratio becomes a rate-limiting step for ethanol oxidation. Alcohol dehydrogenase (ADH) is mainly classified into class I-V, alcohol dehydrogenase class I is one of the main enzymes in ethanol metabolism, mainly found in the liver, adrenal glands, kidneys, blood vessels (mainly ADHIB), gastric mucosa (mainly ADHIC) and lungs. The polymorphisms of ADHIB are an important reason for the difference in ethanol oxidation capacity between different populations. ADHII is concentrated in the liver and works better when regulated by high concentrations of ethanol. ADHIV is mainly expressed in the gastric mucosa, upper gastrointestinal tract, and cornea, and ADH7 has a greater influence on first-pass metabolism of the stomach [2]. Catalase plays a negligible role in liver metabolism, but it is the main ethanol-metabolizing enzyme in the brain and increases acetaldehyde levels in the brain. CYP2E1 is metabolized with ethanol in endoplasmic reticulum microsomes on a smooth surface, and elevated CYP2E1 levels with long-term heavy drinking are thought to exhibit ethanol tolerance. Notably, CYP2E1 metabolism produces large amounts of reactive oxygen species (ROS) in addition to acetaldehyde. ROS reacts with reactive nitrogen to form nitrite, peroxy nitrite and superoxide radicals, which are responsible for oxidative damage and can lead to aging and chronic diseases such as cancer and cardiovascular disease.

In the second stage of ethanol oxidative metabolism, acetaldehyde is oxidized to acetic acid by aldehyde dehydrogenase (ADLH). Effects of ethanol intolerance such as flushing, nausea, and dizziness are thought to be caused by elevated acetaldehyde concentrations. Therefore, increasing the activity of ADLH enzymes has become a focus of attention to slow the manifestations of acute alcoholism. In the third stage of oxidative metabolism, acetic acid leaves the liver and enters the peripheral tissues, where it is metabolized as acetyl-coA and eventually turned into carbon dioxide

and water. In addition to these three major oxidative metabolic enzymes, although non-oxidative metabolic pathways play a small role in ethanol metabolism, they can be used to monitor ethanol consumption due to their long half-life.

### 3. Ethanol Injuries and Diseases

Ethanol in the stomach can stimulate abnormal gastric peristalsis, affect the normal metabolism of the gastric mucosa, and cause damage. Ethanol and acetaldehyde also lead to cysteine accumulation and  $\text{Ca}^{2+}$  outflow due to endoplasmic reticulum stress response, and mitochondrial function is impaired, and fat oxidative metabolism is hindered. Thus, they will accumulate in the liver to cause fatty liver or even develop cirrhosis. Acetaldehyde can also bind to amino acids, affect protein function and trigger inflammation. In particular, the binding of acetaldehyde and glutathione reduces the body's antioxidant capacity, and ROS, the most important organ of ethanol metabolism, can induce lipid peroxidation and DNA damage. Ethanol and acetaldehyde can also activate stellate cells to produce myofibroblasts, leading to fibrosclerosis, increasing cytokine secretion, triggering an inflammatory response and promoting apoptosis [3].

In the nervous system, neurons and glial cells are affected by ethanol metabolism, and the diencephalon, cerebral cortex, hippocampus, and white matter are targeted for their myelin content. Changes in TLPs in microglia and macrophages affect the immune regulatory function of brain nerves, which is responsible for and recognizes infection, inflammation and tissue damage, induces the release of cytokines and inflammatory mediators, activates and triggers downstream signaling pathways and transcriptional nuclear factor activation after binding with ethanol, and ultimately leads to overexpression and nerve cell death. Ethanol can also induce cell apoptosis caused by excessive mitochondrial division. ROS also plays a role in nerve damage [4]. In addition, slowing of hepatic ethanol metabolism can exacerbate cerebral ethanol toxicity.

In the cardiovascular system, acetaldehyde causes myocardial damage, while increased pro-inflammatory factors, ROS, mitochondrial dysfunction and endoplasmic reticulum stress lead to muscle hypertrophy and affect cardiac contractility. In addition, long-term alcohol abuse can affect the reproductive system, leading to cancer and blood disorders as well as osteoporosis.

## 4. Compounds That Speed up Ethanol Metabolism

### 4.1. Polyphenols

Polyphenols usually refer to compounds with a molecular weight of more than 600 Da and containing a variety of phenolic hydroxyl structures, mainly derived from plant metabolism. Based on previous experiments, Rosa roxburghii Tratt. Polyphenols, moringa seed polyphenols, cauliflower album L. polyphenols, Clinacanthus nutans polyphenols, seaweed polyphenols (from Ecklonia Cava), monofloral tricochinal honey polyphenols, tea polyphenols, rice bran polyphenols, emblica polyphenols, cinnamon polyphenols have been shown to accelerate alcohol metabolism and protect against alcohol damage. The main effects can be summarized as increasing the activity level of ADH and ALDH, increasing the activity of antioxidant enzymes such as SOD, GSH and CAT, stabilizing the intestinal flora, reducing the expression of inflammatory factors, and inhibiting apoptosis. Table 1 summarizes some of the proven commonalities [6-16].

In addition to the above-mentioned polyphenols, Rosa Roxburg Gill Tratt. Polyphenols can also alleviate alcoholic liver injury by upregulating the expression of Nrf2 in liver tissue in the Nrf2/ARE signaling pathway and activating the antioxidant enzyme HO-1 [6]. Polyphenols mainly include shortleaf forest, hypericin, ellagic acid, and 3,3'-di-O-methylcellulose acid, which can play an anti-cancer and inhibition of cancer [8]. Ecclonia cava polyphenols can reduce ethanol-induced apoptosis, and inhibit the activation of NF- $\kappa$ B and JNK pathways by upregulating the expression of bcl-2 and AKT, downregulating the expression of bax, caspase-9 and caspase-3. The inflammatory response caused by liver secretion of TNF- $\alpha$  can be reduced by reducing oxidative stress level [10]. Honey

polyphenols are similar to Ecklonia Cava polyphenols in alleviating ethanol-induced oxidative stress and apoptosis [12]. The difference is that it can also regulate the gut flora and improve metabolic function by providing the gut microbes with metabolic substrate and inhibiting the growth of harmful bacteria [11]. Tea polyphenols also regulate lipid balance in the liver [13]. The study of bran polyphenol is aimed at gastric mucosal injury [13].

**Table 1.** Effects of polyphenols on ethanol metabolism

Polyphenol effect	ADH	ADLH	Antioxidant enzyme	Intestinal flora	Inflammatory reducing factor	apoptosis
Rosa roxburghii Tratt. Polyphenol [6]	+	+	+	-	-	-
Moringa seed polyphenol [7]	+	+	-	-	-	-
Cuarium album L. Polyphenol [8]	+	-	+	-	-	-
Clinacanthus nutans polyphenol [9]	+	+	-	-	-	-
Seaweed Polyphenol (from Ecklonia Cava) [10]	-	-	+	-	+	+
Monofloral Triadica Cochinchinensis Honey Polyphenol [11, 12]	-	-	+	+	+	-
tea Polyphenol [13]	-	-	+	+	+	-
rice bran polyphenol [14]	-	-	+	-	-	+
polyof Phyllanthus emblica L., [15]	-	-	+	-	-	-
cinnamon polyphenol [16]	-	-	+	-	-	-

#### 4.2. Polysaccharide

Polysaccharides are biological macromolecules widely existing in nature, and have rich biological activities in anti-tumor, anti-oxidation, anti-bacteria and anti-virus. Previous studies have also shown that it has potential applications in speeding up ethanol metabolism and protecting ethanol damage. Nostoc Commune Vauch. Polysaccharides are found to improve the antioxidant activity of liver tissue, inhibit lipid peroxidation and regulate intestinal flora [17]. Geesteranus mycelial polysaccharides can improve antioxidant capacity, inhibit inflammatory damage, and promote lipid metabolism by mediating Keap1/Nrf2, AMPK/SREBP, TLR4/NF- $\kappa$ B and other multi-signaling pathways. It also reduces intestinal permeability and stabilizes the intestinal flora [18]. Yam polysaccharide has also been proved to protect liver cells by affecting ethanol metabolism and lipid peroxidation, but the specific mechanism is not clear [19]. Sulfated Hippophae rhamnoides L. Liaf Polysaccharide can improve the activity of ADH, accelerate the oxidative metabolism of ethanol and eliminate free radicals [20]. The fractional alcohol sedimentation experiment of Mori Fructus Polysaccharides showed that it could improve the activity level of antioxidant enzymes such as SOD GSH-Px, and protect liver damage caused by ethanol, in which S-FPS-90-1 was prominent and had potential application value [21]. Fucoidan has been found to reduce fat accumulation, decrease secretion level of inflammatory factors, inhibit mTORC1/p70S6K autophagy pathway and reduce autophagy of hepatocytes [22].

### 4.3. Flavonoids

Flavonoids are mostly flavonoid derivatives containing hydroxyl, which are mainly distributed in higher plants and have a wide range of biological activities. Table 2 is a review of some flavonoids that can relieve alcoholic liver disease by Jiayan Shen et al [23].

**Table 2.** Mechanism of action and molecular targets of natural flavonoid compounds on alcoholic liver disease

class	name	Pharmacological activity	Molecular targets and pathways
flavone	Baicalin	Antioxidant	NRF2/HO-1/NQO1
		Antioxidant	NRF2, CYP2E1
		Antioxidant, anti-inflammatory	SHH, Smo, Ptc-1, GLI-1
		Anti-inflammatory	TLR4
	Baicalein	Antioxidant, anti-apoptotic	iNOS
		Reduces lipotoxicity	PPAR $\alpha$ , AdipoR2
		Anti-inflammatory	PPAR $\gamma$ , NF- $\kappa$ B
		Anti-fibrosis	Caspase-3, Caspase-9, Bax/Bcl-2
	Xylenose	Regulates cell proliferation	GSK-3 $\beta$
		Anti-inflammatory, anti-cell pyrozois	PGC-1 $\alpha$ /Mfn2/NLRP3, Caspase-1
		Reduces lipid synthesis and enhances lipid metabolism	SREBP-1c, Fasn, SCD1, PPAR $\alpha$ , CPT-1A, HIF-1 $\alpha$
		Anti-fibrosis	YAP/HIF-1 $\alpha$
	Vitex	Anti-inflammatory, activates autophagy, antifibrotic	PI3K/AKT/mTOR
		Regulates cell proliferation	PKM1/HNF4 $\alpha$
		Anti-apoptotic, antioxidant	Sirt1/P53
		Enhances lipid metabolism, antioxidant	PPAR $\alpha$ , SREBP-1c, FASN
flavonol	Quercetin	Regulates cell proliferation	P38-P21
		Enhances lipid autophagy	LC3, P62, PLIN2, AMPK
		Relieves steatosis	P2X7R, PI3K/Keap-1/NRF2
		Antioxidant	NRF2/HO-1
Dihydroflavonoids	Tangerine peel Hesperidin	Reduces iron deposition	BMP6/SMAD4
		Antioxidant, enhances lipid metabolism	AMPK, NRF2
	Naringenin	Enhance lipid metabolism, reduce endoplasmic reticulum stress, anti-apoptosis	Cyp2y3, Cyp3a65, Hmgcra, Hmgcrb, Fabp10, Fads2, Echs1, Fasn, Chop, Edem1
		Anti-inflammatory	TNF- $\alpha$ , IL-6, NF- $\kappa$ B, COX-2, MIP-2, CD14
Dihydroflavonols	Silymarin	Anti-inflammatory	TNF- $\alpha$
		Antioxidant, anti-inflammatory	IL-10, TNF- $\alpha$ , IFN- $\gamma$ , VEGF-A, TGF- $\beta$ , IL-14
	Dihydromyricetin	Antioxidant, anti-inflammatory	NF- $\kappa$ B, ICAM-1, IL-6
		Enhance lipid metabolism and reduce ethanol toxicity	AMPK, ACC, CPT-1A
Isoflavones	Puerarin	Enhances autophagy, antioxidant	P62, Keap-1, HO-1, CYP2E1
		Regulates cell proliferation and migration	TGF- $\beta$
		Enhances lipid metabolism, reduces endoplasmic reticulum stress, anti-inflammatory	Cyp2y3, Cyp3a65, Adh8a, Adh8b, Hmgcrb, Fasn, Chop, Edem1, ATF6, IL-1 $\beta$ , TNF- $\alpha$
		Antioxidant, enhances lipid metabolism	ALOX-5, COX-2

#### 4.4. Amino Acid

Some amino acids have also been found to accelerate ethanol metabolism and protect against ethanol damage. For example, leucine enhances liver activity of ADH and ALDH, inhibits proteolysis of hepatocytes, and stimulates stellate growth factor secretion. Alanine directly accelerates ethanol oxidation, stimulates glucose-alanine cycle, increases the NAD/NADH ratio, accelerates ethanol metabolism, and participates in malate-aspartic acid shuttle as a precursor to determine the liver ethanol metabolism rate [24]. L-arginine has also been shown to increase ADH and ALDH activity [25]. Combined with rice embryo glutathione extract, it was found that it can increase the mRNA expression of ADH and ALDH, inhibit the mRNA expression of CYP2E1, and reduce lipid peroxidation by enhancing antioxidant activity, which has great application prospect [26].

#### 5. Conclusion

This article first introduces the main metabolic pathways of ethanol, as well as the diseases or injuries that may be caused, and then summarizes some compounds that accelerate ethanol metabolism and reduce damage. After ethanol enters the human body, a small part is metabolized in the stomach, while most of it is absorbed by the upper part of the small intestine, enters the liver through the portal vein, and spreads through the blood to various parts of the body without being metabolized. Even a small part is metabolized by the brain after passing through the blood-brain barrier, and most of the alcohol is eventually metabolized back to the liver after circulation. The most important enzymes for ethanol metabolism are alcohol dehydrogenase, catalase and cytochrome P450, and the main metabolites include harmful acetaldehyde and ROS. Many polyphenols, polysaccharides and flavonoids have been shown to accelerate ethanol metabolism and protect ethanol damage, mainly by increasing the activity level of ADH and ALDH, inhibiting the activity of CYP2E1, restoring antioxidant activity, stabilizing intestinal flora, inhibiting the secretion of inflammatory factors, etc., with great application prospects.

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