

COMPREHENSIVE REVIEW

Natural medicines for alcoholism treatment: a review

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Abstract

Alcoholism is a serious problem throughout the world. The development of alcoholism remedies have medical, social and economical significance. In view of the pitfalls of psychological dependence and adverse behavioural effects of synthetic drugs, the development of low toxicity and high efficiency medicines derived from natural products exhibits expansive market prospects. Based on these considerations, we summarize briefly folk application of traditional hangover remedies and clinical application of herbal complex and patent medicines for alcoholism treatment. We have reviewed the effects of natural medicines on intake, absorption and metabolism of alcohol, as well as the protective effects on alcohol-induced acute and chronic tissue injury. [Xu B], Zheng YN, Sung CK. Natural medicines for alcoholism treatment: a review. Drug Alcohol Rev 2005;24:525–536]

Key words: alcoholism, hangover, natural medicine.

Introduction

Alcoholism is a serious public health problem that often results in medical, social and economic consequences throughout the world [1,2]. As we know, alcohol affects our entire body, and daily excessive consumption of alcohol generally induces unpleasant physical symptoms such as headache, nausea and vomiting. Taking large quantities of alcohol at one time induces acute alcohol toxicity with acidosis, heart failure and respiratory depression caused by an autonomic nerve and cerebrum dysfunction. Long-term consumption of alcohol in large quantities induces a number of disorders, e.g. fatty liver, alcoholic hepatitis, hepatocirrhosis, gastrointestinal disorder, chronic pancreatitis, peripheral nerve disorder, myocardosis, hypertension and haematopoiesis disorder. Long-term alcohol consumption also causes phrenopathy and social effects, such as violent crimes and traffic accidents.

In view of the high frequency of drinking in daily life and the increasing consumption of alcohol, research and development of effective anti-alcoholism medicines

is necessary. Despite great progress made in the past two decades, the development of low-toxicity and high-efficiency medicines remains a challenging task for alcohol researchers. In western countries benzodiazepines, complex vitamins, cyanamide disulfiram and aldehyde dehydrogenase inhibitors are administered to alcoholic patients to suppress withdrawal and decrease appetite for drinking. However, it is known that these chemical drugs lead to abuse, psychological dependence and adverse behavioural effects. These drugs could also lead to physiological dependence when taken chronically, and result in dose escalation [3]. Aldehyde dehydrogenase inhibitors, especially disulfiram, have been reported to show serious side effects [4]. At present naltrexone, an opioid receptor antagonist, is being used for treating alcoholism in humans. Although naltrexone suppresses alcohol consumption [5–7], it has some side effects, including the development of withdrawal symptoms, nausea, dysphoria and fatigue [8–10]. In addition, a new drug acamprosate (campral), has been approved by the Food and Drug Administration (FDA) for alcoholism treatment [11]. Although campral has

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been demonstrated to be safe and effective by multiple clinical studies involving alcohol-dependent people [12–15], its efficacy and mechanisms are not fully understood. The most common side effects reported for patients taking campral in clinical trials include headache, diarrhoea, flatulence and nausea [16,17]. Therefore, safer medications and treatments are in demand to prevent alcoholic disorders. Currently, western countries have developed mainly synthetic medicines for treatment of alcoholism, while Asian countries, especially China, Japan and Korea, emphasize the use of natural medicines. Medicinal plants have been used in China for the treatment of alcoholism for centuries, but they have only recently attracted the attention of western scientists. Contrary to synthetic medicines, many traditional medicines and natural products have been known to have preventive and therapeutic effects for alcoholism. Recent experimental evidence and re-examination of empirical data from traditional medicines suggest that novel pharmacological approaches for the treatment of alcoholism might stem from natural substances. In this paper, we review research progress on natural medicines for the treatment of alcoholism by concentrating on the research and development of anti-alcoholism medicines from research papers and patents published from the 1980s to early 2005.

Application of traditional hangover remedies and patent medicines

Folk application of traditional hangover remedies

In China, traditional medicines have been used safely and effectively to treat alcohol abuse for over two millennia. Today, several traditional single formula hangover remedies, such as Radix Puerariae, Flos Puerariae and *Hovenia dulcis*, and complex formulae such as ‘ge-hua-jie-xing-tang’, ‘zhi-ge-yin’ and ‘wu-ling-san’, are being used. In addition, many other natural products such as ginseng, mung bean, rice bean, radish and dandelion are used as hangover remedies in folk medicine [18]. In Korea, the herb Virgate Wormwood is known to be tremendously effective in expelling accumulated alcohol from the body. It removes toxic wastes from the blood and organs and promotes urination. Because of this, doctors of oriental medicine prescribe the herb widely for liver diseases. Some believe that ginseng or Radix Astragali may also overcome hangovers. In addition, there are several traditional foods that are considered to be very effective for removing toxins. Of these, ‘hae-jang-gook’, a bean sprout soup loaded with hot red pepper, is considered the best for recovering from a hangover. In Japan, the typical hangover remedy is apricot with purple perilla. In Mexico, a common

hangover remedy consists of alfalfa seed and dried orange tree leaves, steeped in one cup of boiled water. In Brazil, the herb jurubeba (*Solanum paniculatum*) is the most popular hangover remedy [19,20], which is used after excessive food and alcohol consumption to alleviate indigestion and bloating in the stomach. It has been proved that this herb is helpful in the treatment of liver diseases such as chronic hepatitis, liver obstruction and swelling of the liver. In Egypt, cabbage with vinegar is considered as an effective hangover remedy. It is believed that cabbage consumption allows drinkers to drink more alcoholic beverages (Table 1).

Application of patent medicines

Recently, as the need for alleviation of lingering intoxication has increased, a variety of prescriptions for intoxication have been attempted. In particular, for alleviating lingering intoxication, there is a tendency towards using food or pharmaceuticals prepared from the plants which have been used since ancient times. These prescriptions have been made into functional food, natural tea, beverages and medicines. Many patents have been applied by oriental countries, such as a concoction containing a mixture of alder, licorice root, honey and ground gourd that allegedly helps the liver to detoxify alcohol [21]. Studies on alcohol-induced laboratory rats that were given this tea revealed that it sharply reduced their amount of blood alcohol. A capsule for hangover treatment containing the active ingredient ephedrine in powdered form, vitamin B₆ and charcoal was found effective [22]. This prescription, which was designed to speed the time for recovery from a hangover, also included a therapeutic method for relieving the side effects of alcohol consumption. A galenic composition comprising fructose and an

Table 1. Folk application of hangover remedies in various countries

| Traditional hangover remedies | Application country |
|---|---------------------|
| Radix Puerariae, Flos Puerariae | China |
| <i>Hovenia dulcis</i> | China |
| Ge-hua-jie-xing-tang, Zhi-ge-yin, Wu-ling-san | China |
| Wormwood | Korea |
| Ginseng or Radix Astragali | Korea |
| Hae-jang-gook | Korea |
| Apricot with purple perilla | Japan |
| Jurubeba | Brazil |
| Alfalfa seed and dried orange tree leaf | Mexico |
| Cabbage with vinegar | Egypt |

aqueous extract of Flos Puerariae, Semen Phaseoli Radiati and Rhizoma Pinelliae [23] has been found to possess valuable pharmacological properties in the prevention of the after-effects related to ingesting excessive amounts of alcohol. This composition decreased blood alcohol concentration, reduced the increased content of neutral fat in the blood, and was found effective to increase metabolic activities of alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH) and a pharmaceutically acceptable carrier. An invention [24] pertaining to lower blood alcohol concentration by administering an extract of *Rhus verniciflua*, used traditionally in Korea, Japan and China in making a lacquer paint, overcomes hangover, alcoholic gastritis and alcohol-induced liver damage.

Despite these traditional natural products being used to treat alcoholism safely and effectively, a lack of scientific data has restricted their application in clinical medicine. In the past two decades, some endeavours have been undertaken to seek scientific evidence to support their clinical application. Remarkable progress has been made towards research and development of natural therapeutic agents. Scientific investigation of natural alcoholism remedies have been focused on three aspects, according to the characteristics of alcohol metabolism in the body: (i) decreasing appetite for drinking and suppressing alcohol intake; (ii) inhibiting alcohol absorption in gastrointestinal tract, and reducing alcohol concentration in blood; and (iii) developing medicine to act on the liver – metabolic enzyme system, accelerating the elimination rate of alcohol and its metabolites and alleviating injury to tissue and cells.

Effect of natural medicines on alcohol intake

Reduction of the appetite for alcohol provided a useful means for the treatment of alcoholism. The experimental application of herbal and traditional medicines has been used to cure alcohol dependence. The results indicate that pure compounds daidzin and puerarin from Radix Puerariae (kudzu), extracts from *Hypericum perforatum* (St John's wort) and iboganine from *Taber-*

nathe iboga suppressed alcohol intake in animal models of excessive drinking with minimal effects on other appetitive behaviours. It appears that these substances exert their effects by modulating several neuronal systems implicated in drinking behaviour. The effects of natural medicine and their purified compounds on alcohol intake in alcohol-preferring rats have been summarized in several reviews [25–27]. The reducing effect of Radix Puerariae, *Tabernathe iboga*, *Salvia miltiorrhiza* and *Hypericum perforatum* on voluntary alcohol intake in animal models of alcoholism have been summarized in detail [25,26]. In this section, we make a brief summary on natural substances and their suppressant effect (shown in Table 2) on alcohol intake.

Hypericum perforatum

Several pre-clinical studies showed that extracts of *H. perforatum* (St John's wort) might reduce voluntary intake of alcohol significantly in several strains of alcohol-preferring rats: the fawn-hooded (FH) rats, the high-alcohol-drinking (HAD) rats, the Marchigian Sardinian (msP) rats and the cAA rats [28–34]. Hyperforin has been suggested to be an active compound, which reduces alcohol intake [31]. Although the mechanism of action of the extracts of *H. perforatum* on alcohol intake was not understood fully, the ability of the *H. perforatum* to affect serotonergic, dopaminergic and opioidergic systems in mesolimbic regions in the central nervous system (CNS), directly or indirectly, might help to explain its efficacy in the treatment of mild to moderate depression and alcoholism.

Pueraria lobata

P. lobata, also known as kudzu, has been used as a medicine in China since 200 BC (Shen Nong Ben Cao Jing, Anonymous, about 200 BC). It has a special reputation as an anti-intoxication agent noted in the Chinese Pharmacopeia of AD 600 (Thousand Golden Prescriptions, Sun Simiao, about AD 600) and later as

Table 2. Natural substances with suppressing effect on alcohol intake

| Active substances | Plant sources | Animal models | References |
|---|------------------------|---|----------------------------|
| Extracts, Hyperforin | <i>H. perforatum</i> | FH rats, HAD rats, msP rats, the cAA rats | 28, 29, 30, 31, 32, 33, 34 |
| NPI-028 Extracts, Daidzin, Daidzein, Puerarin (NPI-31G) | <i>P. lobata</i> | Syrian golden hamsters, All alcohol-drinking animals | 38, 39, 40 |
| Ibogaine | <i>T. iboga</i> | FH rats, P rats, AA rats | 58 |
| Tanshinone IIa IDN 5082 | <i>S. miltiorrhiza</i> | sP rats | 54, 55, 56 |

an anti-dipsotropic agent (Li Dongyuan, about AD 1200). Flos Puerariae and Radix Puerariae were typical hangover remedies in the traditional Chinese medicine. The scientists also noted that kudzu suppressed alcohol's intoxicating effects after it entered the bloodstream, tending to confirm the ancient claim that taking kudzu before drinking alcohol helped to stave off intoxication and hangovers. Research with laboratory animals revealed that a drug extracted from kudzu root might help the treatment of alcoholism [35–37]. Keung and coworkers reported that in Syrian golden hamsters, daidzin and daidzein were active isoflavonoids isolated from the kudzu that suppressed alcohol preference [38–40]. Later, the anti-dipsotropic activity of daidzin was confirmed in all alcohol-drinking animal tests [41–44]. Results of studies indicated that daidzin was effective in suppressing the craving for alcohol [35,36,38,39,45,46]. In addition, NPI-028 (kudzu) and one of its pure components, puerarin (NPI-031G), were found to selectively reduce alcohol intake in alcohol-preferring rats [43]. Puerarin is the most concentrated isoflavonoid in kudzu. Although it is not as potent as daidzin [47], the sugar moiety is attached to the carbon molecule instead of the oxygen, leading to a more stable compound than daidzin. After acute intraperitoneal administration, puerarin reduced alcohol intake selectively [43,47,48]. Interestingly, reduction of alcohol intake was observed in all the three strains tested: FH [47,49], HAD [49] and P rats [50]. Further studies found that puerarin could counteract the reduced social interaction exhibited by alcohol withdrawn rats by blocking either benzodiazepine or 5-HT_{2C} receptors or both [51]. This finding indicated that NPI-031G had anxiolytic effects in alcohol withdrawn rats. However, two recent investigations on the effects of Radix Puerariae [52] and its major isoflavone puerarin [53] on voluntary alcohol intake and alcohol withdrawal symptoms in P rats indicated that they suppressed alcohol drinking and withdrawal symptoms without entering the brain. The absence of puerarin in plasma and the brain indicated the possibility that some non-specific mechanism might be involved in the anti-alcoholism effects of Radix Puerariae in P rats.

Salvia miltiorrhiza

Acetone extract from the root of *S. miltiorrhiza* was reported to diminish alcohol preference in Sardinian alcohol-preferring rats. A subsequent experiment showed that the dose of *S. miltiorrhiza* extract, capable of reducing voluntary alcohol intake in sP rats, decreased blood alcohol levels (BALs) by approximately 60% [54]. The latest research demonstrated that IDN 5082, a standardized extract of *S. miltiorrhiza*, dose-dependently delayed acquisition of alcohol-drinking

behaviour [55]. Further studies were also undertaken to investigate whether IDN 5082 was capable of preventing the development of the alcohol deprivation effect (ADE) in sP rats [56]. The acute, intragastric administration of 25, 50 and 100 mg/kg IDN 5082 resulted in the complete suppression of the extra amount of alcohol consumed during the first hour of re-access to alcohol after 7 days of deprivation. The results indicated that IDN 5082 might possess anti-relapse properties.

Tabernaemontana iboga

Ibogaine, one of the principal indole alkaloids found in the root bark of the African shrub *Tabernaemontana iboga*, was found to significantly reduce volitional alcohol consumption in alcohol-preferring P and AA rats. Ibogaine exerted its anti-craving effects on voluntary alcohol intake by interacting with the brain systems involved in stimulating dopaminergic and serotonergic systems [57,58]. Both systems have been implicated in the regulation of alcohol intake [59,60].

Herbal formula

In addition, an Indian herbal formula (SKV), produced by fermentation of cane sugar with raisins and 12 herbal ingredients, could bring down voluntary alcohol ingestion. It appeared to be a promising way to combat alcoholism in India [61].

Effect of natural medicines on alcohol absorption

The gastrointestinal (GI) tract was known as the site of alcohol absorption into the bloodstream. Absorption of alcohol was controlled mainly by gastric emptying and small intestine absorption. Reduction of alcohol absorption was also thought to be a convenient and useful means of preventing alcoholic disorders. Therefore, in the development of natural therapeutic agents, most studies focused on seeking GI tract absorption inhibitors of alcohol. Over the past two decades, some important progresses have been made towards the development of natural therapeutic agents. Among them there was a focus on the species of Araliaceae, and from these, saponins were verified to be the active constituent. Some typical examples are as follows (Table 3).

To assess the effects of *Panax ginseng* on blood alcohol clearance, alcohol (3.2 g/kg) and aqueous extract of red ginseng were administered orally to rats. It significantly lowered the concentration of alcohol in the blood; however, intraperitoneal injection had no effect [62]. Results have indicated that ginseng exerted its anti-intoxication effect by inhibiting GI tract absorption of alcohol. In addition, triterpenoidal saponins

Table 3. Natural compounds with inhibitory effect on GI tract absorption of alcohol

| Compounds | Dose (mg/kg, p.o.) | BALs ^a (mg/dl, 1 h) | Plant sources | References |
|-------------------------------------|--------------------|--------------------------------|--|------------|
| Control | | 0.5–0.7 | | |
| Costunolide | 50 | 0.25 ± 0.05** ^a | Leaves of <i>Laurus nobilis</i> | 72, 73 |
| α-MGBL | 50 | 0.20 ± 0.02** ^a | | |
| Dehydrocostus lactone | 25 | 0.40 ± 0.05 | | |
| Momordin Ic | 50 | 0.29 ± 0.09** | Fruit of <i>Kochia scoparia</i> | 71 |
| | 25 | 0.222 ± 0.044** | | |
| | 50 | 0.217 ± 0.147** | | |
| 2'-O-β-D-Glucopyranosyl-Momordin Ic | 100 | 0.122 ± 0.035** | | |
| | 100 | 0.250 ± 0.049** | | |
| Senegasaponin A | 50 | 0.43 ± 0.02 | Root of <i>Polygala senega</i> var. <i>latifolia</i> | 69 |
| | 100 | 0.06 ± 0.02** | | |
| Senegasaponin B | 50 | 0.45 ± 0.04 | | 70 |
| | 100 | 0.07 ± 0.01** | | |
| Senegin II | 100 | 0.049 ± 0.021** | | |
| Camelliasaponin B1 | 100 | 0.10 ± 0.06** | Seed of <i>Camellia japonica</i> | 68 |
| Camelliasaponin B2 | 100 | 0.43 ± 0.05** | | |
| Camelliasaponin C1 | 100 | 0.35 ± 0.05** | | |
| Camelliasaponin C2 | 100 | 0.32 ± 0.08** | | |
| Escin Ia | 100 | 0.50 ± 0.02** | Seed of <i>Aesculus hippocastanum</i> | 67 |
| Escin Ib | 100 | 0.43 ± 0.03** | | |
| Escin IIa | 50 | 0.37 ± 0.08 | | |
| Escin IIb | 100 | 0.08 ± 0.04** | | |
| | 50 | 0.29 ± 0.010 | | |
| Escin IIb | 100 | 0.14 ± 0.04** | | |
| | 50 | 0.29 ± 0.010 | | |
| Sapindosides | | | Pericarp of <i>Sapindus mukurossi</i> | 66 |
| Elatoside A | 25 | 0.11 ± 0.02** | Root and bark of <i>Aralia elata</i> | 63, 65 |
| | 50 | 0.01 ± 0.01** | | |
| | 100 | 0.00 ± 0.00** | | |
| Elatoside B | 25 | 0.56 ± 0.01 | | |
| | 50 | 0.50 ± 0.04 | | |
| | 100 | 0.25 ± 0.10* | | |
| Spinasaponin A | 25 | 0.26 ± 0.07* | | |
| | 50 | 0.03 ± 0.01** | | |
| | 100 | 0.03 ± 0.02** | | |

^aBALs: blood alcohol levels, **p* < 0.05; ***p* < 0.01. *a*, 30 minutes later.

from other Araliaceae plants, such as *Panax notoginseng* (Burk.) F. H. Chen, *Aralia elata* (Mig.) Seem. [63], *Acanthopanax gracilistylus* W. W. Smith and *Panax quinquefolium* L. [64], had an inhibition effect on GI tract absorption of alcohol.

Yoshikawa *et al.* isolated a number of bioactive saponins from natural medicines, which showed strong inhibition on GI tract absorption of alcohol: for instance, isolation of Elatoside A and B from the bark of *Aralia elata* [63], an oleanolic acid oligoglycoside—spinasaponin A—isolated from the root of *Aralia elata*, [65], sapindosides from the pericarps of *Sapindus mukurossi* (Japanese soapnut tree) [66], escins from the seeds of *Aesculus hippocastanum* (horse chestnut tree) [67] and camelliasaponins from the seeds of *Camellia japonica* [68]. Among these compounds, camelliasaponins B1, B2, C1, C2, escins-Ia, Ib, IIa,

IIb and IIIa could inhibit GI tract absorption of alcohol. Structure–activity relationships studies showed that these active constituents possessed acidylated groups located at the C22 position. Senegasaponin A, B and senegin II, isolated from the root of *Polygala senega* var. *latifolia* [69,70], showed significant inhibition on GI tract absorption of alcohol, whereas tenuifolin (without 28-O-oligosaccharides group) and presenenin (without 3,28-oligosaccharides groups) showed no inhibiting effect, which indicated that acidylated 28-O-oligoglycoside was the key functional group exerting an anti-intoxication effect among the senegasaponins. In addition, momordin Ic and its 2'-O-β-D-glucopyranoside from fruit of *Kochia scoparia* [71] and seven sesquiterpenes such as costunolide (COS) and dehydrocostus lactone, isolated from leaves of *Laurus nobilis* (bay leaf), showed potent inhibitory effects on

blood-alcohol elevation in rats [72,73]. The active moiety in these sesquiterpenes was found to be the α -methylene- γ -butyrolactone (α -MGBL) moiety. Furthermore, the inhibitory effects of costunolide and α -MGBL on blood-alcohol elevation were due to inhibition of gastric emptying and dilution of the alcohol concentration by the increased gastric fluid, and not by acceleration of alcohol metabolic enzyme activity in the liver [72,74].

Some isoflavonoid constituents were responsible for the inhibition of alcohol absorption. Niiho *et al.* [75,76] reported that the isoflavonoid fraction of Flos Puerariae suppressed the concentration of blood alcohol. Further investigation by Han *et al.* [77] showed that kakkalide (isolated from Flos Puerariae) and irisolidone (the metabolites of kakkalide by human intestinal bacteria) were active isoflavonoid constituents. Orally administered kakkalide and intraperitoneally administered irisolidone significantly lowered the level of blood alcohol.

Some dietary components were reported to affect alcohol absorption. For instance, vegetable oils such as soybean oil and coconut oil delay the elimination rate of gastric alcohol and lessen the increase in plasma alcohol concentration [78]. Soymilk products were reported to inhibit alcohol absorption in rats [79].

In addition, medicines from animals also contained many anti-alcohol substances such as pig and bovine bile. According to previous studies [80], bovine bile exerted its anti-intoxication effect by delaying gastric emptying time and inhibiting the absorption of alcohol in the intestinal tract, and taurine was identified to be the effective constituent.

Effect of natural medicines on alcohol metabolism

Alcohol is removed from the body mainly by metabolism in the liver. Approximately 90% of the alcohol is metabolized in the liver by alcohol dehydrogenase (ADH) followed by aldehyde dehydrogenase (ALDH), while the gastrointestinal tract, lungs and kidneys play only a minor role [81]. Because alcohol-metabolizing enzymes such as ADH, ALDH and the microsomal

alcohol oxidizing system (MEOS) contributed to the clearance of alcohol and toxic acetaldehyde [81], substances that stimulated these enzyme activities were expected to ameliorate alcohol toxicity. The development of an alcohol-metabolizing enzymes stimulant was one of the strategies for developing an alcoholism remedy. Some attempts were made to develop an effective alcohol metabolic stimulant from natural dietary components and herbs. For instance, sesamin [82], garlic [83] and soymilk products [79] were found to be effective natural hangover remedies, which enhance alcohol metabolism and acetaldehyde clearance. Some typical examples for herbal remedies are described below (Table 4).

Hovenia dulcis

Among the herbs known to be effective in alleviating lingering intoxication, much attention was paid to *H. dulcis*, which is known traditionally to be effective. Although *H. dulcis* has been used in China to treat alcohol abuse safely and effectively for more than a millennium, its true efficacy, active constituents, sites and mechanisms of action have never been critically examined. Only in the past three decades have serious attempts been made to evaluate its efficacy by understanding the mode of action of its active principles. It has now been proved that the extract of *H. dulcis*, or its complex formulae, hasten detoxification of alcohol [84–86]. *H. dulcis* could decrease alcohol concentration remarkably in blood and promote the clearance of alcohol [87,88,91]. The extracts from *H. dulcis* were also more effective in enhancing ALDH activity than ADH activity. This is one of the possible explanations of how *H. dulcis* could relieve hangovers effectively, by decreasing acetaldehyde concentration quickly in the liver and blood [89].

Isoflavonoids from Pueraria lobata

In an earlier investigation, Keung & Vallee [38] examined the effect of a large number of flavonoids and isoflavonoids on the activities of both ALDH-1

Table 4. Alcohol metabolic stimulant

| Active components | Plant sources | Mechanism of activity | References |
|-------------------|---------------------------|--------------------------------------|------------|
| Crude extract | <i>Hovenia dulcis</i> | Enhancement of ADH and ALDH activity | 89 |
| Water extract | Fructus Mori Albae | Enhancement of ADH activity | 91 |
| Water extract | Semen Alpiniae Katsumadai | Enhancement of ADH activity | 91 |
| Water extract | Semen Dolichoris | Enhancement of ADH activity | 91 |
| Crude extract | <i>Ginkgo biloba</i> | Enhancement of ADH activity | 92 |
| Crude extract | <i>Poria cocos</i> | Enhancement of ADH activity | 92 |
| Water extract | <i>Aloe</i> spp. | Enhancement of ADH activity | 93, 94 |

(mitochondria) and ALDH-2 (cytosol). They found that certain compounds, such as daidzin and prunetin, seem to be particularly potent inhibitors of ALDH-2. The inhibition reaction was investigated further by Sheikh & Weiner [90], who suggested that isoflavonoid prunetin was an allosteric inhibitor of ALDH-2.

Other natural medicines

In addition, metabolic stimulants of alcohol were also found in other natural medicines. Sakai *et al.* [91,92] found that water extracts of Fructus Mori Albae, Semen Alpiniae Katsumadai, Semen Dolichoris, *Ginkgo biloba*, *Poria cocos* and Aloe could decrease alcohol concentration in the blood of rats after orally administered alcohol, with their mechanisms relating to ADH activity. Korean researchers demonstrated that a water-soluble fraction of *Aloe* spp., when administered orally to rats, caused a significant decrease in the serum alcohol concentration as well as enhancement of liver cytosolic ADH activity [93], and isolated four compounds: aloe-emodin, aloenin, ethylidene-aloenin and β -sitosterol, which inhibit activities of ADH and ALDH [94]. Aloin, when administered orally 12 hours before oral administration of alcohol, resulted in significantly lowering concentrations of alcohol in blood by 40% and increasing the alcohol elimination rate by 60% in the body [95]. Studies showed that both (–)-epigallocatechin gallate (EGCG) and caffeine, the principal components of green tea (*Camellia sinensis*), had an effect on alcohol metabolism in ICR male mice by decreasing alcohol and acetaldehyde levels in blood and liver [96].

Protective effect of natural medicines on tissue injury

Many natural medicines with anti-intoxication activity also possess significant free radical scavenging activity *in vivo*. This indicates that natural anti-alcoholism medicines also possess hepatoprotective and other protective effects of tissue injury induced by alcohol.

Protective effects on acute alcoholism

Hovenia dulcis. Among the natural medicines with protective effects for tissue injury, much attention has been paid to *H. dulcis*. *H. dulcis* could eliminate excessive free radicals caused by drinking alcohol [87] and block lipoperoxidation [97], thereby alleviating alcoholic liver tissue injury [98] and avoiding various dysfunctions and diseases caused by alcoholism. Aqueous extract (100 mg/kg body weight administration) of *H. dulcis* could significantly increase GSH-PX activity (6.70 ± 1.55 activity unit), which was reduced by acute

alcohol toxicity compared to the alcohol control group (4.39 ± 1.14 activity unit). Results of studies indicate that enhancement of GSH-PX activity might be one of the mechanisms of alcohol detoxification by *H. dulcis* [99]. In addition, methanol extract from the fruit and seed of *H. dulcis* was found to show an inhibitory effect on alcohol-induced muscle relaxation [86].

Flos Puerariae. Yamazaki *et al.* [100] reported that intraperitoneally administered kakkalide, which was isolated from Flos Puerariae, reduced mortality associated with administration of alcohol and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities. However, Han *et al.* [77] showed that intraperitoneally administered kakkalide and irisolidone (the metabolites of kakkalide by human intestinal bacteria) did not reduce alcohol toxicity, while orally administered kakkalide and intraperitoneally administered irisolidone significantly reduced the mortality and reduced serum AST and ALT activities in alcohol-intoxified mice. These results indicated that kakkalide was a prodrug of irisolidone in protecting against alcohol-induced lethality and hepatic injury.

Protective effects on chronic alcoholism

Pueraria lobata. A study was performed to investigate the effects of water extract from Flos Puerariae (FP) and Radix Puerariae (RP) on the activities of three hepatic anti-oxidant enzymes in alcohol-treated male Sprague–Dawley rats, which were orally administered alcohol (25% v/v, 5g/kg b.w.) once a day for 5 weeks. The FP and RP supplementation resulted in significant increase in the Cu/Zn SOD and/or CAT activities and a decrease in the GSH-Px activity in the alcohol-treated rats. The hepatic glutathione content, which was significantly lowered in the alcohol-treated group compared to the control group, was also normalized to the control level by supplementing with either FP or RP [101]. Further investigation [102] found that water extract of RP might increase SOD and CAT activities significantly and decrease the plasma and hepatic thiobarbituric acid reactive substance (TbARS) and the GSH-Px activities in the alcohol-treated rats.

Protective effects of herb complex on acute and chronic alcoholism

The effect of a medicinal herb complex, saeng-maek-san (SMS), composed of *Panax ginseng*, *Liriope platyphylla*, *Schizandra chinensis*, *Astragalus membranaceus* and *Cucurbita moschata*, on rat hepatocytes exposed to alcohol was investigated [103]. SMS treatment resulted in a significant reduction in the levels of AST, ALT and triglycerides (TG) compared to the control rats. Electron microscopy showed that administration of

SMS preserved the structure of organelles, including the nucleus and mitochondria. Recently, another herb complex, composed of *Astragalus membranaceus*, *Salvia miltiorrhiza* and *Pueraria lobata*, exhibited inhibition effects of alcohol-induced lipid accumulation on male Sprague–Dawley rats. The activities of plasma AST and ALT were significantly decreased in the herb complex-treated group compared to the alcohol-fed group [104]. These results suggest that this herb complex could be used as a remedy for alcoholic fatty liver.

Clinical trials of natural medicines

Although preclinical studies with several strains of alcohol-preferring rats have shown that acute oral administration of some natural products and their active constituents could reduce voluntary alcohol intake significantly, some traditional Chinese medicines, such as *Hovina dulcis*, Radix Puerariae and Flos Puerariae, have been used for centuries in China to relieve intoxication and hangover from excessive drinking. To date, only a few clinical trials have been conducted. One early investigation to assess the effects of *P. ginseng* extract revealed that it enhanced blood alcohol clearance in 14 healthy male volunteers [105]. Only one study has suggested the beneficial effect of *Hypericum perforatum* L. for the treatment of alcoholic patients [106]. One pilot clinical study was reported on Radix Puerariae [107], and none on its active constituents: daidzin and puerarin. However, due to the study design negative results were obtained, and firm conclusions could not be drawn. Anecdotal reports from China and a well-designed toxicity study in rats [108] indicate that these isoflavones have very low toxicity and should be tolerated well by human patients. All the evidence available to date indicates that puerarin and Radix Puerariae extracts can be tested clinically. It is time to take the next step and test the effects of puerarin in human subjects [26]. One clinical study performed on Flos Puerariae [109] showed that its extracts had no influence on blood alcohol and acetaldehyde concentration in humans. However, the extracts increased the elimination rate of blood acetaldehyde, and thereby might passively relieve acetaldehyde toxicity. Extract of globe artichoke (*Cynara scolymus*) is promoted as a possible preventive or cure for alcohol-induced hangover symptoms, although a few rigorous clinical trials have assessed the effects of artichoke extract and the results of a randomized controlled trial [110] suggested that artichoke extract was not effective in preventing the signs and symptoms of alcohol-induced hangover. However, extensive studies are required to confirm these findings. A recent randomized, placebo-controlled, cross-over trial [111] was performed to investigate the effect of *Opuntia ficus indica* (OFI) on

symptoms of alcohol hangover. It was considered that three hangover symptoms—nausea, a dry mouth and loss of appetite—were reduced significantly by the OFI extract. Overall, the symptom index was reduced by 2.7 points on average and the risk of a severe hangover was reduced by half. The people who took the OFI extract also had higher scores of well-being than those who had taken the placebo.

Potential toxic effects of natural medicines

A number of attempts have been made to develop clinical useful compounds from chemical synthesis to ameliorate or cure alcohol-related disorders [112,113]. However, it is well documented that these compounds may exhibit severe cytotoxicity, reproductive toxicity and other side effects. Therefore, an alternative strategy has focused on the development of therapeutic agents based on natural products. Although a number of investigations have been carried out on natural products, few studies have evaluated the toxicity and safety of natural remedies used for alcoholism. A typical example is anti-dipsotropic Chinese herbal mixture XJL (NPI-028), whose potential toxicity and safety in rats following sub-chronic (3-month) exposure via daily oral consumption were investigated [108]. NPI-028 ingested orally at doses up to 2.0 g/kg per day in the rat diet for up to 3 months resulted in normal growth with no change in haematological or hepatic parameters, and only minor alterations in renal and blood chemistry parameters. Results have indicated that long-term daily oral consumption of NPI-028, as a part of the daily diet for 3 months, was safe in rats. Thus, NPI-028 might be potentially safe for clinical use as anti-dipsotropic agent.

Prospects for the development of natural remedies

From the literature on anti-alcoholism, active substances from natural products and structure–activity relationships of gastrointestinal tract absorption inhibitors were clearly elucidated, and triterpene saponins were found to be the common active compounds. Although great progress has been made on alcohol metabolic stimulants from natural products, research at single compound level was sparse and the active moiety was not identified. With the current information, it can be concluded that several natural medicines and their pure compounds, such as hyperforin, daidzin, puerarin and ibogaine, showed significant reduction in alcohol intake in several animal models of excessive alcohol consumption. Although neurotransmitter systems were implicated in their attenuation effects on alcohol intake, the true mechanisms of action of these substances were not understood fully. For traditional hangover

treatment complex prescriptions, extensive studies need to be undertaken on their true efficacy, active constituents, sites and mechanisms of action using modern pharmacological and chemical techniques in order to develop a high-efficacy, low-toxic ADL and ALDH exciter.

In the field of treatment of alcoholism, despite great progress made in the past two decades, the development of low-toxicity and high-efficiency natural medicine remains a challenging task for alcohol research. In addition, the role of natural remedies in the future of pharmacotherapy for alcoholism will depend upon the outcome of carefully conducted clinical trials. The use of these medications alone or in combination remains a challenging area for research.

Finally, special attention needs to be applied regarding the clinical use of medications for alcoholism treatment. Psychosocial treatments designed to improve motivation to undergo treatment and adhere to the medication regimens are important adjuncts to pharmacological treatment. The use of compliance-enhancing strategies can be integrated safely and effectively into primary care models, bringing addiction treatment to a wide range of health-care providers, thereby providing more people with successful therapy for alcoholism.

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