Hovenia dulcis – An Asian Traditional Herb

Authors Tae Kyung Hyun[1], Seung Hee Eom[1], Chang Yeon Yu[2], Thomas Roitsch[1]

Affiliations
[1] Institute for Plant Sciences, Karl Franzens-University of Graz, Austria
[2] Bioherb Research Institute, Kangwon National University, Chunchon, Korea

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Abstract

Hovenia dulcis Thunb., known as Japanese raisin tree, is commonly found in East Asia. It has a long history as a food supplement and traditional medicine in Japan, China and Korea, but is little known and used in Western countries so far. This minireview summarizes traditional uses and current knowledge on the pharmacology and phytochemistry of *H. duclcis* and covers, in particular, literature from specialized Asian journals that are not readily accessible. Extracts from *H. dulcis* accelerate detoxification of ethanol, and possess hepatoprotective, antioxidative, antimicrobial and antidiabetic properties. Although the underlying molecular mechanisms are not fully understood, free radical scavenging and enhancement of ethanol catabolism have been reported.

Introduction

The traditional use of medicinal plants is typically limited both by the natural occurrence or the availability of a given plant species as well as knowledge about the potential pharmaceutical application. Despite great pharmaceutical benefits and application in Asia for more than a millennium, *Hovenia dulcis* Thunb. (commonly known as Japanese raisin tree, alternatively named Japanese cherry tree or Chinese raisin tree) is typically not used in Western countries for medicinal treatment and thus is absent in standard pharmacognosy textbooks [1,2].

Hovenia belongs to a small genus of Rhamnaceae that is indigenous to East Asia. The natural occurrence ranges from Japan, Korea and East China to the Himalayas up to altitudes of 2000 m, growing preferentially in a sunny position on moist sandy or loamy soils. It is cultivated in plantations in China, invasive in South American rainforests and Tanzania, and has been introduced as a rare ornamental in different countries including the USA, Australia, New Zealand and Central Africa. It is a glabrous tree with lenticular branches, and grows up to 10 m. The membranous leaves (**Fig. 1 a, b**) with up to 6 cm long petioles are broadly ovate, 8–15 cm long and 6–12 cm wide, short-acuminate, rounded to shallowly cordate at the base, with obliquely triangular obtuse teeth, green on the upper side, pale green beneath and becoming deep brown when dry. The foliage is glossy green in summer, and the color is a mixture of yellows in fall. After three or four growing seasons, plants begin to form florescence in the upper axils that are terminal cymes, 5–7.5 cm in diameter, consisting of many 1/3-wide greenish white hermaphrodite flowers (**Fig. 1 c**). The globose fruits, about 7 mm across, are initially green (**Fig. 1 d**) and become a reddish-brown drupe with 3 seeds (**Fig. 1 e**). They develop at the end of fruit stalks which swell to form a type of accessory fruit. The taste of the fleshy peduncles is like a combination of raisin, clove, cinnamon and sugar. The peduncles contain high levels of sugar, while leaves of *H. dulcis* contain several dammarane-types of sweetness inhibitors [3]. In East Asia, *H. dulcis* has long been used in traditional herbal medicine for the treatment of liver diseases and detoxification after alcoholic poisoning [4]. In ancient Chinese medicine, its fruit and peduncle were used as a febrifuge and administered to treat parasitic infections [5]. Seeds were used as a diuretic and cure for alcohol overdosing, whereas the fruit was also used as antispasmodic, febrifuge, laxative and diuretic agent. Moreover, the stem bark was introduced as a natural drug to treat rectal diseases [6]. Current pharmaceutical studies have revealed further pharmaceutical applications of *H. dulcis* based on its hepatoprotective effect, inhibitory effect on the ethanol-induced muscle relaxation [6–9] and ability to reduce al-

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Correspondence
Prof. Dr. Thomas Roitsch
Institut für Pflanzenwissenschaften
Schubertstr. 51
8010 Graz
Austria
Phone: + 43 31 63 80 56 32
Fax: + 43 31 63 80 98 80
Thomas.roitsch@uni-graz.at

Fig. 1 *Hovenia dulcis* Thunb. (Japanese raisin tree) is characterized by broadly ovate, glassy dark green foliage and sweet, fleshy and swollen peduncles. **a** *Hovenia dulcis* Thunb, **b** leaf, **c** flower, **d** unripe fruit, and **e** ripe drupes. Source for **c, d, e**: http://www.hovenia.com.

cohol concentration in the blood [4,10,11]. In addition, several patent applications have been filed based on different pharmaceutical applications of *H. dulcis,* in particular those related to treatment of acute alcohol poisoning [12–15].

The aim of the present review is to introduce *H. dulcis* as a medicinal plant by highlighting its traditional applications in East Asia as well as recent pharmacological findings. We also discuss putative mechanisms for the effect of *H. dulcis* extracts on the blood alcohol levels and for liver protection as a consequence of alcohol detoxification (summarized in ▶ **Table 1**). In particular, we have tried to cover original publications on *H. dulcis* that have been published in specialized Asian journals that are not readily available in standard data bases.

Alcohol Detoxification

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H. dulcis has been used in Korean and Chinese traditional medicine for a long time to relieve intoxication due to alcohol poisoning after excessive drinking. There are a number of reports describing the influence of *H. dulcis* extracts on lowering alcohol

Table 1 Pharmacological activities of *H. dulcis*.

Tissue	Effect	Type of extract	Test model	Result	Ref
Fruit	detoxification after alcoholic poisoning	hot water	mice/rat	increasing activity of ADH, ALDH and GST, reducing alcohol concentration in the blood	[4, 6, 9, 10, 18]
		water	rat	increasing activity of GST, reducing alcohol concentration in the blood	[17]
		MeOH	rat	inhibition of ethanol-induced muscle relaxation	[8]
	hepatoprotective against CCl_4 or D-GalN/LPS	MeOH	mice	inhibition of serum GTP and GOP activity	[8]
		MeOH	mice/rat	reducing the increased level of serum AST and ALT	[7]
		MeOH-insoluble fraction from hot water extract	rat	reducing the increased level D-GalN/LPS-induced serum GTP and GOP activity	[6]
		hot water	rat	reducing the increased level CCl_4-induced elevating serum AST, ALT and LDH	[9]
	antioxidant activity	EtOAc fraction from 80% MeOH extract		free radical and superoxide anion radical scavenging activity	[56]
	antidiabetic	hot water	streptozotocin-induced diabetic mice	decreasing the blood glucose concentration, recovering langerhans islets of the pancreas	[55]
		EtOAc fraction from 80% MeOH extract	streptozotocin-induced diabetic rat	decreasing plasma glucose, triglyceride and total cholesterol concentration in microsome of liver tissue	[56]
Bark	anticancer	diethyl ether fraction from EtOH extract	Hep3B cells, MCF7 cells	inhibition of growing cells (IC_{50} values of 0.25 $mg \cdot mL^{-1}$), inhibition of growing cells (IC_{50} values of 0.1 $mg \cdot mL^{-1}$)	[72]
	neuroprotective effect	EtOAc fraction from MeOH extract	mouse HT22 cells	inhibition of decreasing cell viability during response to glutamate	[47]
	antioxidant activity	EtOAc fraction from MeOH extract		free radical, superoxide anion radical, and ABST cation radical scavenging activity	[47]
Leaf	antipathogen effect	DCM faction from MeOH extract		inhibition of *Giardia lamblia* growth	[5]
	antimicrobial effect	MeOH fraction from hot water extract		inhibition of bacteria growth	[58, 78]
	antimutagenic effect	chloroform fraction from MeOH extract	*S. typhimurium* strains TA98 and TA100	inhibition of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) and benzo[*a*]pyrene-induced mutagenicity	[70]
	anticancer	chloroform fraction from MeOH extract	HepG2 and HT29 cells	inhibition of growing cells	[70]

concentrations in blood [4,6,9–11,16–18]. In a detailed study, the effect of a hot water extract from *H. dulcis* on alcohol concentration in mice blood has been evaluated [4]. The groups of mice administered orally with alcohol and hot water extract from *H. dulcis* showed a faster reduction in blood alcohol concentration compared to control groups. The catabolism of ethanol is mediated by alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) activity. ADH converts ethanol into acetaldehyde which is then further oxidized by ALDH into the nontoxic acetyl-CoA. Thus possible mechanisms of the *H. dulcis* extracts involve the direct or indirect regulation of the level or activity of these two enzymes. In fact, *H. dulcis* extracts were shown to enhance the alcohol-induced ADH and ALDH activities in the liver of rats and mice [4,9–11]. Treatment with 5 g of hot water extracts from *H. dulcis* fruits resulted in highly increased levels of liver ADH activity in the ethanol-fed mouse [4]. In addition, when hot water extracts from *H. dulcis* fruits were orally administered to CD strain rats 30 min before feeding with alcohol, the activity of liver ADH and ALDH highly increased compared to control groups [10]. Interestingly, the group orally administered with *H. dulcis* extracts showed a 10% higher activity of ALDH compared to ADH activity in rat livers, whereas both enzyme activities were simultaneously increased in control groups during the alcohol decomposition [10]. The increased level of alcohol-induced liver ALDH activity by treatment with *H. dulcis* extracts suggests that *H. dulcis* can effectively relieve the alcohol hangover through enhancing the catabolism of ethanol.

A number of medicinal plants are reported to have preventive and therapeutic effects on alcoholism and alcohol dependency, but their active components and the possible mode of action are mostly unknown so far. Recently, pure compounds isolated from Kudzu (*Radix pueraria*), St. John's wort (*Hypericum perforatum* L.) and Ibogaine (*Tabernanthe iboga*) clearly showed effects in suppressing alcohol uptake in animal models of excessive drinking [19]. Novel compounds from the genus *Hovenia* were found to contain phenolics and alkaloids [20] and the (2*R*,3R)-5,7,5′-trihydroxy-3′,4′-dimethoxydihydroflavonol (**Fig. 2**), named as hovenodulinol (**1**), was isolated and suggested as an active compound from the fruit of *H. dulcis* [13,21]. Hovenodulinol (**1**) has a different effect on the catabolism of ethanol compared to the well-known 7-*O*-glucosyl-4′-hydroxyisoflavone (daidzin) from Kudzu [22,23]. Treatment with daidzin resulted in the suppression of ethanol uptake as a consequence of the inhibition of liver mitochondrial ALDH (ALDH-2) activity in alcohol-preferring laboratory animals [23–26], whereas the administration of 1 $mg \cdot kg^{-1}$ hovenodulinol (**1**) in rats 30 min before feeding with alcohol enhanced the alcohol-induced ADH and ALDH activities in rat livers, and resulted in the rapid reduction of blood alcohol levels, which occurred 2–3 hours faster than in nonadministered control animals [13,21]. Similarly, it has been shown that 7-[2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyloxy]-2,3-dihydro-4′,5,7-trihydroxyflavone (naringin) in grapevine fruit [27], 5-*N*-ethylglutamine (theanine) in tea [28] and hispidulin 7-*O*-neohesperidoside from *Cirsium japonicum* var. *ussuriense* [29] enhanced the activities of both ADH and ALDH in the livers of alcohol-fed rats. Although the mechanism of the increased activity of both enzymes by these compounds has not been studied, ALDH activity is commonly maintained by synthesis of new protein during the catabolism of ethanol [30,31]. However, when ADH (EC 1.1.1.1.) or ALDH (EC 1.2.1.5.) was incubated *in vitro* with reaction buffer containing the hot water extract from *H. dulcis* fruits, an elevated level of NADH production was observed [32], supporting the hypothesis that the *H. dulcis* extracts posttranslationally promote the corresponding enzyme activities. Similarly, the effect of sesamin {5,5′-(1*S*,3a*R*,4*S*,6a*R*)-tetrahydro-1*H*,3*H*-furo[3,4-*c*]furan-1,4-diylbis(1,3-benzodioxole)} from sesame oil on ethanol catabolism was shown not to be mediated by the induction of ALDH-2 expression [33], which is responsible for > 90% of acetaldehyde oxidation in the liver [32]. Both ALDH-2 and ADH contain thiol groups in their active sites, and oxidation or modification of these critical thiol groups interferes with their enzymatic functions [34–36]. Since the antioxidant activities of *H. dulcis* fruit extract and hovenodulinol (**1**) are well established (see below), it may be speculated that this property may also contribute to their proven positive effect on ethanol catabolism. The antioxidant activity of *H. dulcis* fruit extract and hovenodulinol may be important for interfering with the oxidation of critical thiols in ADH and ALDH, thus circumventing their inactivation. Although the impact of *H. dulcis* fruit extract and hovenodulinol (**1**) on human metabolism in the context of alcohol detoxification is still a matter of further investigation, these findings support the possibility of utilizing phytotherapy in the treatment of alcohol hangover. It will be interesting to investigate the relationship between hovenodulinol (**1**) and the liver mitochondrial proteins including ALDH-2 with respect to the possible modification of the redox/thiol status, which occur following alcohol consumption. Further analyses of the posttranslational redox modification of ALDH-2 should contribute to the elucidation of the effect of hovenodulinol (**1**) during the alcohol detoxification process.

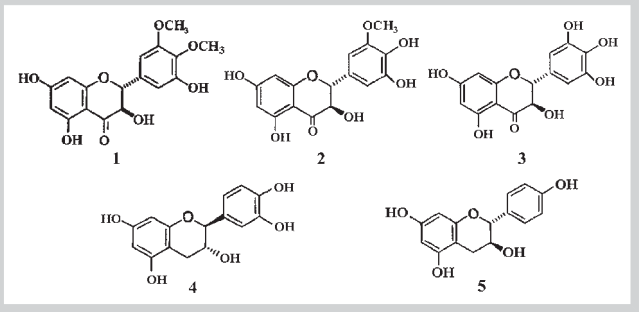

Fig. 2 Structures of active compounds from *Hovenia dulcis* Thunb.

Hepatoprotective Effects

The liver is the largest organ in the human body that plays a key role in the metabolism of xenobiotics and endogenous substances that affect vital functions. Although herbal medicines have long been used for the treatment of liver diseases, these herbal medicines are still the basis of current efforts to develop improved drugs to treat liver diseases.

Studies on the hepatoprotective effect of fruit peduncle extracts in mice and rats by a liver injury model suggest that the extract of *H. dulcis* may protect the liver against chemically induced injuries [6,7–9,37–39]. It has been shown that the MeOH extract of *H. dulcis* fruit peduncles significantly inhibited the increase of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels during response to carbon tetrachloride (CCl_4) in rats when 100 $mg \cdot kg^{-1}$ extract were administered twice a day for 1 week before CCl_4 intoxication [7]. CCl_4 caused significantly decreased levels of protein synthesis in rat liver slice culture,

whereas the pretreatment with the MeOH insoluble fraction from the hot water extract of fruit peduncles (1 hour before CCl_4 treatment) resulted in the inhibition of CCl_4-induced depression of protein synthesis in sliced liver [6]. In case of D-galactosamine/lipopolysaccharide (D-GalN/LPS)-induced mice liver injury, the group pretreated twice, 18 h and 2 h before D-GalN/LPS treatment, with the 200 $mg \cdot kg^{-1}$ MeOH extract of *H. dulcis* fruit peduncles displayed lower levels of blood ALT [7], serum glutamic oxaloacetic transaminase (GOT) and serum glutamic pyruvic transaminase (GPT) activities compared to non-pretreated controls [8]. In addition, the hot water extract of *H. dulcis* fruits and the aqueous extract of *H. dulcis* seeds also showed hepatoprotective effects towards alcohol-induced rat liver injury [9,40]. It is well-known that free radicals derived from oxygen and other chemicals are important factors related to liver injury [41]. The production of toxic free radicals during the metabolism of CCl_4 and formation of acetaldehyde during alcohol catabolism [42] in the liver are the major causes of liver injury. D-GalN/LPS-induced liver injury also is directly or indirectly mediated by ROS [43,44]. Although the precise underlying mechanisms are not yet understood, it is possible that prevention against liver injury by *H. dulcis* is partially due to its antioxidant activity as described below. Furthermore, the aqueous extracts of *H. dulcis* have been shown to enhance the glutathione-S-transferase activity in *in vitro* tests [4,17], which plays an important role in the detoxification of xenobiotics and ROS [45], indicating that *H. dulcis* may also act as an enzyme modulator in a way that is unrelated to its antioxidant properties. The available literature suggests that there are likely multiple potent mechanisms responsible for the hepatoprotective effects of *H. dulcis*. However, further investigations to fully elucidate the exact mechanism of effects mediated by *H. dulcis* are necessary.

Free Radical Scavenging and Antidiabetic Effect

Free radicals are highly reactive molecules that have been implicated in the development of over 100 diseases including cardiovascular diseases, cancer, Parkinson's disease, diabetic complications, inflammation, etc., through oxidative damage to various biomolecules [46]. Eight phenolic compounds which were purified by chromatography from the EtOAc-soluble faction of the methanolic extract of *H. dulcis* stem bark were shown to exert a protective activity on glutamate-induced neurotoxicity in HT22 cells and on free radical scavenging [47]. Two out of the eight purified compounds, (−)-catechin (**4**) and (+)-afzelechin (**5**), showed cell protective effects on the glutamate-induced neurotoxicity, although these compounds display less protective activity than vitamin E. (−)-Catechin (**4**) was found to detoxify ABTS cation radicals (IC_{50} of 7.8 µM), superoxide anion radicals (IC_{50} of 8.0 µM), and DPPH free radicals (IC_{50} of 57.7 µM) [47]. In addition, (+)-afzelechin (**5**) acted as an ABTS cation radical scavenger with IC_{50} values of 23.9 µM [47].

High oxidative stress, which is typically found in patients suffering from diabetes, increases the blood cholesterol level, promotes lipid peroxidation, and leads to various further metabolic complications. A number of studies have described that treatment with antioxidants prevents diabetes and hyperglycemia-induced impairment of endothelium-dependent relaxation [48–52], indicating that oxidative stress is a major factor in the development of complications in diabetes [48,53]. In addition, the treatment of streptozotocin (STZ)-induced diabetic animal models with antioxidants including lipophilic free radical scavengers such as vitamin E, β-carotene, butylated hydroxytoluene and probucol as well as hydrophilic scavengers such as acetylcysteine and vitamin C has suggested that the development of diabetic neuropathy might be mediated by oxidative stress and vascular dysfunction [48]. Studies carried out in alloxan-induced diabetic mice and STZ-induced diabetic rats have shown antidiabetic effects of *H. dulcis* extracts [54–56]. The STZ-induced hyperglycemic mice exhibited lower levels of blood glucose concentration and significantly higher number of pancreatic islets and pancreatic β-cells when 40 $mg \cdot kg^{-1}$ of hot water extract of fruit peduncle were administered once a day for 6 weeks [55]. The accumulation of ROS provoked by hyperglycemia *in vivo* plays a significant role in the induction of β-cells apoptosis in type 2 diabetes [49], because the expression of antioxidant enzymes is known to be very low in islet cells compared to other tissues and cells [57]. In diabetic C57BL/KsJ-*db/db* mice, the β-cell density (number per mm^2 pancreas) was significantly increased in diabetic mice treated with antioxidants (*N*-acetyl-L-cysteine, hydrogen peroxide scavengers, combined with vitamin C plus vitamin E) compared to the untreated control group [49]. The similar effects of *H. dulcis* and other antioxidant agents suggest that the antioxidant properties of *H. dulcis* may prevent and/or delay β-cells dysfunction in diabetes mediated by providing protection against glucose toxicity (the formation of excess ROS levels), and results in the reduction of blood glucose concentration in STZ-induced hyperglycemic mice. As support for this, Lee et al., [56] showed that the treatment of STZ-induced diabetic rats with 20 $mg \cdot kg^{-1}$ or 50 $mg \cdot kg^{-1}$ of the ethyl acetate fraction from an 80% methanolic extract of *H. dulcis* fruits, which contained the highest antioxidant activity, resulted in decreasing levels of lipid peroxide, plasma glucose, triglycerides and total cholesterol in liver microsomes, in parallel with increasing levels of glutathione in the liver cytosol. Although the decrease of lipid peroxides with concomitantly increased glutathione levels mediated by *H. dulcis* extracts in STZ-induced diabetic rats indicates that free radical scavengers of *H. dulcis* may be the important factor in the cytotoxic protection mechanism, the exact mechanism of *H. dulcis* extract at the molecular level is still obscure. Further studies investigating the interplay of *H. dulcis* extracts and the alteration of redox balance in diabetes may further contribute to our understanding of antidiabetic mechanisms by *H. dulcis*. In addition, it has been suggested that some flavonoids from plants can also act through other mechanisms by interacting with protein function, modulating intracellular cascades and modulating gene expression, since their antioxidant properties have been linked with the prevention of β-cell destruction in models of drug-induced diabetes [58]. In this respect, it is interesting that procyanidins from grape seeds have been shown to interact with insulin signalling pathways, resulting in the modulation of β-cell function, insulin secretion and proliferation [58,59], whereas treatment with resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) from grape skins increased insulin secretion by blocking K_{ATP} and K_v channels in mouse β-cell lines [58,60]. Therefore, these finding may also indicate the possibility of interaction between *H. dulcis* extract and insulin signalling, although this will require further investigations.

Antimicrobial and Antiparasitic Effects

Recently, *H. dulcis* extracts were reported to possess an antigiardial activity [5]. The dichloromethane (DMC) fraction from the MeOH extract of *H. dulcis* leaves inhibited the growth of *Giardia lamblia* trophozoites (IC_{50} of 12 µg·mL^{-1}), which are the flagellated protozoan parasite and the causative agent of giardiasis. Although the antigiardial effect of *H. dulcis* extracts has been established *in vitro*, the not detectable cytotoxic effect of *H. dulcis* extracts on rat intestinal epithelial cells (IEC-6 line) suggests the potential of *H. dulcis*, but further studies are needed including isolation of active compounds.

Hot water extracts from leaves and stems of *H. dulcis* have shown antimicrobial activity against gram-positive and gram-negative bacteria, and yeast [61]. These extracts contain significant amounts of 3-methoxy-4-hydroxybenzonic (vanillic acid) and 3-methoxy-4-hydroxycinnamic (ferulic acid), which may contribute to the antimicrobial activity.

Noncaloric Sweeteners and Sweetness Inhibitors

The isolation of noncaloric and noncariogenic sweet compounds from sweet-tasting plants as a substitute for sugars and artificial sweeteners that have potential harmful side effects has been a focus to prevent obesity and for the therapy of diabetes. It has been shown that high levels of sugars and polyols (18.4% w/w of the dried plant material) are present in the edible peduncle of *H. dulcis* Thunb. [3], whereas sugar cane (*Saccharum officinarum*) contains 15–20% w/w sucrose. Interestingly, the dammarane-type triterpene saponins hodulosides I–V (**6**–**10**) were isolated from leaves of *H. dulcis* (**Fig. 3**), and were reported as sweetness inhibitors [62]. Therefore, *H. dulcis* was recognized as a potential source for sweeteners and for sweetness-modifying substances of natural origin in East Asia [3].

Biologically Active Compounds

H. dulcis contains a variety of biologically active compounds including saponin derivatives, dammarane-type triterpene saponins [hodulosides I – V (**6**–**10**)] and flavonoids [hovenodulinol (**1**), hovenitin I (**2**), (+)-ampelopsin (**3**), (−)-catechin (**4**) and (+)-afzelechin (**5**)] [8,13,18,21,47,62,63].

In 1992, hodulosides I–V (**6**–**10**) were isolated from the leaves of *H. dulcis*, and the antisweet potency of hoduloside I (**6**) corresponds to ca. 50% of that of ziziphin that is isolated from the leaves of *Ziziphus jujube* [62]. A number of dammarane-type saponins used as antisweet substances have been proposed to alter the taste receptor surface, therefore the originally stimulating sweet molecules provoke a lesser degree of stimulation of sweet receptors [64]. Hoduloside I (**6**) as a sweetness inhibitor might be useful for elucidating the receptor mechanism of sweet taste.

A broad spectrum of pharmacological activities has been reported for dihydroflavonols, including hepato- and gastroprotective, antioxidative, antifungal, and antineoplastic activities [65, 66]. The dihydroflavonols hovenitin I (**2**) and hovenodulinol (**1**) have been isolated from the fruit and/or seed of *H. dulcis* as compounds enhancing alcohol catabolism by increasing ADH and ALDH activities [13,21]. This resulted in inhibition of the ethanol-induced muscle relaxation in rats [8]. In addition, hovenitin I (**2**) showed a hepatoprotective effect on rat liver injuries induced by CCl_4 or D-GlaN/LPS [8]. Apart from the compounds indicated above, (+)-ampelopsin (**3**) was reported to possess numerous pharmacological activities, such as anti-inflammatory, antimicrobial, antioxidant, antihypertensive, hepatoprotective and anticarcinogenic effects [67]. (+)-Ampelopsin (**3**) also enhanced the activity of ADH and inhibited ethanol-induced muscle relaxation in rats in a dose-dependent manner [8,18,63]. Higher yields of (+)-ampelopsin (**3**) can be achieved by hydrolysis [18]. The development of products highly enriched in (+)-ampelopsin is currently being pursued. A procedure for large-scale purification from *H. dulcis* extracts to 50% content has been published [63].

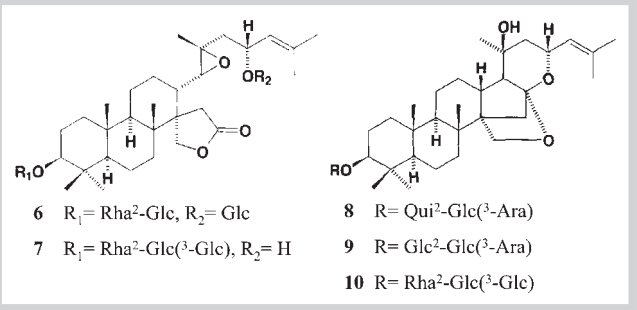

Fig. 3 Structures of antisweet compounds from *Hovenia dulcis* Thunb. Ara = arabinopyranosyl, Glc = glucopyranosyl, Qui = quinovopyranosyl and Rha = rhamnopyranosyl.

Cytotoxicity Studies

Even though medicinal plants have a long tradition of human use, there is a need to evaluate the potential toxic effects of herbal medicines on the liver, kidney, nervous system, cardiovascular system and skin, and also to evaluate their mutagenicity and carcinogenicity [68].

In the case of *H. dulcis*, the literature reviewed did not indicate any cytotoxic effects of extracts from stem barks (EtOAc fraction from MeOH extract and EtOH extract) [47,69], leaves (MeOH extract) [5,70] and fruits (hot water and EtOH extract) [69] on mammalian cells (IEC-6, HEL299 and Chang cells) and in mouse hippocampal HT22 cells. 1 g·L^{-1} hovenodulinol (**1**) exhibited a less than 25% inhibition effect on cell growth of WRL 68 human liver cells [13]. The absence of detectable or significant cytotoxic effects of *H. dulcis* extracts and its active compounds support the safe use of *H. dulcis*. This corroborates the use of *H. dulcis* as a food ingredient in Asian countries including Taiwan and South Korea [71,72]. Traditionally, the dried fruits and leaves, which contain a high amount of sweeteners [73] and aroma glycosides [74], have been used as tea. More recently, the use of *H. dulcis* as functional food ingredient in noodles, beverages and other food products has been proposed [75–77]. In China, Japan and Korea, *H. dulcis* extracts are processed to tablets, powders, liquids or granules and commonly used as dietary supplements. An industrially produced health drink containing fruit extracts was shown to reduce levels of blood alcohol concentration compared with control groups when 10 mL·kg^{-1} of the health drink was orally administered to rats 30 min before or after alcohol feeding [76,77]. Although these products have been introduced based on experimental evidence, they are not yet approved to treat, cure or pre-

vent any kind of disease according to the Korea Food and Drug Administration (KFDA) [72]. This reflects the lack of systematic clinical studies on *H. dulcis* extracts. It is generally believed that the standardization of plant materials is not needed when used by the local communities for their primary health care. However, a systematic scientific evaluation is required for application in modern medicine. Most importantly, clinical trials with standardized products will be needed for further development.

Conclusions

This minireview summarizes current knowledge on one of Asia's lesser known medicinal plants. Based on the available literature, *H. dulcis* has useful pharmacological properties that include detoxification after alcoholic poisoning, hepatoprotective effects, antioxidative, antimicrobial and antidiabetic effects. However, several issues still need to be addressed by basic research as well as clinical studies. This includes better characterization of the pharmacologically active components of *H. dulcis* as well as the elucidation of the underlying molecular mechanisms of action. Thus, any clinical application will only be possible when thorough studies demonstrate the safety, quality and potency of *H. dulcis* in a systematic manner. For these reasons, extensive pharmacological and clinical investigations will be a major focus for the future. Last but not least, we hope that this minireview will stimulate research on *H. dulcis* outside Southeast Asia also.

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