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Hovenia dulcis Thunb. Revisited: a mini critical review and call for further research to insightfully elucidate

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Abstract
Hovenia dulcis (H. dulcis) has attracted substantial attention because it is been used as a medicinal herb in traditional folk medicine for treatment of liver diseases and detoxification by alcoholic poisoning. To support its functional attributes, many investigations have been carried out to find out its antioxidant, anti-inflammatory, antimicrobial, anti-diabetic, anti-tumor, hepatic-protective activities. However, some cases of toxic hepatitis have been reported in both adult and children patients after ingesting *H. dulcis*. So we strongly emphasized that hepatic-protection is not potential pharmacological marker to evaluate the quality of *H. dulcis* and its products due to this science inconsistency. Based on this mini review, we discussed and suggest that thorough scientific scrutiny is necessary in future researches to insightfully elucidate science opinion. The authors hope that this work will be helpful to give insight knowledge for readers, researchers, reviewers, and editors who interested in the related field of *H. dulcis* studies.

Keywords: *Hovenia dulcis*, alcoholic poisoning, hepato protection

1. Introduction
Hovenia dulcis Thunb (*H. dulcis*) belongs to the Rhamnaceae family and is commonly known as a food supplement and traditional medicine in China, Japan and Korea. The full taxonomic hierarchy is shown below in Table 1 [1].

Table 1: Taxonomic hierarchy of *Hovenia dulcis* Thunb

Kingdom	Plantae
Subkingdom	Viridiplantae
Infra kingdom	Streptophyta
Superdivision	Embryophyta
Division	Tracheophyta
Subdivision	Spermatophytina
Class	Magnoliopsida
Superorder	Rosanae
Order	Rosales
Family	Rhamnaceae
Genus	Hovenia Thunb
Species	*Hovenia dulcis* Thunb

2. Traditional uses and ethno pharmacology
H. dulcis has been used as traditional folk remedies for the treatment of liver diseases and detoxification by alcoholic poisoning. The fruit of *H. dulcis* has traditionally employed as an antispasmodic, febrifuge, laxative and diuretic agent, while its seeds have been consumed as a diuretic and a cure for alcohol intoxication [2, 3].

3. Phytochemistry
The first indentified component of *H. dulcis* is (+)-ampelopsin isolated from the fruits in 1997 by Hase [4]. 3(Z)-dodecenedioic acid was isolated by Cho [5]. Phenolic acids (vanillic, ferulic and trihydroxybenzoic acid), flavan-3-ols (catechin and afzelechin), (+)-aromadendrin (a dihydroflavonol), 3,5-dihydroxystilbene, and methyl vanillate have been found in *H. dulcis* stem bark [6]. (+)-dihydromyricetin (ampelopsin) was isolated from the fruits [7]. Various flavonol glycosides derived from kaempferol and quercetin including kaempferol 3-O-α-L-rhamnopyranoside-7-O-[α-D-glucopyranosyl(1-3)-α-L-rhamnopyranoside], kaempferol 3,7-O-α-L-dirhamnopyranoside, kaempferol 3-O-α-L-rhamno-pyranosyl (1-6)-O-β-D-glucopyranosyl

(1-2)-O-β-D-glucopyranoside, E-3-carboxyl-2-petenedioate 5-methyl ester, quercetin 3-O-α-L-rhamnopyranoside, kaempferol 3-O-α-L-rhamnopyranoside, quercetin 3-O-β-D-glucopyranoside isolated from the leaves [8]. Oxalic acid, tartaric acid, malic acid, ascorbic acid, citric acid and fumaric acid were found in *H. dulcis* peduncles [9]. Ampelopsin, taxifolin and myricetin were found in the fruit-stalk of *H. dulcis* [10] and kaempferol and quercetin also is from the fruits [11]. 7-O-protocatechuoyl-3-dehydroxyisoceanothanolic acid, 27-O-protocatechuoyl-3-dehydroxycolubrinic acid, 27-O-protocatechuoyl-3-dehydroxyepicolubrinic acid, 27-O-protocatechuoylbetulinic acid, 27-O-p-hydroxybenzoylbetulinic acid, 27-O-syringoylbe-tulinic acid, 27-O-vanilloylbetulinic acid, 3-O-trans-P-coumaroylalphitolic acid, 3-O-cis-p-coumaroylalphitolic acid were found in the roots [12]. Epi-gallocatechin, (+)-catechin, trihydroxyflavanone di-C-glucoside, myricetin-O-rutinoside, myricetin-3-O-glucoside, quercetin-O-rutinosyl-glucoside, phloretin-3',5'-di-C-β-glucoside, quercetin-3-O-rutinoside (rutin), quercetin-3-O-glucoside and isorhamnetin-O-rutinosyl-glucoside were found in *H. dulcis* peduncles [13]. Chemical structures of several compounds are showed in Figure 1.

4. Analytical methods

High performance liquid chromatography (HPLC) has been the most frequently used for quality evaluations of *H. dulcis* because of its ready availability, easy operation, high sensitivity and reproducibility, good resolution and linearity, and ability to analyze multiple components. The separation was performed on a column of Xbridge™ Shield RP18 (4.6 mm I.D. x 150 mm, 3.5 µm), the mobile phase was 0.1% acetic acid and 100% acetonitrile under a flow rate of 1.0 mL/min in a gradient elution manner, and detection wavelength was set at 365 nm. Four markers (ampelopsin, taxifolin, myricetin and quercetin) stimultaneously determined for quality of *H. dulcis* [10]. HPLC has also been used successfully to screen the main potential active compound ampelopsin (dihydromyricetin) from *H. dulcis* [7] and to screen kaempferol and quercetin [11]. In the optimal condition, oxalic, tartaric, malic, ascorbic, citric and fumaric acids were determined by an HPLC-UV methodology after samples extraction with 4.5% m-phosphoric acid. The mobile phase was distilled water with 1.8 mM H_2SO_4 (pH = 2.6) under a flow rate of 0.9 mL min for ascorbic acid and 0.4 mL/min for other acids [9].

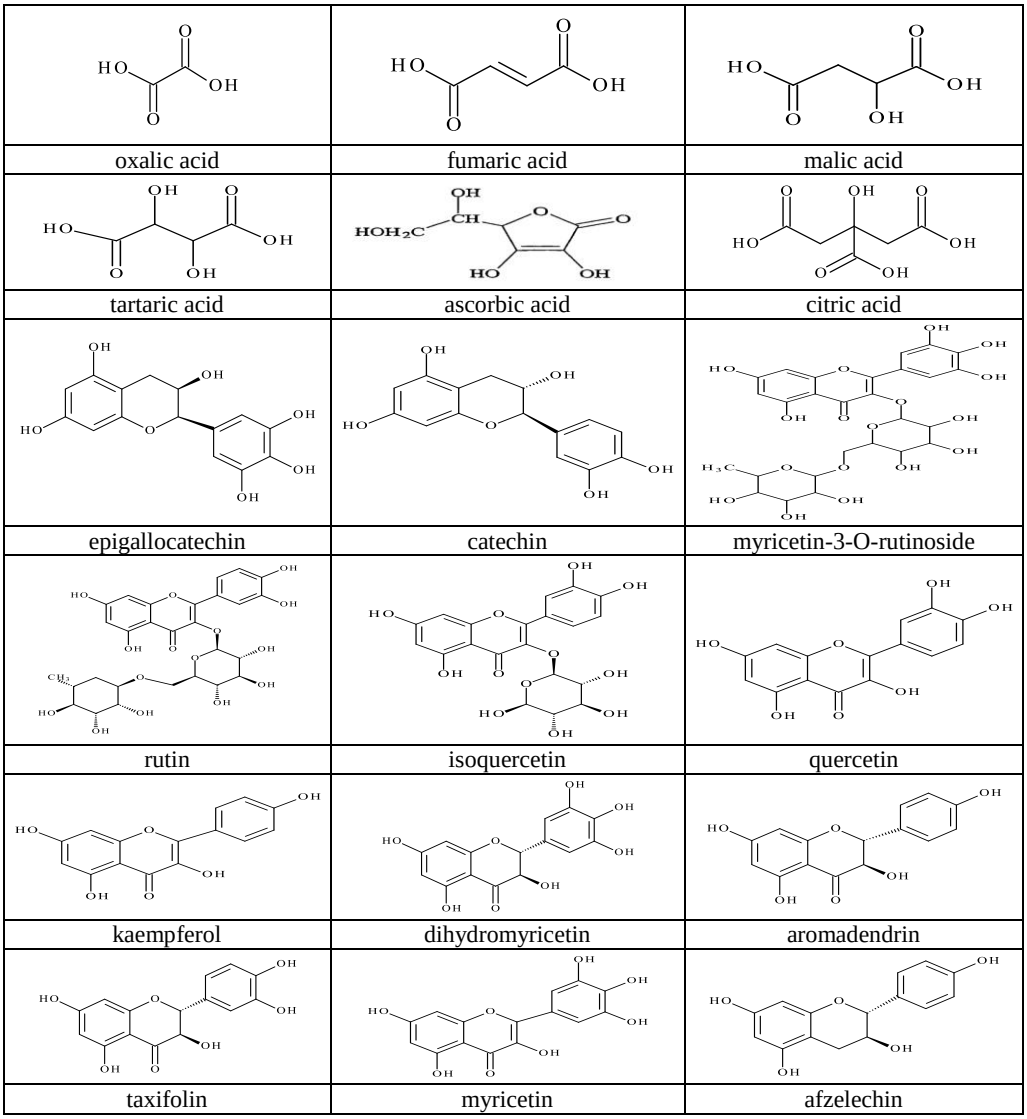

Fig 1: Chemical structures of several compounds in *H.dulcis*

Reversed-phase High performance liquid chromatography was performed to determine the phenolic compounds by using an Agilent 1100 series. Double online detection wavelength was set at 280 nm and 370 nm, as well as a mass spectrometer API 3200 Qtrap equipped with an ESI source and a triple quadrupole-ion trap mass analyzer that was controlled by the Analyst 5.1 soft were. Phenolic compounds were separated using a Spherisorb S3 ODS-2 C18 column (3 µm, 4.6 x150

mm), the mobile phase was 0.1% formic acid in water and 100% acetonitrile under a flow rate of 0.5 mL/min in a gradient elution manner. Based on this method, epi-gallocatechin, (+)-catechin, trihydroxyflavanone di-C-glucoside, myricetin-O-rutinoside, myricetin-3-O-glucoside, quercetin-O-rutinosyl-glucoside, phloretin-3',5'-di-C-β-glucoside, quercetin-3-O-rutinoside (rutin), quercetin-3-O-glucoside and isorhamnetin-O-rutinosyl-glucoside were found in *H. dulcis* peduncles [13].

5. Modern pharmacological research

5.1. Antioxidant activity

The evolution of antioxidants in *H. dulcis* pseudofruits through maturation process was evaluated. The mature period was determined by a maturity degree (MD) calculated as % soluble sugars/titratable acidity expressed as % tartaric acid. The most immature peduncles (Hd01) with MD of 0.52 and followed by Hd02-Hd05 with MD (0.64, 4.61, 9.19, 8.31) were collected. The immature peduncles (Hd01 or Hd02) have greater antioxidant capacity compared to another which revealed that antioxidant properties of *H. dulcis* peduncles may be optimized at immature stage [9]. Likewise, Antioxidant activities of *H. dulcis* pseudo fruits at different ripening stages also were evaluated [13].

5.2. Inflammatory effects

Evidences of anti-inflammatory capacity of extracts from fruits and seeds of *H. dulcis* were developed in chronic alcohol-fed rat model. These extract reduced hepatic lipid contents and droplets, serum lipid concentration and hs-CRP, TNF-α and IL-6 levels. The extract administration significantly up-regulated gene expression of *Ppargc1a, Ppara, Cpt1a* and *Acsl1*, and down-regulated gene expression of *Myd88, Tnfa* and *Crp*. Extract supplementation also significantly reduced hepatic activities of fatty acid synthase and phosphatidate phosphohydrolase , plasma alcohol and acetaldehyde levels, hepatic enzyme activity and protein expression of CYP2E1 in chronic alcohol-fed rats, which demonstrated that both of extracts are effective in anti-steatotic and inflammatory activities via regulation of lipid and inflammation metabolism [14].The ethanol extract of *H. dulcis* fruits was investigated the anti-inflammatory effect in mouse macrophage Raw 276.7 cells model. This extract significantly constrained the lipopolysaccharide-stimulated nitric oxide, inducible nitric oxide synthase, COX-2, IL-1β and TNF-α expression and suppressed the phosphorylation of inhibited kappa B-alpha and p65 nuclear translocation [11].

5.3. Antitumor activities

Antitumor activity of *H. dulcis* fruits and leaves against different cancer cell lines was reported in some researches**.** Lee et al. (1999) reported that ethanol extract of fruits has Hep3B and MCF-7 cell lines growth inhibitory capacity while this extract is not effective in against growth of HEL299 cells [15]. Ethanol extract of pseudo fruits was reported to have high degree of selectivity against SP2/0 mouse myeloma and BW lymphoma cell [16]. Anticancer activities of *H. dulcis* pseudo fruits at different stages were evaluated on some cell lines including MCF7, HCT15, HeLa and HepG2. Only extracts of the most immature pseudo fruits exhibited antitumor activity against all tested tumor cell lines but they are safe for normal cell [13]. Compound ampelopsin from *H. dulcis* exhibit potent antiangiogenic activities and therefore could be valuable for the prevention and treatment of angiogenesis-related diseases including cancer [17].

5.4. Antimicrobial activities

It has been reported that extracts of fruit stalk and leaves for *H. dulcis* could inhibit the multiplication of trypanosome cruzi [16]. A compound named as 3(Z)-dodecenedioic acid isolated from leaves of *H. dulcis* showed growth inhibitory effects of *Staphylococcus aureus* and Escherichia coli at concentration of 500 µg/mL [5]. Anti-bacterial properties of the biosynthesized gold nanoparticles from *H. dulcis* fruits were found to be significant [18]. Extracts of the most immature pseudo fruits showed higher bacteria inhibitory capacity compared to another [13].

5.5. Antidiabetic activities

To the author's best knowledge, anti-diabetic studies of *H. dulcis* pseudo fruits are scarce. In 2012, Wu et al reported that antioxidant effect of the ethanol extracts of *H. dulcis* via streptozotocin diabetic mice models. An up-regulating the concentration of superoxide dismutase decrease and a down-regulating the levels of malondialdehyde and iNOS were recorded after treatment of ethanol extracts [19].

5.6. Hepatic protection

The hepatoprotective effect of polysaccharides from the peduncles of *H. dulcis* was evaluated in alcohol- induced liver injury in mice. The supplementation of polysaccharides significantly reduced alanine aminotransferase and aspartate aminotransferase levels and the liver level of malondialdehyde. The liver activities of superoxide dismutase and glutathione peroxidase remarkably restored in alcohol-induced liver injury mice. Authors suggested that *H. dulcis* has a significant protective effect against acute alcohol-induced liver injury [20].

The hepato-protective effect of the fruit extract from *H. dulcis* on liver fibrosis induced by carbon tetrachloride treatment *in vivo* rat model was evaluated. The alanine aminotransferase and aspartate aminotransferase activities, bilirubin levels and expression volume of collagen I and III in the carbon tetrachloride + extract were found to be lower than in the only carbon tetrachloride group. Additionally, fruit extract administration decreases the accumulation of collagen in liver tissue and inhibited Hepatic Stellate Cell proliferation [21]. The hepatoprotective effect also was reported by Hase et al 1997 [4]. *H. dulcis* fruit extract may have potential to improve hangover symptoms and alcohol-induced hepatic damage [22].

Recently, continuously reports have indicated that extracts from the fruit stalk are effective in preventing liver cirrhosis and protecting the liver, which resulted in increased interest in the application of *H. dulcis* in Korea [23]. In Vietnam, *H. dulcis* also is used in pharmacological industry to made hepatoprotective products in recent years. However, in Korea, two cases of toxic hepatitis have been reported in adult patients after ingesting *Hovenia dulcis* [24, 25]. A case of toxic hepatitis induced by *H. dulcis* in a 3-year-old boy after consuming water boiled with *H. dulcis* for about 1 year have also been reported by Kim [26].

6. Discussion

H. dulcis was considered as a medicinal herb which has been reported that it can be used as a functional food [9, 13] and used as functional foods under a kind of extract or capsule products in Japan, Korean and Vietnam for liver disease remedies. But a thorough scientific research on component analysis for judging the nutritional quality and bio-activity of *H. dulcis* is necessary. Al thought the herb-drug interactions of *H. dulcis* fruit extracts via the modification of pharmacokinetic

regulators, such as cytochrome P450 (CYP) enzymes have been reported *in vitro* [27], there are not any studies *in vivo* on pharmacokinetics, internal metabolism, proper usage and side effects of *H. dulcis*. Some cases of toxic hepatitis have been recorded. Hence**,** there is a need for *in vivo* substantiation on human to certify its health potential.

7. Conclusions

H. dulcis has attracted substantial attention because it was thought to have outstanding benefits for treatment of liver intoxication. Some pharmacological studies have been performed *in vitro* and also developed *in vivo* in animal models**.** Though several pharmacological mechanisms related to biological activity have already been explained, the comprehensive pharmacological mechanisms of *H. dulcis* need to be elucidated. Based on pharmacological research and reported cases of toxic hepatitis induced by *H. dulcis*, we strongly recommended that hepatoprotective effect is not potential pharmacological marker to evaluate the quality of *H. dulcis* and its products due to this science inconsistencies. Pharmacokinetics studies on the main components, especially the bioactive components are still largely lacking, therefore firm evidence for further clinical application is necessary in order to assess the therapeutic potential of *H. dulcis* and its pharmaceutical commodities.

8. Conflicts of interest

The authors declare no conflicts of interest

9. References

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