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EDITORIAL

Are herbals more hepatotoxic than prescription medications?

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In this issue, Huang et al. report the results of a prospective study of 1297 Taiwanese patients with liver injury attributed to either herbal and dietary supplements (HDS) (HDS-induced liver injury; HILI) or conventional prescription medications (DILI) [1]. DILI is a notoriously difficult diagnosis to establish even when there is only a single purified suspect drug since the onset of liver injury is largely independent of the dose or duration of use and may be associated with varying phenotypes and severity of liver injury. With an incidence of only 1 in 10,000 to 1 in 100,000 medication exposed individuals, idiosyncratic DILI is believed to be mediated via rare genetic polymorphisms involving host metabolic and/ or adaptive immune pathways. HILI accounted for 22% of the Taiwanese cases and was associated with significantly higher MELD scores at presentation and mortality during follow-up (12.6% vs 8.0%). Of note, the latency of HDS product use to liver injury onset was also significantly longer compared to the DILI cases (38 vs 28 days) which may be due to delayed recognition of the herbal product as a cause of liver injury or reluctance of HDS consumers to seek medical care [2]. The latter hypothesis has previously been implicated for the consistently poorer outcomes seen in acute liver failure patients attributed to HDS products compared to conventional medications in the United States [3, 4]. The authors also found that crude "home grown" HDS products were the most commonly implicated type of herbal products and independently associated with a higher mortality rate compared to those who consumed processed, commercial HDS products that are federally regulated and prescribed by licensed providers in Taiwan.

This study adds to a growing body of literature regarding the clinical features and outcomes of HILI versus DILI (Table 1). Of note, the implicated agents in the East Asian studies are nearly all traditional Chinese medicines or crude herbs, whereas in the West synthetic anabolic steroids or multi-ingredient nutritional supplements are most commonly identified. The differences in implicated agents likely explain the age and gender differences across regions wherein HILI in East Asia is more often seen among females and older individuals taking them for presumed specific health benefits while there is a preponderance of younger patients and males in the West consuming body building supplements and other products to "boost" their energy, facilitate weight loss, or improve their sense of well-being. It is also noteworthy that there are other important demographic differences in HILI compared to DILI patients that vary by country. In the West, HDS products are taken by more highly educated people in an effort to improve their general health status while Huang et al. found that HILI was more commonly identified in individuals with lower levels of education and socioeconomic status [1, 5]. The preponderance of traditional Chinese medicine users in the HILI group is likely due to cultural traditions and a perception that these "natural" products used for thousands of years have few, if any side effects. Since recent studies demonstrate that > 60% of Taiwanese adults use TCM and the majority of Americans also report regular use of over-the-counter supplements, a rising incidence of HDS hepatotoxicity will likely be encountered for years to come [5, 6].

In the current study, the observation that chronic hepatitis B was an independent risk factor for mortality in both the HILI and DILI cases was interesting but not entirely unexpected [1]. Prior studies of anti-tuberculosis therapy in Asia have demonstrated a higher rate of DILI and poorer outcomes in individuals with pre-existing chronic hepatitis B compared to those without [7]. Although it is difficult to determine if the liver injury episode was truly due to the drug versus HBV flare, the poorer outcomes in patients with pre-existing liver disease have been previously reported. The United States Drug-Induced Liver Injury Network and other groups have reported significantly higher 6-month mortality rates in patients with pre-existing liver disease (i.e. non-alcoholic fatty liver disease), presumably due to the lower

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Table 1 Herbal and Dietary supplement (HDS) hepatotoxicity cases compared to prescription medication cases in International DILI Registries

DILI Registry	Huang 2021 (1)	Shen 2019 (2)	Suk 2012 (4)	Navarro 2014 (5)	Medina-Caliz 2018 (6)	Bessone 2021 (7)
Country	Taiwan	China	South Korea	United States	Spain	Latin America
Number of HILI cases (% total)	285 (22%)	6951 (27%)	240 (65%)	130 (16%)	52 (6%)*	45 (12%)*
Inclusion criteria	ALT > 5 × ULN ALP > 2 × ULN or bili > 2.5 mg/dl	No specific cutoffs	ALT > 3 × ULN or bili > 2 × ULN	ALT > 5 × ULN ALP > 2 × ULN or bili > 2.5	ALT ≥ 5 × ULN ALP ≥ 2 × ULN or ALT ≥ 3 × ULN and bili ≥ 2 × ULN	ALT ≥ 5 × ULN ALP ≥ 2 × ULN or ALT ≥ 3 × ULN and bili ≥ 2 × ULN
Causality method	RUCAM ≥ 6	RUCAM ≥ 6 or DILIN score 1–3	RUCAM ≥ 3	DILIN score 1–3	RUCAM ≥ 3	RUCAM ≥ 3
Leading implicated HDS agents	Xiao Chai Hu Tang (5), *Dysosma pleiantha* (5), snake gallbladder (5), *Polygonum multiflorum* (4), Long Dan Xie Gan Tang (4)	Heshouwu (381), other traditional Chinese medicine (765)	N/A	Anabolic steroids (45), Herbalife™ products (5), Hydroxycut (5), green tea products (4)	Anabolic steroids (20), green tea products (8), Herbalife™ products (6), *Phyto soya* (3)	Anabolic steroids (16), green tea products (7), Herbalife™ products (5), *Garcinia cambogia* (4)
Demographic differences	HILI had less education and lower income. Gender and age similar	HILI more often female. Age similar	HILI more often female. Age similar	HILI younger and more often male	HILI younger and more often male	HILI younger and more often male
HILI lab profile		Not reported				
% Hepatocellular	62%		78%	57%	81%	80%
% Mixed	23%		7%	20%	19% cholestatic or mixed	20% cholestatic or mixed
% Cholestasis	15%		15%**	17%		
HILI severity	Higher peak bili and ALP	Not reported	Higher peak ALT	Higher onset bili	Higher onset bili and ALT	Higher onset bili, ALT, and ALP
HILI mortality or liver transplant	Higher in HILI (12.6 vs. 8.0%)	102 overall (0.39%)	No difference (1.5 vs. 1.0%)	Higher in HILI (13% vs. 3%)	No difference (3.8 vs. 4.1%)	No difference (11.1 vs. 4.3%)
HILI latency period	Longer	Longer	Similar	Similar	Similar	Similar

ALT alanine aminotransferase, *ALP* alkaline phosphatase, *Bili* total bilirubin, *DILI* conventional drug induced liver injury, *HILI* herbal and dietary supplement induced liver injury, *RUCAM* Roussel Uclaf Causality Assessment Method, *ULN* upper limit or normal

*The original manuscripts separated anabolic steroid-related DILI from other HDS-related DILI, whereas we combine them

**Approximate as includes patients taking both HDS and conventional drugs

level of hepatic reserve and impaired regenerative capacity [2, 8, 9].

A few limitations of the current study are worthy of comment. First, the Roussel Uclaf Causality Assessment Method (RUCAM) is an objective, standardized causality tool used in DILI research but many of the data fields are not evidence based and it was never developed or tested for use in HDS cases. Furthermore, the RUCAM has a lower inter-rater reliability compared to expert opinion adjudication [10]. In addition, the authors excluded DILI patients who were taking both HDS and conventional medications together, which ignores a large segment of the overall population and therefore reduces the generalizability of the study findings. In the DILIN prospective study, more than 20% of patients were taking multiple suspect drugs or HDS products simultaneously [2]. Finally, the actual incidence of bona fide DILI cases in the general population of Taiwan is not possible to assess in the current study. Although the processed herbs mentioned in the Huang study are regulated and dispensed by the government, the denominator of exposed individuals was not reported. Furthermore, the encatchment population for the current multicenter study of 6 major medical centers and the Taiwan Food and Drug Administration was not reported. In addition, many patients with DILI are asymptomatic and may never present to medical attention as was seen in the population based studies of idiosyncratic DILI in Iceland and France [11, 12]. Nonetheless, with the easily searchable and well codified electronic medical records in Taiwan, we are hopeful that more reliable data on the denominator of use of both prescription medications and processed HDS products may allow for more accurate estimations of DILI incidence in the future.

The Huang et al. study also highlights several key limitations in modern hepatotoxicity research. Firstly, chemical ingredient analysis of HDS products may not only improve HILI diagnosis but also improve our understanding of the mechanism of liver injury. The manufacturing, testing, and regulation of HDS products is minimal in most countries but requires greater regulatory oversight and interventions due to the rising incidence of HILI worldwide (Table 1). For example, crude, unprocessed herbal products and botanicals can have substantial variation in active ingredients from batch to batch due to differences in the soil, climate and growing conditions of the plants. This frequently leads to questions about what the active ingredient(s) of a given HDS product are and what the actual hepatotoxicant might be. Going forward, ingredient analysis of the suspect products using quantitative HPLC and Mass spectroscopy methods may increase confidence that a product is the causative agent if it verifies presence of a known hepatotoxin, exonerate a product if there is no evidence of known hepatotoxins (especially when a patient is taking multiple products), or even identify unreported or unsuspected adulterants [13]. Furthermore, additional in vitro toxicology studies of potentially hepatotoxic herbal products may further improve our understanding of the intracellular mechanisms of liver injury and associated risk factors.

Finally, the current study highlights the need for increased collaboration amongst international networks to accelerate research in rare diseases like idiosyncratic DILI [14]. These efforts will not only improve our understanding of the clinical features and natural history of DILI, but also help identify and validate genetic risk factors, which may vary by patient race/ethnicity. In support of this, one of the top causes of HILI in Huang et al. was *Polygonum multiflorum*, a widely used product to improve fertility and hair color in both China and Taiwan. Recently, HLA-B*35:01 was linked to an increased risk of *Polygonum* HILI in Han Chinese with an odds ratio of over 80 that was confirmed in a validation cohort [15]. Interestingly, HLA-B*35:01 was also associated with green tea extract liver injury amongst 40 Caucasian individuals in the United States as well as nevirapine hypersensitivity reactions [16, 17]. Therefore, future collaborative analyses of genetic risk factors across race and medication/HDS consumption may yield insights into the mechanism and immunopathogenesis of idiosyncratic DILI which is a worldwide health problem of growing concern to patients, providers and regulatory authorities.

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Declarations

Conflict of interest Vincent Chen has no competing interests and Robert Fontana has received research support from Gilead, BMS and Abbvie.

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