Speaking of the (Barely legal) elephant in the room: Herbal or dietary supplement related acute liver failure

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Abbreviations: DILI: drug-induced liver injury; ALF: acute liver failure; HDS: herbal and dietary supplements; FDA: Food and Drug Administration; HLA: Human leukocyte antigen; ICD: International Statistical Classification of Diseases and Related health problems; TCM: Traditional Chinese Medicine

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Titled ‘Barely legal’, Banksy’s first United States (USA) exhibition showcased Tai, an Indian elephant, painted with pink and gold pattern to blend in with the wallpaper of the living room, intended to mock the art world’s claim for the true portrayal of the state of the world where over 650 million people live below the poverty line, yet, never actually doing anything about it [1]. Irony befitting the title of the exhibition was that Los Angeles’s Animal Services Department which had permitted the elephant’s appearance at the exhibition, later stated that the ‘paint that was used although non-toxic, was unsafe according to government regulations’. Tai appeared unpainted in the living room the following day!

Dietary supplements are not subject to the premarket safety evaluations in the USA since the amendments brought in by the Dietary Supplement Health and Education Act of 1994. Population-based studies from the United States have estimated the annual incidence of drug-induced liver injury (DILI) to be 2.7 per 100,000 [2] and drug-induced acute liver failure (ALF) as 1.6 per 1,000,000 [3]; herbal and dietary supplements (HDS) account for 43% of DILI and 19% of ALF [2,3].

Ghabril and colleagues investigated the trends in listing and outcomes of drug-induced ALF in the USA between 1995 and 2020 using the United Network for Organ Sharing database (n=267,615) [4]. Proportion of patients listed with drug-induced ALF overall decreased (0.5%) during 2013-2020 compared to that in 1995-2003 (0.9%) and 2004-2012 (1%). Analysis included the determination of the year of approval from Food and Drug Administration (FDA) for all implicated medications. While 38 cases of drug-induced ALF were due to 28 drugs approved in 1995-2003 and 7 cases due to 6 drugs approved in 2004-2012, no drugs approved in 2013-2020 were among in the list of causative agents. In contrast, of the 2146 patients included in the analysis, proportion of cases attributed to HDS increased from 2.9% during 1995-2003 to 24.1% by 2013-20.

Kesar and colleagues focused on association between ethnicity and DILI-induced ALF related to specific agents [5]. Among patients with HDS-induced ALF, 60% were listed and 70% were transplanted between 2010 and 2020. Asians had >5-fold risk of HDS as an agent underlying ALF as well as receiving liver transplant for HDS-related ALF compared to white people.
Some caveats have to be highlighted at the outset; two research groups using the same data base identified different number of cases with an implicated drug or class: 2146 (61 HDS-related) or 1875 (69 HDS-related) [4, 5]. These bring out potential variability in the interpretation of the diagnosis codes and free text field. In addition, no distinction between HDS and different forms of complementary and alternative medicine can be made.

Association of HDS-related ALF with Asian ancestry may be due to selection bias; access to transplant services may be affected by the health insurance coverage. However, during the study period, Medicaid insurance increased in all ethnic groups and this was significantly higher among Asians [4]. Therefore, had the access to transplant service been equal among different ethnic groups, more Asian’s could have been identified with HDS-related ALF strengthening the association. Genetic risk factors might explain the association of drug-induced ALF with ethnicity. Such risk factor-outcome pairs include: severe DILI leading to transplantation due to Co-trimoxazole among African Americans (linked to HLA-B*35:01) and Co-amoxiclav in South-Asians (linked to HLA-DRB1*15:02). Association of HLA-B*35:01 with herb-induced liver injury has also been demonstrated in relation to Polygonum multiflorum among Han Chinese and Green tea in white people highlighting shared mechanisms underlying DILI due to different causative agents [6]. Beyond genetics, other factors inextricably linked to ethnicity such as health literacy, immigration and acculturation that potentially affect HDS use and hence their adverse effects haven’t been evaluated. Finally, size of the population exposed would be a key determinant of the HDS-induced liver injury. A systematic review found the prevalence of HDS use by African Americans to be 17 % (range 1–46%); for Hispanics, 30 % (4–100 %); and for Asians, 30 % (2–73 %) [7]; range of reported prevalence is too wide to draw any conclusion.

In contrast to 8-fold increase HDS-induced ALF, the downward trend in drug-induced ALF attributed to FDA approved drugs [4] accentuates the quandary. Opportunities for regulatory actions regarding dietary supplements are limited to those deemed ‘adulterated or misbranded’; burden of proof to demonstrate lack of safety of a particular product rest on the government. Therefore, it is important to raise patient and public awareness through dissemination of findings of these studies [4, 5]. Educational activities focusing on the community particularly at risk would ensure that people can readily identify trustworthy sources of evidence.
On a sobering note, the 11th version of International Statistical Classification of Diseases and Related health problems (ICD-11 will replace ICD-10 on 1st January 2022) will contain information about Traditional Chinese Medicine (TCM). For the first time, ICD codes will include terminology such as Liver Qi stagnation (vital energy that flows along the channels called meridians) [8]. World Health Organisation’s (WHO) stated goal in bringing TCM into the folds of ICD-11 is to achieve universal health coverage. In the same breath, WHO calls for ‘the integration of traditional medicine of proven of proven quality, safety and efficacy’ without setting any means of establishing these. Mahathma Gandhi said ‘Means are foreseeable, ends are not’.
References


4) Ghabril M, Ma J, Patidar KR, Nephew L, Desai AP, Orman E, et al. Eight fold increase in the dietary supplement related liver failure leading to transplant waitlisting over the last quarter century in the US. Liver Transpl. 2021;xxx


