Liver Injury Following Tinospora Cordifolia Consumption: Drug-Induced AIH, or *de novo* AIH?

There has been significant interest to study *idiosyncratic* liver injury due to conventional drugs and herbal and dietary supplements (HDS) over the last two decades in both, Europe[1–3] and the United States.[4–6] Several very interesting papers on this subject from Asian countries such as South Korea,[7] China,[8] Taiwan,[9] and India[10] have also been published. In prospective studies from the United States and Iceland, HDS-induced liver injury has accounted for 15–20% of cases,[3–5] whereas a larger proportion of cases due to HDS has been reported from Asia.[7–9] However, in a recent large prospective study from India, almost half of the recruited patients suffered from drug-induced liver injury (DILI) due to antituberculosis drugs and 14% had HDS-induced liver injury,[10] which is similar to the 16% reported in two studies from the West.[3,4] In the current issue, Nagral et al. reported a series of 6 patients suspected to have liver injury after consumption of *Tinospora cordifolia*.[11] *T. cordifolia* (TC) is used frequently by Indian Ayurveda medicine and is called Giloy in Hindi.[12] Although TC or its extract is extensively used in India for general health benefits, only a single case report of suspected liver injury has been previously published.[13] This convincing case report involved a 68-year-old South Asian female living in the United States who consumed Giloy Kwath and developed hepatocellular jaundice. Apart from a weakly positive antinuclear antibody (ANA), thorugh diagnostic testing failed to identify any other cause of liver injury. Within a month of discontinuing Giloy Kwath, the liver tests normalized.[13]

In the current series, 4 out of 6 patients were of female gender, -median age of 55 and a median duration of use of 3 months (range 3 weeks–7 months). The Giloy was taken both as commercially available syrup containing ingredients of the plant or boiled TC plant twigs. According to the authors, Giloy has recently gained popularity during the COVID-19 pandemic as the plant is believed to serve as an "immunity booster" and might fight the SARS-CoV-2. The indications for Giloy in the current series are not clearly stated but presumed to be related to the pandemic. All patients presented with hepatocellular jaundice, and AST was higher than ALT at presentation in all patients. Interestingly, 5 out of 6 had evidence of serological markers of autoimmunity, such as elevated ANA, smooth muscle antibody (SMA), and/or elevated IgG, and liver histology was compatible with autoimmune hepatitis in all patients. Three patients received corticosteroids. One patient died of liver failure, whereas the others recovered seemingly without sequelae. Unfortunately, currently, there is no diagnostic biomarker that can be used to confirm the diagnosis of drug- or herbal-induced idiosyncratic liver injury. How convincing are these cases reported by Nagral et al.? The authors of this editorial, with combined decades-long research experience in DILI, readjudicated each case using the DILIN causality adjudication process. The consensus causality of liver injury by TC was highly likely in two (cases 1 and 3), probable in two (cases 2 and 6) and possible in 2 cases (cases 4 and 5) (Table 1).

All individuals included in this series had clinical, laboratory, and histological features indicative of autoimmune hepatitis (revised AIH score was definite in four and probable in two cases). So, are these cases of *de novo* AIH or drug-induced autoimmune hepatitis (DI-AIH)? DI-AIH has a well-documented clinical, immunological, and biochemical phenotype and can be due to drugs such as nitrofurantoin, alpha-methyl dopa, hydralazine, minocycline, and infliximab[15,16] More than 30 drugs and HDS have been suspected of causing DI-AIH.[17–19] However, for many of these drugs, the documented evidence is very limited and consists of a single report and/or short follow-up, which makes it difficult to distinguish DI-AIH from AIH.[19] It is well known that autoantibodies can found in patients with other liver diseases than AIH, such as in chronic liver diseases such fatty liver disease,[20,21] acute liver failure,[22] DILI due to prescription agents or HDS.[23,24] Unfortunately, there is still no consensus on the criteria for DI-AIH and the experts do not agree on the definitions.[23,24]

Patients with DI-AIH present similarly to *de novo* AIH clinically, immunologically, and histologically. The only feature that may distinguish DI-AIH from *de novo* AIH is the lack of relapse after discontinuation of the immunosuppression in DI-AIH. Another pertinent question is, when is it reasonable to use corticosteroids in patients with suspected DI-AIH, as was undertaken in 3 of the 6 patients in the current report. We agree with the authors that corticosteroids are unnecessary in patients who show prompt improvement in liver tests after the implicated agent has been stopped (i.e., positive dechallenge). However, patients with DILI with autoimmune features who show worsening of liver tests and/or no improvement or slow and incomplete recovery, clinically and biochemically, should be treated with corticosteroids.[16]

Notwithstanding the autoimmune aspects of the cases presented by Nagral et al, there are other factors to consider whenever HDS are implicated as the cause for

Abbreviations: ANA: antinuclear antibody; DI-AIH: drug induced autoimmune hepatitis; DILI: drug-induced liver injury; HDS: herbal and dietary supplements; HPLC: high-performance liquid chromatography; PM: polygonum multiflorum; SMA: smooth muscle antibody; TC: *T. cordifolia*; TCM: traditional Chinese Medicine

https://doi.org/10.1016/j.jceh.2021.11.014

Table 1 Three Editorialists' Readjudication of Six Reported Cases by Nagral et al.

Case #	Causality Score	Likelihood that liver injury event is related to drug exposure	Comments from the editorialists
Case 1	Highly likely	>75%–95%	Temporal relationship to consumption of TC plant twig, exclusion of common competing etiologies, recovery without corticosteroids upon dechallenge, and 5-month follow-up make this a convincing case of TC-related liver injury. This is a case of DI-AIH that was resolved upon stopping the implicated agent.
Case 2	Probable	>50%–75%	Prolonged exposure to TC plant twig, unimpressive autoimmune markers, normal immunoglobulin G levels, and mixed pattern liver injury on liver biopsy favor DILI, but the response to steroid therapy and lack of follow-up upon tapering off prednisolone lower our confidence.
Case 3	Highly likely	>75%–95%	Prolonged exposure to TC plant twig-boiled and extract, unimpressive autoimmune markers, normal immunoglobulin G levels, liver histology consistent with DILI, and recovery without corticosteroids upon dechallenge make this a convincing case of TC-related liver injury. Ultrasound showed diffuse fatty infiltration, but there is no description of hepatic steatosis on liver biopsy.
Case 4	Possible	>25%–50%	Relatively brief exposure to TC extract containing syrup, high ANA, positive ASMA, underlying cirrhosis, and relapse following steroid withdrawal indicates that this individual likely had longstanding AIH leading to cirrhosis with an acute flare, which possibly may have been triggered by TC consumption. Overall, this case is more likely to represent *de novo* AIH rather than one that is related to TC.
Case 5	Possible	>25%–50%	Relatively brief exposure to TC plant boiled extract, high immunoglobulin G, underlying cirrhosis, response to corticosteroids, and maintenance steroid therapy indicates that this woman likely had longstanding AIH with an acute flare that may possibly have been triggered by TC consumption. Overall, this case is more likely to represent *de novo* AIH rather than one that is related to TC.
Case 6	Probable	>50%–75%	Three-month exposure to commercially available TC containing tablet high immunoglobulin G levels, liver histology consistent with autoimmune hepatitis, recovery without corticosteroid upon dechallenge favor DI-AIH. However, bridging fibrosis on liver biopsy raises the possibility that there may have been chronic injury initiated before the exposure to TC started.

liver injury; that is, how can one be sure that the HDS is the cause for liver injury? Among the most critical factors in this context are the complexity of HDS and the approach to diagnosing HDS DILI.

In reality, although products may be marketed as a specific agent or ingredient, the actual HDS consumed are highly complex and contain many different ingredients (or phytochemicals). This is the case simply because of the complex nature of naturally occurring compounds, unpredictable growing conditions, and methods of commercial preparation. Additionally, it is well-known that HDS are susceptible to inaccurate labels and intentional or inadvertent inclusion of ingredients. In fact, the Drug-Induced Liver Injury Network has shown that supplements implicated in liver injury are frequently mislabeled in the United States.[25] Such ingredients can be botanical or nonbotanical and could have been intentionally added to achieve some specific result, or inadvertent as may occur during the production process. Importantly, botanical ingredients could result from various raw material plant parts such as the leaves, stems (twigs), or roots. In the current case series, four patients consumed TC after boiling the twigs. The method of the commercial preparation of a processed botanical compound may affect its hepatotoxic potential. An example of this phenomenon is Polygonum multiflorum *(PM)*, a popular botanical product in traditional Chinese Medicine (TCM) used for myriad purposes that has been implicated in hepatotoxicity.[26] The hydrolysis of PM plant glycosides during preparation is thought to affect toxicity.[27] Other manufacturing methods and approach to extraction may affect the chemical composition, potency, and toxic potential of the phytochemicals within HDS, as has been shown with Kuding tea (Kudingcha), another popular agent in TCM.[28]

Chemical analysis of implicated HDS would seem to be a useful tool to identify a culprit ingredient for injury. Chemical analysis is performed commonly through High-Performance Liquid Chromatography (HPLC). Through this, phytochemicals and other agents such as pharmaceuticals appear as peaks on a chromatogram, which then can be compared against a library of known peaks for actual identification. Ostensibly, such an

approach would be very useful to identify an ingredient that may explain the injury. However, most botanical products have many ingredients, any one of which (or combination thereof) may be responsible. Therefore, chemical analysis in the diagnosis of HDS-induced liver injury, or identifying the culprit ingredient, has a very limited role in a clinical setting.

The causality assessment in cases of suspected HDS DILI is challenging, and we believe it is best addressed with a structured causality assessment approach complemented by expert opinion. The addition of expert opinion permits flexibility to consider information that may be excluded in structure causality assessment but pertinent to HDS associated liver injury. For example, some products may be used for a very long time before toxicity arises (prolonged latency) and have specific patterns of injury that trigger the diagnostician's memory to link injury to the product.

In summary, the report by Nagral et al., suggests that some patients may very rarely develop liver injury following TC consumption. Temporal relationship to exposure, positive dechallenge, and clinical picture suggest that this liver injury represents DI-AIH, at least in some cases, rather than *de novo* AIH. This report raises more questions than answers. TC has been consumed for a very long time in the Indian subcontinent with no previous reports of liver injury, so why now? One might speculate that it could be due to a spike in its usage due to the ongoing pandemic. It is unclear if TC caused the toxicity or if there was a contaminant that contributed to the liver injury. Further, it is unknown if there are any predisposing factor such as dose, duration, or type of preparation, genetic variants, comorbidities, or concomitant medications for developing liver injury upon consuming TC. If there are continued reports of liver injury associated with TC consumption, the hepatology community should consider a systematic approach to investigate the risk factors and optimal ways to mitigate the risk.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

All three authors contributed equally to this editorial.

CONFLICT OF INTEREST STATEMENT

Dr. Björnsson reports no conflicts of interest.

Dr. Navarro reports no conflicts of interest related to this paper.

Dr. Chalasani declares no conflicts of interests related to this paper. For disclosure, Dr. Chalasani has had paid consulting agreements with Abbvie, Zydus, Galectin, Madrigal, Foresite, Altimmune, and Boehringer-Ingelheim. He receives research grant support from Exact Sciences, DSM, and Galectin. He has equity ownership in RestUp, LLC, a healthcare placement start-up company.

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