Author Response to Letters on the Manuscript “Herbal Immune Booster-Induced Liver Injury in the COVID-19 Pandemic – A Case Series”

We would like to thank all the readers for the overwhelming response to our case series on Tinospora cordifolia (TC)/Giloy drug-induced liver injury (DILI).1 Our experience of an autoimmune like hepatitis has been shared by Ajay Kumar et al who report three cases with biochemical, serological, and histopathological findings similar to ours. Two of their three patients too had autoimmune diseases in the form of hypothyroidism and SLE. In fact, one of their patients had an inadvertent rechallenge and developed hepatotoxicity the second time too. This would strongly support the causality of TC causing DILI, which is being questioned. Phillips et al also have reported nearly 30% of patients with HILI (Herb-induced liver injury) having some serological evidence of autoimmunity. Gupta et al report two cases of Giloy-related DILI, with one of them being severe enough to merit a liver transplantation. These reports further substantiate our findings of DILI seen in those consuming TC.

Readers from the Ayurveda community have suggested that our case series is misrepresenting the herb T. cordifolia (TC) that is described as a flagship herb of Ayurveda. We feel that most of the authors have used emotional arguments rather than a scientific rebuttal and seem to perceive the report as a critique of the herb. We would like to reiterate that this is not the message of our case series. In fact, a closer reading of our report would have clarified many of their doubts and questions.

In general, we do not dispute that TC may be safe, well tolerated, and beneficial, and have cited references to this effect.2–5 However, we have emphasized caution while using the herb in a specific subset of the population prone to the unmasking of latent autoimmune phenomenon owing to the “immune stimulant” properties of the herb. In fact by mentioning this, we support the postulated immune-stimulant properties of the herb, which have possibly helped many individuals as quoted in reports as quoted by us. However, these very properties may work adversely in those predisposed to autoimmune problems. So there is obviously no bias or indifference toward scientifically validated products. Nevertheless, we agree with Phillips et al who mention that the term “immune booster” is too generalized and should not be used. If one accesses the “Web MD” site, a popular health portal https://www.webmd.com/ vitamins/ai/ingredientmono-1157/tinospora-cordifolia, it has been mentioned that TC needs to be avoided in those with autoimmune disorders. Our report just highlights a similar phenomenon in the liver. We believe that TC caused a drug-induced autoimmune like hepatitis as described in literature by Czaja.6 It has been described to be an “idiosyncratic reaction” (derived from the Greek word idiosynkrasia meaning “a peculiar temperament, habit of body” or “particular mingling”), which can be potentially caused by any drug under the sun as has been seen with many commonly used allopathic drugs like amiodarone7 and isoniazid.8 This also means that the injury may not be dose related and may occur with a very small dose as well. We need to perform further larger multicentre studies to determine the mechanism of the DILI. There are life-saving drugs in allopathy, like antituberculous drugs with well-established hepatotoxic potential. We always sensitize our patients to the possible hepatic side effects before starting these medications, and monitor them closely. This does not imply that we are deriding the drug and its benefits. We continue to use them with caution. We have also mentioned that hypothyroidism is an autoimmune disorder and that the immune stimulant effects of TC are actually causing an exaggerated immune response against the liver, leading to drug-induced autoimmune like hepatitis. In a pre-existing autoimmune state such as in DM, TC worsens the autoimmune state. Even in DM, where there is evidence of TC to lower sugars, one may need to be cautious while using the drug, especially in a subset of diabetics with an autoimmune basis.

We agree that the denominator of people consuming Giloy will be very large. However, it does not detract from the documentation of liver injury in this group of patients for the first time. We do not claim this to be a randomized control trial. This is an observational study, and all evidence in scientific literature originates from simple observations. It is worth noting that we have seen several other patients after the study period with a history and presentation similar to those elucidated in our case series, but we did not biopsy these patients since they clearly fit the autoimmune serological and biochemical profile and all improved after TC withdrawal. A common query raised was the amount of herb consumed and the method in which the decoction was prepared. As pointed out, the first patient consumed a concoction of the extracts of TC, cinnamon, and cloves. On
enquiry, the patient was taking about seven half thumb size stem pieces (twigs) with five cloves and two cinnamon pieces after boiling them in water. We are not aware of their interactions. Four of our 6 patients took extracts of stem alone, while two consumed a commercial preparation of the same. The size of the twigs varied from half thumb size to little finger size, 4–7 in number for durations mentioned in the paper. We are thankful to the authors for highlighting the fact that the herb needs to be taken under the strict supervision of trained Ayurveda practitioners. This is exactly what we have tried to emphasize as all our patients had self-medicated themselves. None of the others took other drugs prior to or along with TC except thyroxin supplements in the 2 patients who were hypothyroid and oral hypoglycaemic agents in the two who were diabetic. Most OHAs have minimal adverse effects on the liver.10 11 Iatrogenic hyperthyroidism can be accompanied by serum enzyme elevations and even jaundice.12 However, our patients were evaluated with thyroid function tests that were within normal limits. We could not get any reference for interaction between these drugs and TC. Having said that, we cannot disclaim that there could have been some interaction between the products leading to injury, and therefore, the need for caution, supervision, and monitoring. Further drug interactions between Ayurveda and Allopathy are few and not well described. By that logic, no Ayurvedic drugs should be taken with allopathic drugs unless the interaction has been studied.

It is also pointed out that our patients who were self-medicating, taking the extract of the stem, may have taken Tinospora crispa (which has been described to be hepatotoxic) instead of Tinospora cordifolia due to their similar appearance. We agree a qualified botanist’s opinion would have helped identification. However, two patients took commercial forms of well-established brands, making it unlikely that they contained T. crispa. One took tablets, and another syrup, in manufacturer recommended doses mentioned on the label. The label did not mention any other components except T. cordifolia. Nevertheless, we agree that we could have identified the plant parts that were consumed by the patients, which was not possible due to labs not functioning at full capacity at the given time in the pandemic. We have seriously taken up the suggestion and are getting the contents of the plants and preparations analyzed for our further study.

Balkrishna et al have rightly supported our statement that RUCAM scoring is not very reliable in chronic liver disease. We mentioned the scores only because it is customary to do so in reports of DILI. We believe that RUCAM scores could, in fact, have been higher if the other rare viruses HSV, EBV, CMV were tested or the herb rechallenged. Our aim of stating the lack of serological testing for these viruses being a limitation was to clarify that if these had been tested, we would have had stronger evidence for establishing causality. We considered it unethical to rechallenge with the same herb as patients showed a dramatic reduction in their elevated liver profiles on TC withdrawal. Nevertheless, Ajay Kumar et al had one patient with an inadvertent rechallenge, and DILI was documented on both occasions.

Sharma et al suggested the likelihood of subclinical COVID-19 infection as being the possible cause of elevated liver enzymes. Attributing raised liver enzymes to COVID-19 infection would be inappropriate as raised liver enzymes are usually a sign of severe COVID-19 infection,12 and therefore, one would have expected our patients to become symptomatic for COVID-19 in due course, which did not happen.

In conclusion, our case series neither repudiates the benefits of TC nor states that it should not be used. We have only highlighted the hepatotoxic effects of TC and advised caution in its use in those with autoimmune problems. We also want to dispel the misconception that “All herbs are safe,” as that encourages self-medication. We understand the emotional attachment of our Ayurveda colleagues to their science. However, to portray our report as a critique of either Ayurveda or TC is completely misplaced.

All authors repeatedly emphasize the use of Ayurvedic drugs under supervision, which is indeed true for drugs of all systems of medicine. To ensure this, we would suggest that they also take the lead in stopping the widespread advertising of TC on television and social media without cautioning about the possibility of side effects and then state that the herb should be consumed under medical supervision.

A registry documenting further observations and analysis of the herbs consumed will throw further light on our observations. In cases where the plant has been consumed, identification of the species by a botanist and a phytochemical analysis would be worthwhile. Also, as suggested by Phillips et al, it will be worthwhile to perform multicentre studies as mandated by the Drug Controller of the Government of India (DCGI) and determine the concentration of various bioactive phytochemicals that play a role in efficacy and immune-mediated side effects. We suggest that the way forward is to use an integrated approach to utilize the benefits of the immune stimulant properties of drugs like TC by substantiating them through the use of modern research methodology both for their efficacy and adverse effects as has been done by the Chinese who have successfully integrated modern medicine and Traditional Chinese medicine and set up structured diagnostic and management algorithms.13

CREDIT AUTHOR STATEMENT

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