

Herbal Immune Booster-Induced Liver Injury in the COVID-19 Pandemic – A Cautious Interpretation is Desired Before Any Generalization is Attempted

Sir,

We read with great interest an observational study on “Herbal Immune Booster-Induced Liver Injury in the COVID-19 Pandemic - A case Series” by Nagral *et al.* published recently in *Journal of Clinical and Experimental Hepatology*.¹ Raising the concern about possible adverse effects associated with any unsupervised use of herbal/CAM or modern medicines should be welcomed by all. Indeed, Ayurveda recognizes the fact of drug related adversities depending upon their processing, dose, intake methods, and strategy of administration.² Naturally a drug from any source, natural or synthetic, if taken unsupervised, may cause adverse effects.³

While we agree with the authors that a common belief about the safety of drugs of natural origin added with their easy OTC access and guided by unreliable resources often leads to self-medication⁴ adverse effects have been observed in all drug classes used in the COVID-19 pandemic.⁵ Thus, increasing the awareness about the mechanisms of drug effects, and their potential harms, if taken unsupervised, should be undertaken by practitioners, manufacturers and regulatory authorities.⁶ Despite agreeing to these generic observations made by the authors, we, however, disagree with the generalization that has been attempted by the authors by finding a commonality in all cases clubbed together in the series. Table 1 shows the dose frequency and duration of use of TC used in the study and the associated comorbidities. Authors own statement that “most drug induced autoimmune liver injuries are an acute idiosyncratic reaction supported by the fact that one patient taking the drug for only 3 weeks on alternate days,”

is in variance to another case having a history of 7 month regular consumption of the drug in the same series. Similarly two cases who have consumed commercially available syrup containing TC/15 ml per day and TC in the form of commercially available tablet raises a concern about other ingredients of the compound formulations, which may have contributed to the net adversity.

The authors have also not made any attempt to identify the prior consumption or coconsumption of other medications especially when four out of six cases in the series were found to have autoimmune morbidity like hypothyroidism and diabetes. Both hypothyroidism and diabetes are reported to have DILI upon consumption of routine medications like levothyroxine and hypoglycemic agents.⁷⁻⁹ This co-consumption of medication, in light of accumulated evidences, may have played an important role in the outcome, which have been observed in the cases unless proven otherwise. Further, the generalization about adverse outcomes attributed to Guduchi (*Tinospora cordifolia*) should also have been examined in the context of its consumption by millions of people during the pandemic in both supervised and unsupervised form. Guduchi had been one of the foremost prescribed drug by Ayurveda practitioners for inflammatory conditions dominated by fever. This is one among several drugs that has been identified initially for their possible role in mitigation of SARS-CoV-2 infection.¹⁰ It has also been used successfully in the treatment of COVID-19 and other clinical conditions without any adversity as is evident from the results of many clinical trials and case studies.^{11,12} A study in a

Table 1 Dose Frequency and Duration of Use of TC Used in the Study and the Associated Comorbidities.

Case number	Dose of TC consumed	Duration of TC consumption	Co morbidity
1	10-12 pieces of twig boiled in ½ glass water	Once in two days for three months	None
2	1 twig/day boiled and extracted	7 months	Type 2 Diabetes
3	3-4 twig boiled in water, 15 ml/day	6 months	Thalassemia minor
4	Commercially available syrup containing TC/15 ml per day	Every alternate day for one month	Type 2 Diabetes
5	Boiled extract of one twig	2-3 days in a week for 3 weeks	Hypothyroidism
6	TC plant formulation in the form of commercially available tablet	1 pill/day for 3 months	Hypothyroidism

mouse model has showed that TC treatment did not display clastogenicity and DNA damaging effect in bone marrow erythrocytes and peripheral blood lymphocytes respectively.¹³ There is clinical evidence for the protective effects of *Tinospora cordifolia* on hepatic and gastrointestinal toxicity due to alcoholism.¹⁴ This is suggested that future research should evaluate standard doses and indications of use of TC and assess the actual content of OTC medications. The public should be cautioned against misleading advertisements, self-prescriptions and off label use of all classes of allopathic and herbal medications. The COVID-19 pandemic has seen unsubstantiated use of drugs of all classes and hence standard reporting of adverse effects and regulatory control should be followed irrespective of the class of medication.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Sanjeev Rastogi: Writing – original draft, Writing – review & editing. **Deep N. Pandey:** Writing – review & editing.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Nagral A, Adhyaru K, Rudra OS, Gharat A, Bhandare S. Herbal Immune Booster-Induced Liver Injury in the COVID-19 Pandemic - A case series. *J Clin Exp Hepatol.* 2021 <https://doi.org/10.1016/j.jceh.2021.06.021>.
2. Tripathi BN. *Charak Chandrika Hindi Commentary on Charaka Samhita.* 1st ed. Varanasi: Chaukhamba Surbharati Prakashan; 1983:47.
3. Rastogi S. Poor quality and improper use: a review of common reasons of possible adversity in Ayurvedic practice. *Int J Risk Saf Med.* 2009;21:121–130.
4. Rastogi S. Ayurveda formulations: a roadmap to address the safety concerns. *J Ayurveda Integr Med.* 2018;9:81–82. <https://doi.org/10.1016/j.jaim.2018.02.002>.
5. Wong YK, Yang J, He Y. Caution and clarity required in the use of chloroquine for COVID-19. *Lancet Rheumatol.* 2020;2:e255. [https://doi.org/10.1016/S2665-9913\(20\)30093-X](https://doi.org/10.1016/S2665-9913(20)30093-X).
6. Rastogi S. Why and how? Addressing to the two most pertinent questions about pharmacovigilance in Ayurveda. *Int J Ayurveda Res.* 2011 Jan;2:48–52. <https://doi.org/10.4103/0974-7788.83187>.
7. Hlaibeh AF, Al-Khairalla MZH. Levothyroxine-induced liver injury followed by complete recovery upon cessation of the drug: a case report. *J Med Case Rep.* 2019;13:311. <https://doi.org/10.1186/s13256-019-2244-z>.
8. Wu Bo1, Xie. Cheng2 Liver injury induced by levothyroxine tablets in a patient with hypothyroidism. *Chinese Med J.* August 20 2019;132:2015–2016. <https://doi.org/10.1097/CM9.0000000000000340>.
9. Chan KA, Truman A, Gurwitz JH, et al. A cohort study of the incidence of serious acute liver injury in diabetic patients treated with hypoglycemic agents. *Arch Intern Med.* 2003;163:728–734. <https://doi.org/10.1001/archinte.163.6.728>.
10. Rastogi S, Pandey DN, Singh RH. COVID-19 pandemic: a pragmatic plan for Ayurveda intervention. S0975-9476(20)30019-X *J Ayurveda Integr Med.* 2020 Apr 23 <https://doi.org/10.1016/j.jaim.2020.04.002>. *Epublish ahead of print.* PMID: 32382220; PMCID: PMC7177084.
11. Kataria S, Sharma P, Ram JP, et al. A Pilot Clinical study of an add on Ayurvedic formulation containing Guduchi and Pippali in mild to moderate Covid-19. *J Ayurveda Integr Med.* 2021 <https://doi.org/10.1016/j.jaim.2021.05.008>.
12. Devpura G, Tomar BS, Nathiya D, et al. Randomized placebo-controlled pilot clinical trial on the efficacy of ayurvedic treatment regime on COVID-19 positive patients. *Phytomedicine.* 2021 Apr;84:153494. <https://doi.org/10.1016/j.phymed.2021.153494>.
13. Chandrasekaran CV, Mathuram LN, Daivasigamani P, Bhatnagar U. *Tinospora cordifolia*, a safety evaluation. *Toxicol Vitro.* 2009 Oct;23:1220–1226. <https://doi.org/10.1016/j.tiv.2009.07.030>.
14. Sharma B, Dabur R. Protective effects of *Tinospora cordifolia* on hepatic and gastrointestinal toxicity induced by chronic and moderate alcoholism. *Alcohol Alcohol.* 2015;1–10.

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