



# ***Tinospora Cordifolia* (Giloy) and Autoimmune-like Liver Injury – A Classic Case of *Primum Non Nocere*, “First, Do No Harm”**

The vague, generalized term “immuno-booster” has become a common household usage during the current novel coronavirus disease (COVID-19) pandemic. It has been used to label products and practices that supposedly improve general immunity, thereby preventing contagion. The use of immuno-boosting or immunomodulating capacity of complementary and alternative medicine (CAM) has limited data in animal models and lacks prospective long-term trials in humans to establish efficacy or safety.<sup>1,2</sup> Various drugs, herbals, activities, and practices are widely advertised as “established” immune-boosters in the absence of tested and validated benefits of immunomodulating properties in humans.<sup>3</sup>

In this regard, the paper by Nagral et al. is of outstanding public-health importance.<sup>4</sup> The authors have painstakingly documented clinical course and outcomes in six patients with possible and probable Giloy herb-induced liver injury (HILI). One patient died after developing acute-on-chronic liver failure. The liver biopsy showed histological evidence of autoimmune-like hepatitis (AILH). The finding of AILH due to herbals, and specifically Giloy, may not be novel but strongly supportive, backed by similar findings in the literature. Philips et al. previously described investigational and histopathological features and associated clinical outcomes in Ayurvedic herbals-related liver injury patients. Autoantibodies were found in 29.6% of patients in the study. Antinuclear antibodies were notable in 25.9%, anti-liver-kidney-microsomal-1 antibody in 7.4%, and antimitochondrial antibody in 3.7%, while antismooth muscle antibodies were not in any patient. The maximal immunoglobulin G (IgG) level documented was 3428 mg/dL. Chronic hepatitis was the commonest finding, with interface hepatitis notable in 70.4%, and those with hepatic necrosis on biopsy had higher mortality. More importantly, Giloy was found in eight different herbal formulations retrieved for analysis.<sup>5,6</sup> Nagral et al. replicate similar findings in their paper but do not comment on necrosis and its pattern among those who survived or died.

Another point to note is the argument that the samples might have been “unintentionally” contaminated with *Timo-*

*spora crispa* (TCR), a related species with known hepatotoxic potential due to the presence of clerodane furano-diterpenoids.<sup>7</sup> However, one must be aware that Giloy also contains clerodane furano-diterpenoids with the potential to harm.<sup>8</sup> The immune-potentiating properties of Giloy have been well documented, which was thought to be due to alkaloids, glycosides, and terpenoids such as cordifoliosides.<sup>9</sup> Thus, in the final Giloy product, the concentration ratios of various potent, bioactive phytochemicals could decide the development of immune-mediated or nonimmune mediated liver injury, a study aspect lacking in marketed Giloy and such herbal preparations. Further multicenter collaborative projects on HILI are warranted to support and confirm Nagral et al. study findings and to identify novel HILI associations for the interest of public health.

Most “immuno-booster” herbal preparations lack prospective validated human studies to establish the specific immune pathways in particular disease conditions, and future prospective trials should be designed to identify active chemical compounds in CAM to reliably identify clinical efficacy and safety, under the strict protocols adopted for drug trials established by the Drugs Controller General of India (DCGI), the head of the department of the Central Drugs Standard Control Organization of the Government of India. Any deviation from the scientific methodology goes against the morals of patient care and the compassionate art of medicine – that, “first, do no harm,” an aspect lacking in alternative medicine practice due to the impaired approach toward science, reasoning, logic, and methodical experiments.<sup>10</sup>

## **CREDIT AUTHORSHIP CONTRIBUTION STATEMENT**

**Cyriac Abby Philips:** Conceptualization, data curation, writing – original draft preparation, reviewing and editing.

**Libin Abraham:** Data curation and writing- revised draft preparation, editing.

## **CONFLICTS OF INTEREST**

The authors have none to declare.

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**Abbreviations:** AILH: autoimmune-like hepatitis; CAM: complementary and alternative medicine; COVID-19: coronavirus disease; DCGI: Drugs Controller General of India; HILI: herb-induced liver injury; IgG: immunoglobulin G; TCR: *Tinospora crispa*  
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**Cyriac A. Philips**

Department of Clinical and Translational Hepatology, The Liver Institute, Center of Excellence in GI Sciences, Rajagiri Hospital, Chunangamvely, Aluva, Kerala, India

**Libin Abraham**

Department of Microbiology & Immunology, University of British Columbia, 2350 Health Sciences Mall, Vancouver, British Columbia, V6T 1Z3, Canada

On behalf of members of Mission for Ethics and Science in Health Care (MESH)

*Address for correspondence.* Cyriac A. Philips, The Liver Institute, Center of Excellence in GI Sciences, Ground Floor, Phase II, Rajagiri Hospital, Chunangamvely, Aluva, Ernakulam, Kerala, 683 112, India.

*E-mail:* [abbyphilips@theliverinst.in](mailto:abbyphilips@theliverinst.in) (C. A. Philips)

11 July 2021.