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Ashwagandha-induced liver injury—A case series from India and literature review

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Abstract

Background: Ashwagandha herb is commonly used in Ayurveda and a "fad" dietary supplement for a host of indications based on low levels of evidence. Recently, ashwagandha was implicated in multiple reports of herb-induced liver injury (HILI), mainly from the United States. We present the first, and currently largest, series of ashwagandha-HILI from multiple centers in India.

Methods: We retrospectively analyzed the respective institutional electronic medical records for ashwagandha-HILI. Patients consuming ashwagandha as part of multiherbal formulations or along with other known hepatotoxic supplements or medicines were excluded. All patients underwent a detailed diagnostic workup to exclude competing causes reasonably. Where possible, the implicated herbal formulation was retrieved and subjected to chemical analysis.

Results: Out of 23 patients with liver injury from ashwagandha (January 2019 to December 2022), we report 8 patients with single-ingredient formulation-related HILI. Study cohort was male predominant, and cholestatic hepatitis was the commonest presentation. Five patients had underlying chronic liver disease; 3 presented with acute-on-chronic liver failure, and all 3 died on follow-up. In others, the liver injury was prolonged, nonetheless self-limiting. Liver biopsy revealed cholestatic features predominantly with hepatocellular necrosis and lymphocyte/eosinophil predominant portal-based inflammation. One patient progressed to chronic HILI. Chemical analysis revealed only natural phytochemicals without adulteration or contamination.

Conclusions: Ashwagandha-HILI presents with cholestatic hepatitis and can

Abbreviations: ACLF, acute-on-chronic liver failure; ALT, alanine transaminase; AST, aspartate transaminase; DILIN, drug-induced liver injury network; HCV, hepatitis C virus; HDS, herbal and dietary supplements; HILI, herb-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method.

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lead to the syndrome of acute-on-chronic liver failure with high mortality in those with pre-existing liver disease. Educating the public on avoiding the use of potentially toxic and unrecommended herbal supplements can help mitigate the avoidable liver disease burden in the community.

INTRODUCTION

Herbal and dietary supplements (HDS) are considered food and nutritional formulations that include vitamins and minerals, whole herbs or botanical parts, amino acids, organ tissues, enzymes, and metabolites that are intended to promote health and well-being or adjunctively restore wellness associated with disease conditions.[1] The HDS is not considered drugs/medications, and the responsibility for the safety of such products lies with the respective manufacturers, while good manufacturing practices approval from concerned health regulatory bodies is required before marketing. The good manufacturing practice establishes minimum standards for raw source utilization and procurement, storage, manufacturing, packaging, and labeling of HDS products to ensure purity, quality, and composition. Manufacturers of HDS formulations are not required to conduct preclinical safety and efficacy studies before product marketing.[2] Hence the adverse events related to the use of such products are usually identified on postmarketing surveillance from responsible public health regulatory bodies, specific adverse-events recognition action groups or reported by physicians and patients themselves. Herbal drugs and dietary supplements are a major growing concern for liver injury, liver failure, and death or liver transplantation globally.[3–6] Ayurvedic herbal supplements have been implicated in serious liver injury, acute decompensation of cirrhosis, and acute-on-chronic liver failure.[7–9] *Withania somnifera*, popularly known as ashwagandha (also Indian Ginseng, Winter Cherry), is a commonly used and marketed herb as part of Ayurvedic herbals and dietary supplements for relieving stress and anxiety, improving sleep, increasing muscle mass and strength, improving sexual function in both males and females, increasing memory and as "immune-booster."[10] Nonetheless, conclusive evidence from rigorous, methodologically sound, well-designed, validated, and replicated trials does not exist for the aforementioned indications.[11–13] The increasing use of ashwagandha for advertised but nonevidence-based indications has led to an increase in published reports associated with its liver toxicity. After the first report on ashwagandha-induced cholestatic liver injury from Japan was published, the United States—(DILI) Network (US-DILIN) and colleagues from Iceland thereafter published a series of 5 patients with ashwagandha hepatoxicity. Multiple reports have been published on ashwagandha-related liver injury, mostly from centers in the United States, along with large numbers of self-reported adverse events, such as severe itching, based on analysis of commercial websites.[14] The estimated production of ashwagandha roots in India is >1500 tones and the annual requirement is about 7000 tones. As per the Charan Singh National Institute of Agricultural Marketing set up by the Government of India, the average annual Indian domestic consumption of ashwagandha within 5 large states was 39,074.592 kg.[15] There are no reports of ashwagandha-related liver toxicity published from the Asian continent. We present 8 cases of severe liver injury due to the ashwagandha herb from 3 tertiary centers in India.

METHODS

Institutional electronic medical records of 3 hospitals were queried to identify 8 cases of ashwagandha-related liver injury from between January 2019 and December 2022. Patients consuming ashwagandha-only formulations were included. Those consuming ashwagandha as part of multiherbal products or ashwagandha along with other potentially toxic herbal supplements or prescription drugs were excluded from this analysis. We also excluded patients with active alcohol use and those with other competing causes of acute liver injury. A detailed diagram of the inclusion methodology of patients is shown in Supplemental Figure S1, http://links.lww.com/HC9/A532. All patients underwent a detailed diagnostic workup to exclude other well-known causes for liver injury. The evaluation included laboratory investigations, viral serologies for acute and chronic hepatotropic viruses, including HEV infection, and others such as Herpes simplex and cytomegalovirus, Ebstein-Barr virus, Dengue virus, the novel coronavirus, and other pertinent nonviral infectious agents such as malaria parasite, Rickettsia, and Leptospira. Biomarkers for autoimmune liver disease and diagnostic cross-sectional imaging were performed in all patients. In all cases, the liver injury was classified into hepatocellular, cholestatic, or mixed type based on the R-ratio, using initial (at the time of presentation to respective centers) values of alanine transaminase and alkaline phosphatase, their respective upper limits of normal. The R-ratio was calculated as

FIGURE 1 The various types of ashwagandha formulations that were retrieved from patients. The products marked with a green tick are single-ingredient ashwagandha products, the use of which was one of the inclusion criteria. This study did not include patients using multiherbal products containing ashwagandha as a predominant or additional ingredient. The products which are marked with a "blue beaker icon" were considered adequate and unspoiled for further chemical analysis.

alanine transaminase/upper limits of normal ÷ alkaline phosphatase/upper limits of normal. When the R-ratio was <2, the liver injury was defined as cholestatic, between 2 and 5 as mixed, and >5 as hepatocellular. Thereafter, the causality assessment was performed to diagnose highly probable (score >8), probable (6-8), possible (3-5), and unlikely(1-2 or less) DILI using the 7-point Roussel Uclaf Causality Assessment Method (RUCAM).[14] Percutaneous or transjugular liver biopsy was performed in all patients after informed consent. Patients were categorized into mild, moderate, or severe DILI based on bilirubin levels and liver failure. Mild DILI was defined when the liver test elevations reached criteria for DILI, but bilirubin concentration was <2.5 mg/dL, moderate when bilirubin ≥2.5 mg/dL or symptomatic hepatitis, severe when the bilirubin level was ≥2.5 mg/dL with signs of liver failure (international normalized ratio ≥1.5, presence of ascites or encephalopathy) or another organ failure directly attributed to DILI and finally, fatal, with death or liver transplantation due to DILI within 6 months of onset.[16] Where possible, the implicated ashwagandha formulations were retrieved for further chemical and toxicology analysis. Heavy metal concentration was determined by an inductively coupled plasma atomic emission spectrometer (Thermo Electron, IRIS Intrepid II XSP Duo, Munich, Germany). The methodology, chemical standards, reagents, and vials were acquired per standards set by the US Environmental Protection Agency (USEPA), method 5021A, 8015, 8021, and 8260. Complete qualitative analyses were performed using triple-quadruple gas chromatography coupled to tandem mass spectrometry method (Varian

TABLE 1 Demography and clinical details of patients with ashwagandha-induced liver injury

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Sex	**Male**	**Female**	**Male**	**Male**	**Female**	**Male**	**Male**	**Male**
Age (y)	75	31	34	58	50	39	68	47
Diabetes	Yes	No	No	Yes	No	No	Yes	No
Hypertension	No	No	No	No	No	No	Yes	No
Overweight or obese	No	No	No	No	Yes	No	No	No
Chronic liver disease	Yes	No	Yes	No	No	Yes	Yes	Diagnosed during event
Etiology of chronic liver disease	NAFLD	—	NASH	—	—	Alcohol (abstinent)	NAFLD	Cryptogenic
Other comorbidities	None	None	None	NHL in long remission	Bipolar disorder	None	None	None
Co-medications	Insulin, oral hypoglycemic agents	None	None	None	Amisulpride and lithium for over 3 y	None	Insulin, oral hypoglycemic agents	None
Indication for ashwagandha use	Insomnia	Postpregnancy "stress"	Appetite stimulant	"Anticancer" preventive	Stress detox and sleep aid	Fever	General wellness and energy booster	General wellness and energy booster
Duration of herb intake (d)	30	14	60	94	540	30	60	17
Dose	Approximately 20 g/d	10–15 g/d	10–15 g/d	500 mg daily	~100 mL daily	Manufacturer instruction	Manufacturer instruction	Manufacturer instruction
Time to symptom onset (d)	24	14	52	96	540	30	62	15
Onset of lab abnormalities (d)	35	14	62	100	546	30	65	16
Predominant symptoms	Lethargy and jaundice	Pruritus	Pruritus and jaundice	Jaundice and pruritus	Pruritus and jaundice	Jaundice and abdominal distension	Lethargy and jaundice	Jaundice and pruritus
Clinical presentation	ACLF	Acute hepatitis	Acute hepatitis	Acute hepatitis	Acute hepatitis	ACLF	Acute hepatitis	ACLF
Steroid use for treatment	No	No	Yes, 40 mg/d for 15 d	Yes, 40 mg/d for 30 d	No	No	Yes, 40 mg/d for 30 d	No
Resolution of HILI	No	Yes	Yes	Yes	Yes	No	Yes	No
Time to resolution (d)		45	30	60	95	—	56	—
Outcome	Dead	Alive	Alive	Alive	Alive	Dead	Alive	Dead
Time from diagnosis to final follow-up (d)	288	375	430	486	235	30	302	242

Ashwagandha product consumed	Homemade powder	Lehyam (herbal jam)	Branded powder	Nonbranded tablets	Detox tea	Branded powder	Branded powder and tablets	Branded powder and syrup
Person who prescribed the herb	Self, OTC	Ayurveda practitioner	Self, OTC	Ayurveda practitioner	Self, OTC	Ayurveda practitioner	Ayurveda practitioner	Ayurveda practitioner

Abbreviations: ACLF, acute-on-chronic liver failure; HILI, herb-induced liver injury; NHL, non-Hodgkin lymphoma; OTC, over-the-counter.

Saturn 2200; Agilent Technologies, USA). The study was performed conforming to the Helsinki Declaration of 1975, as revised in 2000 and 2008, concerning human rights, and the study design and retrospective collection of patient data were approved by the respective institutional ethics and review boards. Owing to the retrospective pooled analysis but not the individualistic scrutiny of existing clinical data, the respective institutional review boards waived the requirement to obtain informed patient consent.

PATIENTS

General features and clinical details

Out of 23 patients with liver injury from herbal supplements containing ashwagandha, we included 8 patients with liver injury due to pure ashwagandha formulations. The other 15 patients were excluded because they had consumed concomitant potentially toxic herbal formulations or were on ashwagandha-based multiherbal preparations, or had other competing causes for liver injury (Supplemental Figure S1, http://links.lww.com/HC9/A532). Of the 8 patients included in the study, 6 were males and 2 were females. The median age was 49 (range 44, minimum 31 to maximum 75) years. Three patients had diabetes or hypertension and had been on medications for the same for decades without any significant prescription drug modifications pertinent to current events. Three patients were known to have pre-existing chronic liver disease, while 2 patients were diagnosed to have underlying chronic liver disease during the evaluation of herb-induced liver injury (HILI). Among the latter 2, one was diagnosed with HILI on the background of NASH on liver biopsy, while the other patient had imaging features of cirrhosis and portal hypertension during the evaluation of HILI. One patient had a history of non-Hodgkin lymphoma in remission for 4 years. Three patients presented with acute-on-chronic liver failure (ACLF) at the outset. The median duration of herb intake was 45 (interquartile range 53.5, minimum 14 to maximum 540) days, and the median time to symptom onset was 41 (interquartile range 59.5, minimum 14 to maximum 540) days. The dose of ashwagandha ranged from 10 to 15 g/d to 500 mg per day based on the type of formulation or as labeled on the product. The most common presenting symptom was jaundice (N = 7/8, 87.5%), followed by pruritus (N = 5/8, 62.5%). The median follow-up from diagnosis of HILI to outcome was 295 (interquartile range 164, minimum 30 to maximum 486) days. The indications for ashwagandha use were insomnia and antistress in 2, postpregnancy detox in 1, appetite stimulant in 1, anticancer prevention (who was already in long-term remission from non-Hodgkin lymphoma) in 1, fever reduction in 1, and as a

"wellness and energy booster" in 2 patients. The various types of ashwagandha formulations consumed by patients included homemade powdered roots, herbal jam preparation (called lehyam), company-manufactured branded ashwagandha root formulations as powders, syrups, and tablets, nonbranded Ayurveda practitioner-prepared tablets, and herbal detox tea. All patients consumed ashwagandha per the practitioner's advice or product labeling. A detailed representation of various ashwagandha formulations retrieved from the patients and the specific formulations that were subjected to chemical analysis and toxicology are shown in Figure 1. A registered and certified Ayurveda practitioner prescribed the ashwagandha supplement to 5 patients, while 3 reported self-use of over-the-counter supplements. The complete general features and clinical details of 8 patients are shown in Table 1.

Investigations and outcomes

The type of liver injury according to the R-ratio was cholestatic in 4, hepatocellular in 3, and mixed in 1. The RUCAM score revealed probable ashwagandha-induced liver injury in 6 and possible liver injury in 2 patients. The HILI was severe in most patients included (N = 6/8, 75%). Three patients died (mortality 37.5%; at 30, 242, and 288 d). All the patients who died on follow-up had index HILI presentation as ACLF. The complete individual investigations of 8 patients are shown in Table 2. Briefly, pertinent pooled findings included median hemoglobin 12.1 g/dL, total white cell count 8.7×10^9/L, platelet count 168.5×10^3/μL, the median total bilirubin 13.8 mg/dL, aspartate aminotransferase 171 U/L and alanine aminotransferase 173 U/L, mean serum albumin 3.51 ± 0.93 mg/dL, and median international normalized ratio 1.85. The mean total IgG level was 16.03 ± 2.97 (normal 6–16) g/L. Two patients were positive for antinuclear antibodies and none for anti-smooth muscle or anti-liver-kidney-microsomal antibodies. Nonetheless, autoimmune hepatitis was unlikely in all patients after exhaustive evaluation. A liver biopsy was performed in 6 patients (percutaneous in 4 and transjugular in 2). The families of 2 patients did not consent to liver biopsy in view of the critical nature of the illness, with both dying on follow-up on best supportive care. The portal area was the commonest site of inflammation, while the predominant type of inflammation was lymphocytic and eosinophilic. Interface hepatitis was not remarkable in the majority, while 50% had the presence of hepatocellular necrosis (spotty in 1, bridging in 1, and confluent in 2) (Figure 2).

In 1 patient (patient 3), a second (percutaneous) liver biopsy (details not shown in Table 2) was performed 5 months after the initial HILI presentation in view of the recurrence of hepatitis (without jaundice) after prior complete resolution. The initial biopsy was consistent with HILI. Associated with severe canalicular and hepatocellular cholestasis with bridging necrosis with background NASH. Even though the histology did not favor classical autoimmune hepatitis, the antinuclear antibody was positive with an elevated serum IgG. The repeat biopsy revealed showed linear cores of liver tissue forming vague nodules separated by fibrous septa. The hepatocytes showed microvesicular steatosis in close to 45% of cells. The portal tract revealed predominantly lymphocytic and clustered macrophage-mediated inflammation, mild to moderate interface hepatitis with neutrophils and eosinophils, and minimal plasma cells. Necrotic areas (notable at baseline biopsy) were absent, cholestasis had resolved, and focal areas showed hepatocyte rosettes —these features were suggestive of chronic HILI with autoimmune-like features.

Five types of ashwagandha formulations from the patients were subjected to chemical and toxicology analysis (marked with a "beaker icon" in Figure 1). None of the formulations revealed potential hepatotoxic contaminants, adulterants, or other synthetic agents. Herb-based natural bioactive compounds were identified in all formulations, including glycosides, lactones, terpenes, saponins, and alkaloid groups. One product was additionally found to have trace amounts of lead (0.21 mg/kg), cadmium (0.038 mg/kg), and arsenic (0.089 mg/kg).

DISCUSSION

We report a series of patients with ashwagandha-related HILI from a multicenter retrospective cohort. The predominant pattern of liver injury was cholestatic, with jaundice as the notable clinical presentation. In our series, all patients underwent a thorough, exhaustive, and pragmatically detailed diagnostic evaluation to rule out other competing causes for acute liver injury. The commonest indication for ashwagandha use in our cohort was for "stress and wellness." Three patients with ashwagandha-induced liver injury and underlying pre-existing liver disease in our cohort died with the development of ACLF, and 1 patient with chronic liver disease and acute liver injury without ACLF survived. In all other patients, ashwagandha-induced liver injury was self-limiting with supportive care. Lymphocytic and eosinophilic portal-based inflammation with cholestasis and hepatocellular necrosis were predominant in histology. Ashwagandha is marketed as clinically beneficial for many conditions, including improved exercise capacity and physical performance, increased testosterone, improved sleep, and reduced stress and anxiety. However, the highest level of clinical evidence from available studies does not clarify these findings (Supplemental Table S1, http://links.lww.com/HC9/A531), and hence the recommendation to use ashwagandha as a preventive or therapeutic modality does not exist in the current literature.

TABLE 2 Pertinent investigations of patients with ashwagandha-related liver injury

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Hemoglobin (g/L)	12.1	13.4	12.6	11.8	12	11.9	11	14.2
Total leukocyte count ($\times 10^9$/L)	8.5	4.6	5.5	8.9	11.2	31	7.6	24.3
Platelet counts ($\times 10^3$ per μL)	148	234	180	215	192	80	112	157
Total bilirubin (mg/dL)	10.4	2	3.6	21.3	16.1	11.4	24.3	31.5
Direct bilirubin (mg/dL)	3.3	1	1.8	16.9	11.5	3.4	19.8	25.3
Aspartate aminotransferase (IU/L)	107	598	647	64	235	47	100	270
Alanine aminotransferase (IU/L)	66	736	409	159	188	97	63	354
Alkaline phosphatase (IU/L)	105	241	199	354	893	59	128	209
Gamma-glutamyl transpeptidase (IU/L)		709	118	268	342	213	178	223
Serum albumin (mg/dL)	2.9	4.9	3.2	4.1	4.2	1.8	3.6	3.4
Serum globulin (mg/dL)	4.3	2.6	3.7	2.2	2.8	5.4	2.6	3.7
International normalized ratio	2.93	1	1.3	2.2	1	6.1	1.5	2.2
Serum total IgG (g/L)	14.8	17.2	20.2	16.4	11.5	18.6	17.2	12.4
Antinuclear antibody	Negative	Negative	Positive	Negative	Negative	Positive	Negative	Positive
Anti-smooth muscle antibody	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Anti–liver-kidney-microsomal antibody	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
R-ratio	1.3	5.6	5.3	1.3	0.6	4.9	1.5	5.1
Type of liver injury	Cholestatic	Hepatocellular	Hepatocellular	Cholestatic	Cholestatic	Mixed	Cholestatic	Hepatocellular
RUCAM score	8, probable	6, probable	8, probable	7, probable	5, possible	5, possible	8, probable	7, probable
HILI severity	Severe	Mild	Moderate	Severe	Severe	Severe	Severe	Severe

TABLE 2. (*continued*)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Liver biopsy done	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Type of liver biopsy	—	Percutaneous	Percutaneous	Transjugular	Percutaneous	—	Percutaneous	Transjugular
Liver biopsy findings								
Main site of inflammation	—	Periportal	Portal	Portal	Portal	—	Lobular	Portal
Predominant type of inflammation	—	Lymphocytes, eosinophils	Lymphocytes, eosinophils	Lymphocytes, eosinophils	No or minimal inflammation	—	No or minimal inflammation	Lymphocytes, eosinophils
Interface hepatitis, severity	—	Yes, mild	Yes, mild	No	No	—	No	No
Necrosis, type	—	Yes, spotty	Yes, bridging	No	No	—	Yes, confluent	Yes, confluent
Fibrosis, stage (Ishak)	Known case of cirrhosis	Stage 1	Stage 2	No	No	Known case of cirrhosis	Stage 2	Stage 6
Steatosis, severity	—	Yes, moderate	Yes, severe	Yes, mild	Yes, mild	—	No	No
Eosinophilic infiltration, severity	—	Yes, moderate	Yes, severe	Yes, mild	Yes, mild	—	Yes, minimal	Yes, moderate
Hepatocyte rosettes	—	No	Yes	No	No	—	No	No
Cholestasis, site, severity	—	No	Yes, cellular and canalicular, severe	Yes, cellular and canalicular, severe	Yes, cellular and canalicular, moderate	—	Yes, cellular and canalicular, moderate	Yes, cellular and canalicular, moderate

Abbreviations: HILI, herb-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method.

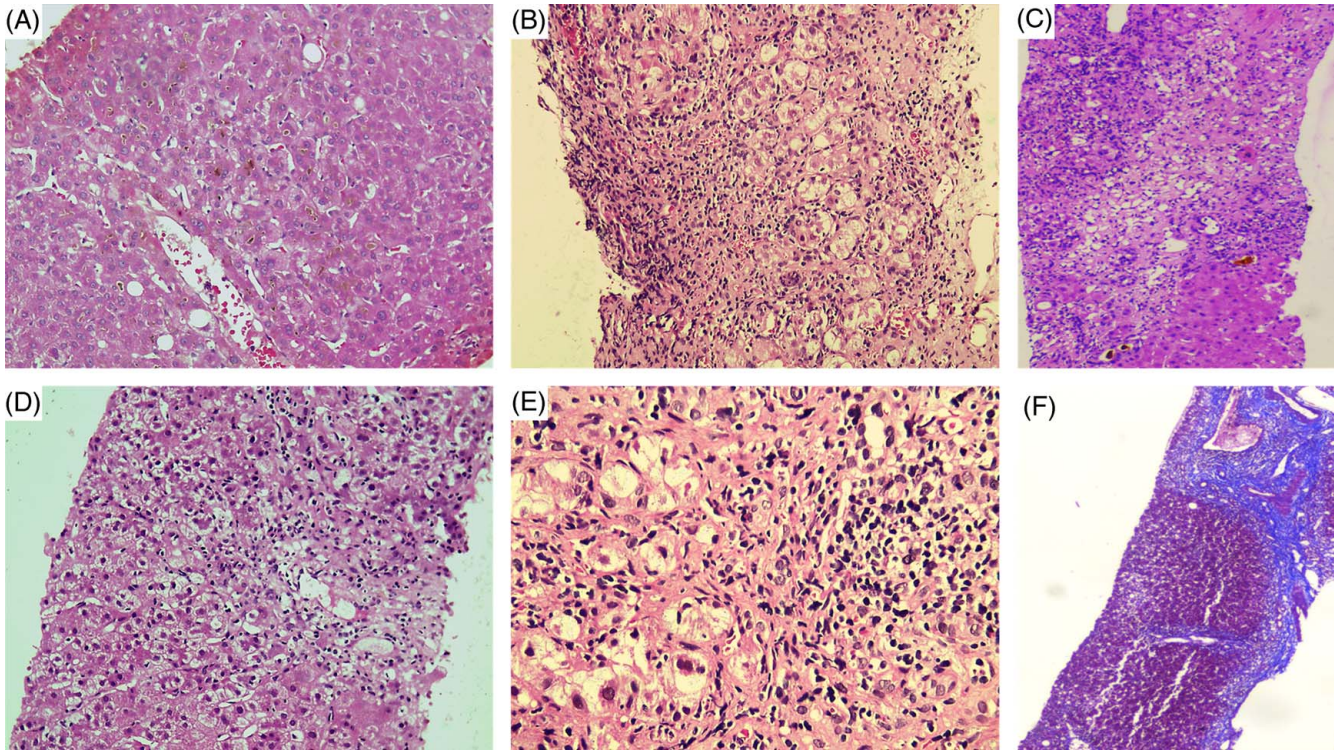

FIGURE 2 Representative liver histology of patients with ashwagandha-induced liver injury. Severe hepatocellular cholestasis (hematoxylin and eosin stain, ×40) (A); lymphocyte and eosinophil predominant portal inflammation (hematoxylin and eosin stain, ×20) (B); bridging necrosis and canalicular cholestasis in the presence of mild to moderate mixed inflammation consisting of lymphocytes, eosinophils, few plasma cells, and neutrophils (hematoxylin and eosin stain, ×20) (C); centrizonal and focal necrosis with minimal inflammation (hematoxylin and eosin stain, ×20) (D); mild to moderate interface hepatitis with lymphocyte predominant and few macrophage-based portal inflammation (E) and in the patient (shown in C) with bridging necrosis and cholestasis, repeat liver biopsy revealed progression to chronic herb-induced liver injury with the formation of vague/incomplete hepatocyte nodules and thick bridging fibrosis (Masson-trichrome stain, ×10) (F).

Reports of ashwagandha-induced liver injury have been notable in medical literature since 2017. An exhaustive summary of all published reports on ashwagandha-induced liver injury is shown in Table 3. The first report was from Japan, followed by multiple reports from United States, Germany, and Poland. Since the first report, a total of 14 cases (excluding the current series) of ashwagandha-induced liver injury are available.[17–26] In the majority of the cases, there are many commonalities. The most common indication for ashwagandha use was stress and anxiety; young or middle-aged males predominated, and clinical presentation was jaundice with cholestasis in the majority. Most patients consumed the herb as per label instructions or as prescribed, and overdosing was seen in only 1.[18] Liver biopsy revealed cholestasis with or without inflammation and sometimes necrosis. The causality assessment tool used was either RUCAM or an exhaustive diagnosis of exclusion. Except for 1 patient who required liver transplantation for survival, all other cases improved with the best supportive care and management of symptoms. In this context, our study has several commonalities and unique aspects.

We present the current largest cohort of ashwagandha-related liver injuries from 3 participating centers that have maintained a DILI database capable of capturing such events. Our findings could only be the "tip of the iceberg" and demonstrate that the nationwide burden of liver injury due to ashwagandha could be more. The previous largest published series of ashwagandha-related liver injuries were from Iceland and the United States. DILI Network concerning 5 patients.[17] Our series included only patients on pure ashwagandha-based formulations. Patients consuming ashwagandha as part of multiherbal preparations, like those included in the paper by Björnsson et al[17], were systematically excluded to remove the confounding effect of complex herbal preparations causing liver injury. Our study included patients with pre-existing liver disease, a novel aspect lacking in the current published literature on ashwagandha-induced liver injury. Chronic liver disease patients developed more severe HILI, and all those who presented with the syndrome of ACLF died in our series, demonstrating the poor prognosis associated with disease severity and clinical progression noted with DILI in the cirrhosis population. In some cohorts, DILI in patients with underlying liver disease has been associated with mortality rates as high as 16%, compared to ~5% in patients without pre-existing liver disease.[8,27,28] Most herbal

TABLE 3 Summary of published studies on liver injury due to ashwagandha

References	Type of study (country)	Clinical indication	Comments
Inagaki et al[16]	Case report (Japan)	Anxiety and stress disorder	Patient: 20-y-old male ashwagandha type: pure supplement Dose: more than twice recommended dose Duration: 1 mo Liver injury: hepatocellular type DILI: high-possibility (DDW-J 2004 criteria) Liver biopsy: canalicular cholestasis Treatment: ursodeoxycholic acid Outcome: complete resolution in 150 d
Björnsson et al[17]	Case series (USA and Iceland)	Anxiety, stress, to increase concentration/focus, general wellness (vitality)	Patients: total of 5, 3 males and 2 females ashwagandha type: pure supplements and ashwagandha containing multiherbal products Dose: as recommended on the label, no over dosages Duration: from 14 to 110 d Liver injury: cholestatic type in 3 patients, mixed in 2 DILI: definite in 1, highly likely in 2, probable in 1, possible in 1 (DILIN expert criteria) Liver biopsy: predominantly cholestasis with portal/lobular inflammation Treatment: supportive care and ursodeoxycholic acid in few Outcome: complete resolution within 60 to 150 d
Weber et al[19]	One case report and various self-reported adverse events on commercial websites (USA)	Not mentioned	Patient: 40-y-old male ashwagandha type: traditional formulation for 1 y, commercial formulation for 20 d Dose: as recommended on the label (450–500 mg once daily) Duration: 1 y and 20 d Liver injury: cholestatic hepatitis DILI: probable (RUCAM criteria) Liver biopsy: not done Treatment: supportive care and withdrawal of offending herb Outcome: resolution details not provided Additional points: from ashwagandha commercial website reporting of adverse events (unconfirmed)—11 with liver damage, 9 with pruritus, 6 with jaundice, 3 with choluria; 6 needed hospitalizations, 2 had acute liver failure (resolved). Additionally, 107 reviews stated severe pruritus as a side effect faced by consumers
Ireland et al[20]	Case report (USA)	Anxiety	Patient: 39-y-old female, 3 months abstinent from alcohol ashwagandha type: an over-the-counter supplement (along with basil leaves and biotin) Dose: as recommended on the label (but on alternate days) Duration: 45 days Liver injury: cholestatic hepatitis DILI: probable (RUCAM criteria) Liver biopsy: cholestatic hepatitis with confluent necrosis Treatment: ursodeoxycholic acid Outcome: complete resolution within 1 month
Rattu et al[21]	Case report (published on the university website as a poster presentation] (USA)	Stress relief	Patient: 44-y-old female ashwagandha type: single-ingredient supplement Dose: as recommended on the label Duration: details not provided Liver injury: cholestatic hepatitis DILI: no causality tools applied, only diagnosis of exclusion Liver biopsy: not performed

TABLE 3. (*continued*)

References	Type of study (country)	Clinical indication	Comments
			Treatment: ursodeoxycholic acid Outcome: resolution details not provided
Patel et al[22]	Case report (USA)	Details unknown	Patient: 65-y-old male ashwagandha type: single-ingredient powdered root Dose: as recommended on the label Duration: details not provided Liver injury: cholestatic hepatitis DILI: no causality tools applied, only diagnosis of exclusion Liver biopsy: severe centrilobular canalicular cholestasis Treatment: ursodeoxycholic acid Outcome: complete resolution in 70 d
Ali et al[23]	Case report (USA)	Stress relief	Patient: 20-y-old male ashwagandha type: single-ingredient over-the-counter supplement Dose: as recommended on the label (450 mg once daily) Duration: 30 d Liver injury: cholestatic hepatitis DILI: no causality tools applied, only diagnosis of exclusion Liver biopsy: not performed Treatment: supportive care, withdrawal of agent Outcome: complete resolution within 30 d
Tóth et al[24]	Case report (Germany)	Anxiety	Patient: 65-y-old female ashwagandha type: single-ingredient over-the-counter supplement Dose: not recorded Duration: 30 d Liver injury: cholestatic hepatitis DILI: no causality tools applied, only diagnosis of exclusion Liver biopsy: spotty necrosis, ceroid-macrophages, hepatocellular, and canalicular cholestasis Treatment: ursodeoxycholic acid Outcome: complete resolution within 60 d
Lubarska et al[25]	Case report (Poland)	General wellness (naturopath prescribed)	Patient: 23-y-old male ashwagandha type: single-ingredient over-the-counter supplement Dose: not recorded Duration: 90 d Liver injury: hepatocellular type DILI: probable (RUCAM criteria) Liver biopsy: not performed Treatment: therapeutic plasma exchange Outcome: complete resolution within 106 d
Suryawanshi et al[26]	Case report (USA)	—	Patient: 41-y-old female, post-thyroidectomy status 2 y ashwagandha type: single-ingredient over-the-counter supplement plus progesterone Dose: not recorded Duration: 60 d Liver injury: hepatocellular type DILI: no causality tools applied, only diagnosis of exclusion Outcome: acute liver failure Treatment: liver transplantation Explant biopsy: submassive necrosis, 20% viable hepatocytes
Philips et al Current series	Case series (India)	Anxiety, stress, general wellness, appetite enhancer, insomnia	Patients: a total of 8, 6 males and 2 females ashwagandha type: pure supplements in the form of powders, pills, herbal jam, detox tea, and syrups

TABLE 3. (*continued*)

References	Type of study (country)	Clinical indication	Comments
			Dose: as recommended on the label or as advised by practitioners, patients reported no overdoses, but dosages could not be recorded Duration: from 14 to 540 d Liver injury: cholestatic type in 4 patients, hepatocellular in 3, and mixed in 1 DILI: 6 probable and 2 possible cases (RUCAM criteria) Liver biopsy: predominantly hepatocellular and canalicular cholestasis with portal inflammation and varying extent of necrosis Treatment: supportive care and ursodeoxycholic acid in those with cholestasis, immunosuppression in 1 patient with recurrence of hepatitis and chronic herb-induced liver injury on serial biopsy Outcome: complete resolution within 45–95 d Additional: included patients with pre-existing liver disease; 3 with acute-on-chronic liver failure died on follow-up

Abbreviations: DILIN, drug-induced liver injury network; RUCAM, Roussel Uclaf Causality Assessment Method.

supplements implicated in liver injury are frequently mislabeled or accurate ingredients not evidently disclosed. Many cases of DILI due to herbal supplements are caused by formulations containing multi-ingredient mixtures, and it can be difficult to prove the exact compound that is responsible for liver injury.[29] In our study, all patients used marketed or prescribed ashwagandha-only formulations, and chemical and toxicology analysis did not detect other hepatotoxic substances, making our conclusions on ashwagandha causing severe liver injury and death among our patients pertinent and concerning. Although ashwagandha is generally considered safe to consume, there has been an increase in reports of DILI due to its use, driven by unscientific and nonevidence-based promotion among general people through print, visual, and social media. The underlying mechanism for liver damage due to ashwagandha could be the presence of herb-specific compounds called withanolides that cause irreversible adduction to hepatocellular DNA.[30] None of the patients had a history of concomitant hepatotoxic prescription or alternative medicine use, alcohol misuse, or i.v. drug use. Even though we did not perform the PCR test for HCV and HEV infection, viral hepatitis was considered very unlikely to cause the pattern of liver injury described in our patient cohort, which was predominantly cholestatic with only mild elevation in aminotransferases. Two patients in our cohort were positive for autoantibodies with high serum IgG without other classical features of autoimmune hepatitis. Initially, in all patients except those with severe ACLF, withdrawal of offending herb and supportive care without immunosuppression resolved jaundice and hepatitis. Unique to our study, we found that in 1 patient, a young man (patient number 3), hepatitis recurred after complete resolution on best supportive care with repeat biopsy suggestive of chronic HILI without the presence of classical autoimmune hepatitis. The second hepatitis episode was well controlled by initiating low-dose immunosuppression (corticosteroids and mycophenolate), with the patient doing well on follow-up. Mild elevations of autoimmune markers are not pathognomonic for autoimmune hepatitis and are very commonly described in patients with DILI, and drug-triggered autoimmune hepatitis is not uncommon, especially in the context of HILI.[7,9,17,31]. Even though RUCAM is the standardized, validated tool to measure causality in DILI, it tends to underestimate the causality associated with herbal supplements because it was designed to assess the causality of a single product, whereas herbal products typically contain multiple herbal and nonherbal ingredients. Nonetheless, published studies on single-ingredient herbal supplements have used RUCAM to approximate the causality, while others have only depended on an exhaustive diagnosis of exclusion without using any causality tools. We understand that the newly developed Revised Electronic Causality Assessment Method and the gold standard DILIN consensus are better tools for causality assessment. However, due to the retrospective nature of our study, we could not gather specific data inputs (such as exact dates of transaminase peak) required for Revised Electronic Causality Assessment Method completion. The approximate days/duration (and not the date) of herb consumption and stoppage was from patient recall which may have suffered recall bias. We lack an organized, core DILI network in our country, there is a deficit of DILI coordinating centers, and paucity of centralized expert-driven electronic/online data assessment system for a rigorous and validating consensus which operates under DILIN in the United States. In our patients, the herbal supplement was a single ingredient (ashwagandha) without any other known hepatotoxic ingredients or concomitant liver toxic

medication use (as such, were excluded), and hence RUCAM use was reasonably justified. We could not retrieve all implicated products for exhaustive chemical analysis. But the chemical analysis of available samples did not reveal hepatotoxic components, contamination, or adulteration that could have indirectly led to liver injury. Multiple prior studies have demonstrated a drug or herb-specific HLA association with DILI. In our study, we could not perform such testing due to a lack of resources. A summary schematic encompassing published literature and novel findings from the current study is shown in Supplemental Figure S2, http://links.lww.com/HC9/A532.

CONCLUSIONS

Ashwagandha herb is used extensively in the Indian systems of traditional medicine, but lately, its use as a dietary supplement for unproven indications has been on the rise in western countries, especially for mental health disorders and as a workout supplement among gym-goers. We present 8 cases of ashwagandha-related liver injury in which patients with pre-existing liver disease suffered high mortality without timely liver transplantation. Educating the public on avoiding unrecommended and potentially harmful herbal supplements can reduce the (avoidable) liver disease burden within the community.

AUTHOR CONTRIBUTIONS

Cyriac A. Philips: conceptualization, methodology, formal analysis, writing—original draft, writing—review and editing. Arun Valsan: conceptualization, data curation, writing—review and editing. Arif H. Theruvath: methodology, data curation, writing—review and editing. Resmi Raveendran: methodology, data curation, writing—review and editing. Tharun T. Oommen: methodology, supervision, writing—review and editing. Sasidharan Rajesh: supervision, writing—review and editing. Saptarshi Bishnu: conceptualization, data curation, writing—review and editing. Philip Augustine: supervision, writing—review and editing. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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