Original Article

Complimentary Medicine (Tinospora cordifolia/Gulvel/Guduchi) Induced Liver Injury

Dr. Maindad Dadasaheb G[1], Dr. Nagpal Akhil[2]

[1,2]Department of Gastroenterology, Bharati Vidyapeeth Medical College, Pune, Maharashtra, India

Abstract

Tinospora cordifolia is a wild herb found in the hills of Western Maharashtra, has been utilized in Ayurvedic medicine to treat hepatitis as a hepatoprotective agent. Furthermore, during the current COVID 19 pandemic, it has recently been ingested by the general public as an immune booster. The purpose of this study was to describe the hepatotoxic effects of Tinospora cordifolia and the clinical outcomes. The study was conducted in Western India's multispecialty tertiary care center. Twenty individuals with impaired liver function test (LFTs), a history of Tinospora cordifolia ingestion, and no additional etiologies were included. These patients were followed until their LFT levels stabilized or they died. We observed 20 patients who had taken Tinospora cordifolia and had clinical hepatitis as well as abnormal LFT. The Roussel Uclaf Causality Assessment Method (RUCAM) score for all of these individuals was larger than 6(6.7±0.3), indicating causation. The severity of the presentation and course ranged from mild to severe, with 95% (n=19/20) of patients recovering with supportive care, while one death is due to acute on chronic liver failure. The average time to recovery was 72.6 ±9.6 days. With large doses, Tinospora cordifolia may induce hepatotoxicity most likely in genetically vulnerable elderly. It is important to raise awareness among community about the risks of the unchecked and indiscriminate use of herbal products and their toxicities.

Keywords: Complimentary medicine, Drug-induced liver injury, Tinospora cordifolia, Guduchi, Gulvel.

Introduction

After removing other etiologies, drug-induced liver damage (DILI) is defined as hepatotoxicity caused by various drugs, botanicals, or xenobiotics, resulting in changes in liver function, with or without clinical symptoms.1 DILI can be caused by a variety of natural supplements, medications, and chemicals. DILI is defined as an increase in liver enzymes, such as alanine aminotransferase (ALT) or aspartate aminotransferase (AST), alkaline phosphatase (ALP), or bilirubin, that is 3-5 times higher than their upper limit of normal (ULN).2

Despite recent advances in diagnostic tools, DILI remains unexpected in the case of various medications and herbs, resulting in a lack of knowledge about the prevalence and incidence of the majority of pharmacological hepatotoxicities.3 In 10% of DILI instances, complementary and alternative medicines (CAM) are thought to be the root cause.4

Plant products having therapeutic properties are useful in clinical research and practice because they are thought to have fewer side effects than allopathic medications.5 Tinospora cordifolia is a big climber with many long branches. Simple, alternating, roundish, and pulvinate leaves with petioles up to 15 cm in length. The lamina is seven nerved, broadly elliptical, and deeply cordate at the base, measuring 10 to 20 cm long, 8 to 15 cm wide, and membranous. There is a whitish tomentose with an upper pubescent zone and a reticulum that is less apparent.6

Address for correspondence: Maindad Dadasaheb G
Department of Gastroenterology, Bharati Vidyapeeth Medical College, Pune, Maharashtra, India
Email: dadasahebmaindad@yahoo.com

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(Figure A) Tinospora cordifolia is a member of the Menispermaceae family and is known by the common names Guduchi, Moonseed, and Giloy.6 Alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides are among the active ingredients extracted from the plant, all of which are said to have miraculous pharmacological properties. These components are extracted from several portions of the plant, including the body, root, stem, and starch.7 It is used to treat a variety of illnesses and is available in syrup, tablet, and powder form.

It thrives as a wild plant in hilly locations, making it widely accessible to the general public. A large number of patients use the herb in various forms as self-medication. It is important to note that the literature on Guduchi (Tinospora cordifolia)-induced hepatotoxicity is extremely limited. Mild hepatotoxicity was identified among the subjects in research on Rasasindura, an Ayurvedic mercurial medicine in which Tinospora cordifolia is a component.8 Huang et al. reported case that the use of Tinospora crispa (TCP), which is hepatotoxic, rather than Tinospora cordifolia (TCF), which is believed to be hepatoprotective, was the cause.9

Many people are reported to have self-medicated with Guduchi (Tinospora cordifolia) for its immune-boosting effects during the current COVID 19 outbreak. There may be a risk of harm to a metabolically active organ and increases when it is consumed in raw form in large doses over long periods without medical supervision. We described the hepatotoxic effects of Tinospora cordifolia and the clinical outcomes of these patients in this study.

Material and Methods

Between June 2020 and May 2021, we describe the clinical course and outcomes of 20 patients with acute hepatitis-like illnesses who presented to Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital in Pune, Maharashtra which is the multispecialty tertiary care center in western India.

All the patients had a history of self-administration of Guduchi (T. cordifolia) in a variety of forms and doses and for variable durations. A thorough clinical history was taken, including any alcohol or drug abuse history. All of the patients had a thorough clinical examination and laboratory workup, which included a complete blood count (CBC), renal function tests (RFT), liver function tests (LFT), international normalized ratio (INR), etiological workup, viral markers, autoimmune workup, ceruloplasmin and Kayser Fleischer (KF) ring, ferritin level, and ferritin saturation.

Ultrasonography abdomen was done to rule out chronic liver disease, portal hypertension, and vascular disorders. We also did an upper GI endoscopy and an ascitic fluid analysis (whenever applicable). The Roussel Uclaf Causality Assessment Method (RUCAM) (>6) score was used to determine causality.10

All of the patients were told to stop using Guduchi and given ursodeoxycholic acid 300 mg twice a day, nutritional support, and diuretics as needed. All of the patients were evaluated clinically and with laboratory data every 15 days until LFT normalization or death. Patients with decompensation and those who consented to the liver biopsy were admitted to the hospital. Ethics committee approval was obtained for the study and patient consent was taken.

Results

Our patients ranged in age from 21 to 65 years old (52.6 ± 4.46 years), who had a history of ingesting Guduchi (Tinospora cordifolia /Gulvel) and had abnormal LFTs. Females and elderly patients were found to be more affected (n=13, n=15), with a male to female ratio of roughly 1:1.85. Furthermore, 75% (n=15) of patients were above the age of 50 years of age. Diabetes mellitus, hypertension, and ischemic heart disease were all present in elderly people. Our patients, on the other hand, had no prior history of liver illness. The RUCAM score ranged from 6 to 9 (6.7 ± 0.3, 95% CI), with 11 patients receiving a score of 7, indicating drug causation for liver injury.

Jaundice (n=20), anorexia (n=20), and nausea (n=20) were the most prevalent complaints, followed by vomiting (n=10), ascites (n=7), and pruritus (n=7). Seven of the patients showed cholestatic characteristics, while another seven had ascites complicating their disease. The symptoms ranged from mild anorexia and yellowish discoloration of the eyes and urine to more severe jaundice, ascites, and acute on chronic liver failure (ACLF). Hepatomegaly, prodrome, or right upper quadrant pain, on the other hand, were not served in any of the patients.

Guduchi (T. cordifolia) consumption lasted an average of 90 days (range 15-180 days, 90.7 ± 13.7 days, 95 % CI). The average time it took for symptoms to appear was 66 ± 11.2 days (range 15-120 days). After the commencement of symptoms, it took 24.2 ± 4.7 days to seek medical advice (range 15-60 days).

Eight patients drank leaves juice or boiling extract (mean TB-10.8 ± 2.6 mg/dl), six took roots extract or crushed roots (mean TB-8.9 ± 1.8 mg/dl), and four consumed commercially available preparations (mean TB-7.9 ± 2.4 mg/dl). Two patients took stump extract (mean TB-11.2 ± 1.3 mg/dl). Due to the small size of the sample, we are unable to examine the effects of different preparations on LFT.

One patient out of twenty had a history of Guduchi (T. cordifolia) re-ingestion, which resulted in a recurrence of signs, symptoms, and test abnormalities that had disappeared after intake cessation. (Table 1)

Table 1: Demographic characteristics, Guduchi consummation-related information, and on admission laboratory parameters of the included patients

Parameter		Mean	Range
Age		52.6 ±4.46 years	21-65 years
Male		7	
Female		13	
Presenting symptoms	Vomiting	10	
	Jaundice	20	
	Anorexia	20	
	Nausea	20	
	Ascites	7	
	Pruritis	7	
Comorbidity	DM	7	
	HTN	12	
	IHD	2	
	Pneumonia	1	
	History of T.Cordifolia consummation	1	
Duration from Guduchi consummation to the onset of symptoms in days		66 ±11.27 days	15-120 days
The total duration of Guduchi consummation in days		90.75 ±13.7 days	30-180 days
Duration to the onset of symptoms to seek healthcare facility in days		24.25 ±4.76days	15-60 days
Form of Guduchi consummation	Leaves	8	
	Root	6	
	Stump	2	
	Ready preparation	4	
RUCAM Score	<7 (6)	8	
	>7	12	
Treatment pattern	OPD	17	
	IPD (One for ACLF/ two for liver biopsy)	3	
Hemoglobin		9.62 ±0.51gm%	7.7-12 gm%
Total count		5,075 ±390.74 cells/mm^3	3800-7200 cells/mm^3
Platelets		1.929 ±0.42 lakhs	0.8-4.2 lakhs
		0.86 ±0.07mg/dl	0.5-1.2 mg/dl
Ascites	Number of patients	7	
	Total count	2.14±13.11 cells/mm^3	40-100 cells/mm^3
	Total protein	1.68±0.21gm/dl	1.2-2.2 gm/dl
	Albumin	1.08 ±0.08gm/dl	0.9-1.2gm/dl
	SAAG >1.1	7	
	SAAG < 1.1	0	

Abbreviations: DM, Diabetes Mellitus; HTN, Hypertension; IHD, ischemic heart disease; OPD, Outpatient Department; IPD, Inpatient Department, SAAG, serum-ascites albumin gradie

Sixteen of the patients were anemic, while the rest of the baseline assessments were within the normal range. Four patients had altered echotexture of liver on USG abdomen, out of which only one of these had small esophageal varices and dilated portal vein. Serum ascites albumin gradient (SAAG) (>1.1) was high in all ascetic patients. Significant portal hypertension is indicated by the presence of high SAAG ascites and thrombocytopenia.

Three patients were hospitalized, in which two patients were admitted for liver biopsy, and one patient was admitted for ACLF. Other patients were managed as OPD patients.

All 20 patients tested negative for Hepatitis B surface antigen (HbsAg), Anti-hepatitis C virus (HCV), and Human immunodeficiency virus (HIV). The levels of ceruloplasmin and serum ferritin were all within normal ranges. Antibodies to antinuclear antibodies (ANA), anti-liver/kidney microsome (LKM1), and antismooth muscle antibodies (ASMA) were negative, and serum immunoglobulin levels

were normal. Only one patient had esophageal varices.

The mean and standard deviations of baseline laboratory parameters on presentation (n=20) were as follows: total bilirubin (9.7 ± 1.4 mg/dl), direct bilirubin (mean 6.6 ± 1.1 mg/dl), indirect bilirubin (3.0 ± 0.4 mg/dl), AST (299.6 ± 51.8U/L) and ALT (340.5 ± 52.9U/L), ALP (226 ± 19.4 U/L), albumin (3.1 ± 0.2 g/dl), prothrombin time (17.6 ± 0.9 seconds). At the start of the trial, 14 (< 3.5 g/l) patients had hypoalbuminemia, and 18 (>14sec) patients had a high prothrombin time.

In almost all of the patients, liver function tests returned to normal after supportive treatment or hospitalization. At 45 days, the values were as follows: (n=19) total bilirubin (2.7 ± 0.7 mg/dl), direct bilirubin (1.7 ± 0.6 mg/dl), indirect bilirubin (0.98 ± 0.1 mg/dl), AST (80.7 ± 13.5 U/L) and ALT (89.7 ± 15.1 U/L), ALP (164.1 ± 7.8 U/L), albumin (3.5 ± 0.13gm/dl), prothrombin time (14.7 ± 0.3 seconds). In 19 patients, all the parameters of LFT improved significantly on or after the 45th day ($p < 0.001$) (Figure 2, Table 2). It indicates a causal link with the drug.

Table 2: Laboratory Data

	On presentation LFT								After 15 days LFT								After one and half months LFT (45days)									
	TB (mg/dl)	DB (mg/dl)	IB (mg/dl)	AST (U/L)	ALT (U/L)	ALP (IU/L)	ALB (g/dl)	PT (Sec.)	TB (mg/dl)	DB (mg/dl)	IB (mg/dl)	AST (U/L)	ALT (U/L)	ALP (IU/L)	ALB (g/dl)	PT (sec.)	TB (mg/dl)	DB (mg/dl)	IB (mg/dl)	AST (U/L)	ALT (U/L)	ALP (IU/L)	ALB (g/dl)	PT (sec.)	Time required for LFT normalization (days)	P-value
1	11.2	7.2	4.0	321	400	290	2.8	20	7.8	5.0	3.8	150	141	225	3.2	18	4.0	2.5	1.5	100	110	170	3.3	16	90	<0.001
2	7.2	4.8	2.4	359	390	268	3.9	18	5.1	2.8	2.3	123	139	190	3.95	15	1.0	0.4	0.6	40	36	168	4.0	15	45	<0.001
3	8.5	5.6	2.9	260	312	300	2.9	18	6.2	4.0	2.2	144	200	210	3.5	17	2.2	1.2	1.0	65	78	180	3.6	14	90	<0.001
4	5.6	3.0	2.6	400	410	310	2.3	17	3.6	3.0	0.6	120	136	210	2.6	14	2.0	1.3	0.7	65	68	175	3.5	14	60	<0.001
5	6.6	3.6	3.0	220	320	200	3.9	16	3.2	2.2	1.0	125	156	170	3.9	14	1.0	0.4	0.6	45	55	160	4.0	14	45	<0.001
6	10.2	7.8	2.4	210	300	206	2.8	20	7.4	5.8	1.6	160	182	166	2.8	17	3.8	2.0	1.8	112	142	160	3.2	16	105	<0.001
7	8.3	5.0	3.3	300	320	296	4.0	16	6.0	4.5	2.5	150	156	178	4.0	15	1.0	0.4	0.6	45	50	163	4.0	15	45	<0.001
8	6.1	4..2	1.3	220	230	190	3.9	14	3.2	1.9	1.3	120	132	176	4.0	14	1.1	0.5	0.6	45	55	160	4.1	14	45	<0.001
9	10.8	8.0	2.8	280	302	200	2.9	19	7.5	5.5	2.0	196	196	180	3.0	17	4.2	3.0	1.2	100	106	160	3.1	16	90	<0.001
10	12.8	8.1	4.7	300	330	260	2.8	20	8.0	5.1	2.9	210	216	190	3.1	18	4.5	2.8	1.7	140	152	170	3.2	16	90	<0.001
11	16.2	11.6	4.6	210	250	170	2.3	20	20.0	16.0	4.0	201	246	177	2.0	22	The patient expired due to ACLF and multi-organ failure									
12	5.3	3.0	1.3	210	320	160	3.8	14	3.5	2.3	1.2	197	128	166	3.9	14	1.0	0.4	0.6	45	42	162	3.9	14	45	<0.001
13	10.1	7.0	3.0	310	340	210	3.2	18	6.5	4.0	2.5	200	182	192	3.2	17	3.0	1.8	1.2	106	120	178	3.5	14	90	<0.001
14	13.4	11.0	2.4	500	546	189	2.8	19	9.6	7.5	2.1	410	435	180	3.1	17	5.4	4.4	1.0	116	120	170	3.4	15	90	<0.001
15	7.5	5.2	2.3	250	278	180	3.4	16	4.1	3.0	1.1	150	162	170	3.4	15	1.5	0.8	0.7	80	85	170	3.8	14	60	<0.001
16	8.2	5.0	3.2	222	238	230	3.2	15	4.5	3.0	1.5	152	168	200	3.3	14	2.3	1.3	1.0	90	94	100	3.5	14	60	<0.001
17	12.2	7.5	5	300	326	210	3.1	18	8.2	6.0	2.2	175	201	196	3.2	17	4.2	3.0	1.2	100	120	166	3.6	14	90	<0.001
18	10.2	8.0	2.2	241	266	211	3.4	17	6.5	4.0	2.5	158	166	190	3.5	16	2.0	1.0	1.0	61	77	146	3.5	14	75	<0.001
19	17.0	12.2	4.8	700	750	230	2.0	21	14	10	4	256	281	200	3.0	18	6.2	5.2	1.0	120	126	180	3.4	16	105	<0.001
20	7.2	5.0	2.2	180	182	210	3.5	15	4.0	3.0	1.0	142	138	190	3.5	14	2.0	1.3	0.7	60	70	180	3.5	14	60	**<0.001**

TB: Total bilirubin; DB: Direct bilirubin; IB: Indirect bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; ALB: Albumin; PT: Prothrombin time

The liver function of nine patients returned to normal within 60 days, while the LFT of 11 patients took longer than two months to return to normal. Those patients who required a prolonged recovery time (> 60 days) had more severe illness upon presentation, as evidenced by a higher total bilirubin level (12.0 ± 6.9 mg/dl vs.6.89 ± 1.1 mg/dl, p<0.001)

All patients were given 300 mg of ursodeoxycholic acid twice a day, nutritional supplements, and diuretics as needed in cases of ascites. The LFT was normalized in 19 individuals, and the average recovery period was 72.6 ± 9.6 days. (The lowest and maximum periods were 45 days and 105 days.) Patients with bilirubin levels more than 7 mg/dl took longer to recover time (79 ± 2.0 vs. 48.7 ± 7.5 days, p < 0.009).

Seven patients had moderate ascites, and they had the more severe disease as compared to non-ascitic patients. Total bilirubin (13.0 ± 2.6 vs. 7.9 ± 1.9 mg/dl, p < 0.001), albuminemia (2.6 ± 0.3 vs. 3.4 ± 0.4 g/dl, p <0.001) also other LFT parameters were affected more severely in the ascitic group (table 3). In these ascites patients, the recovery was significantly slower, with a duration of more than three months (95 ± 7.7 vs. 62.3 ± 18.2 days, p=0.001).

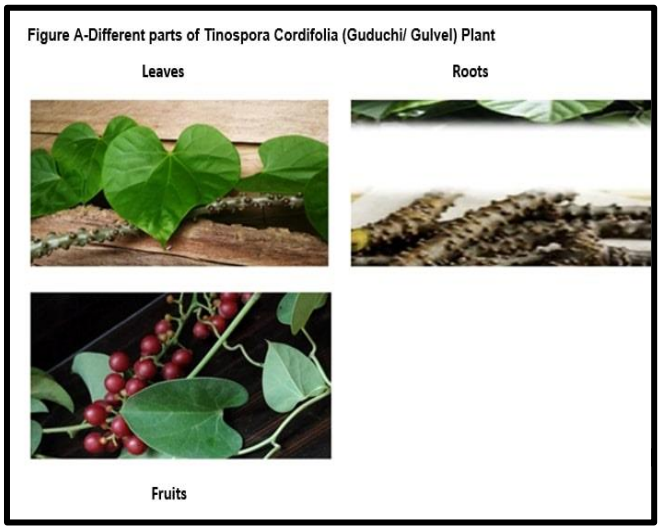
Table 3. Comparison between ascitic non ascitic sub-groups

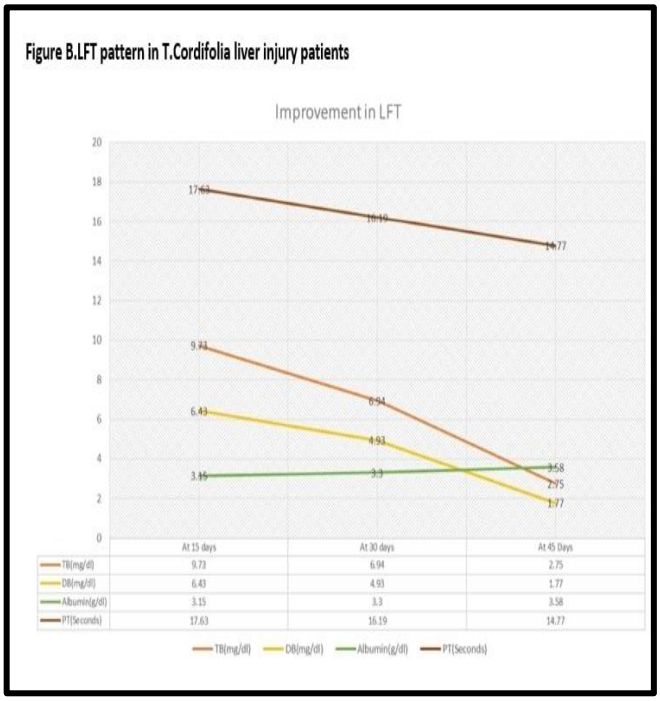
	On presentation LFT						**After 15 days LFT**						After one and half months LFT [Ascites group(n=6)]						
	TB (mg/dl)	**DB (mg/dl)**	**AST (U/L)**	**ALT (U/L)**	**ALB (g/dl)**	**PT (Sec.)**	**TB (mg/dl)**	**DB (mg/dl)**	**AST (U/L)**	**ALT (U/L)**	**ALB (g/dl)**	**PT (sec.)**	**TB (mg/dl)**	**DB (mg/dl)**	**AST (U/L)**	**ALT (U/L)**	**ALB (g/dl)**	**PT (sec.)**	**Outcome (Days)**
Ascites group (n=7)	13.08	9.41	360.14	372.2	2.62	19.83	10.61	7.84	226.4	242.4	2.88	18.1	4.68	3.31	114.6	126	3.2	15.83	95
Non ascites group (n=13)	7.92	5.14	267.07	302.4	3.42	16.31	4.96	3.36	150	158.7	3.53	15.0	1.86	1.06	65.15	73.07	3.7	14.15	62.30
P value	<0.001	<0.001	0.109	0.05	<0.001	<0.001	<0.001	<0.001	0.004	0.003	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
All patients (n=20)	9.73	6.43	299.65	340.5	3.14	17.63	6.94	4.93	176.95	188	3.30	16.1	2.75	1.77	80.78	89.78	3.58	14.77	72.63

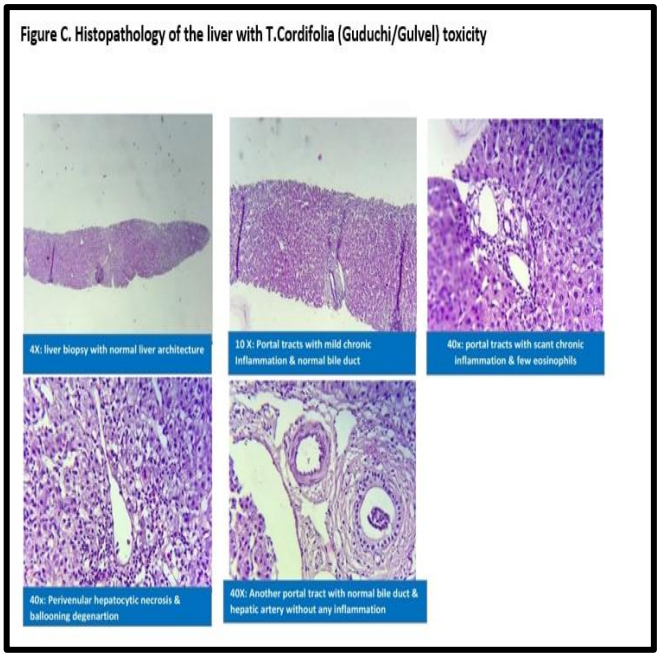
TB: Total bilirubin; DB: Direct bilirubin; IB: Indirect bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; ALB: Albumin; PT: Prothrombin time

Even at 45 days, difference in LFT parameters of ascitic and non-ascitic patients was significant (p < 0.05) (Table-3). In 19 patients, the alkaline phosphatase was more than the upper limit of normal (226 ±19.4 IU/L), but in none of the patients, ALP increased above two times the upper limit. Short-duration cholestatic symptoms were seen in seven patients even with ALP less than two times ULN.

Out of 20 patients, only two patients gave consent for liver biopsy. One patient had drug-induced hepatitis, and the other had drug-induced hepatitis with underlying chronic liver diseases. Histopathology revealed mild chronic inflammation with eosinophils, normal-sized bile ducts, and bile ductules; no enlargement of portal regions, florid ductular reaction, or interface hepatitis in the portal tracts. Hepatocytes displayed ballooning degeneration within the parenchyma, with patches of localized perivenular necrosis and moderate macrovesicular steatosis. Lymphocytes and eosinophils were mixed in a diffuse lobular inflammation (Figure 3).







The length of time it takes to recuperate is determined by the severity of the sickness. One patient died from liver-related multi-organ failure, while the other died from COVID pneumonia. By stopping the intake of Guduchi (T. cordifolia), the LFT in the COVID pneumonia patient had stabilized before death. Tinospora cordifolia hepatotoxicity turned into ACLF and death in one patient (n=1/20).

Discussion

Guduchi (T. cordifolia) has several substances that have different characteristics and are commonly used in Ayurveda as immune-modulators. Guduchi is also readily available in Western Maharashtra, where it is used to prevent COVID 19. It has also been utilized as a hepatoprotective drug in the treatment of alcohol, anti-TB drugs, and cyclophosphamide-induced hepatitis.11, 12, 13 Tinospora cordifolia was found to cause neutrophil adhesion hemagglutination, macrophage activation, and delayed hypersensitivity in a study of its immune-modulatory potential. 14,15 At 300 mg/kg dosage the good immunomodulatory potential was detected.15

Studies conducted an experimental analysis in laboratory rats with various doses that were shown to be safe when given at a level of 8 gm/kg.16 Huang et al. looked into the hepatotoxic effects of Tinospora cordifolia consumption and found just one case of liver damage and acute liver failure. It could be due to Tinospora crispa being mistaken for Tinospora cordifolia because both plants have similar leaves. 9

Genetic predisposition can be used to explain isolated incidences of jaundice in families who consume T. cordifolia. We were unable to quantify the dosage element of our study, necessitating additional investigations. The hepatoprotective or hepatotoxic effect may bet is dose-dependent. T. cordifolia reduces AST, ALT, ALP, and total bilirubin at 200 mg/kg, but has hepatotoxic effect at 400 mg/kg, according to an experimental study of paracetamol overdose. This could be attributed to Satwa's toxicity at greater quantities, as T. cordifolia grows on Neem trees.17

Hepatotoxicity can also be predisposed by an underlying liver illness that is unclear. One liver damage case was described in an experimental investigation after consuming Tinospora cordifolia for 90 days and recovering within a month after halting the consumption.18

Twenty cases of hepatotoxic illness have been documented as a result of indiscriminate self-administration of Tinospora cordifolia (Guduchi). The RUCAM score for DILI was used to confirm the etiology in these patients.

The liver injury was self-limiting, benign, and mostly hepatocellular in nature. In 19/20 individuals, clinical and biochemical abnormalities were completely resolved, however one patient died as a result of DILI. The expired case had preexisting CLD (Chronic liver disease) (hypoalbuminemia, changed hepatic echotexture, and tiny esophageal varices) and died of ACLF. Another person died as a result of COVID pneumonia. Because LFT is normalized on the cessation of Guduchi before death in COVID pneumonia patients, death was not caused by T. cordifolia - induced DILI.

Seven patients had high SAAG ascites, but only one had pre-existing chronic liver disease symptoms. Transient and reversible sinusoidal portal hypertension and hypoalbuminemia could explain this. Because ascites seen in seven out of twenty patients (35%), it can be assumed that Tinospora cordifolia can cause severe but reversible liver disease in a significant proportion of those affected.

There was no evidence of a hepatitis-like condition clustering among entire families who used Tinospora. Guduchi (T. cordifolia)-induced hepatotoxicity may be predisposed to the elderly, females, large doses, genetic composition, and pre-existing liver illness. The condition progresses benignly, with good recovery following the cessation of drug use. The patient with underlying CLD, on the other hand, had a negative outcome.

Conclusion

With large doses, Tinospora cordifolia can induce hepatotoxicity, most likely in genetically vulnerable elderly. Ingestion of this herb has the potential to be harmful. In view of the high morbidity from HILI and the high cost of management, its prevention is the best option. We, therefore, suggest an active pharmacovigilance policy for over-the-counter herbal medicines which curb the serious outcomes associated with usage. It is important to raise awareness in the community about the risks of the unchecked and indiscriminate use of herbal products and their toxicities.

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Nil

Disclosure

The author reports no conflict of interest in this work.

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