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Tinospora Cordifolia (Gulvel/Guduchi) Induced hepatotoxicity

Dadasaheb maindad

Department of Gastroenterology, Bharati Vidyapeeth University of Medical College and Hospital, Maharashtra,India

Abstract

Background: Drug-induced liver injury (DILI) is caused due to various types of medications, herbs, or other xenobiotics, in the absence of other etiologies. DILI has been observed with different clinical features and biochemical abnormalities. Herbal products are responsible for DILI in many cases (10%). There exists no specialized gold standard method to diagnose or predict DILI, and the disease has been commonly diagnosed with the RUCAM score. Tinospora Cordifolia (Gulvel/Guduchi), which is readily available in the hilly area of western Maharashtra as a wild plant, has been used in Ayurveda for the treatment of hepatotoxicity. Furthermore, it is consumed as an immune-modulator during the COVID 19 pandemic.

Case presentations: During last year, there is a sudden increase in hepatitis cases. We observed 16 patients who consumed Tinospora Cordifolia (Gulvel/Guduchi) and depicted instability in liver function tests. This research found no other reason responsible for such complaints in these patients. All these patients had a RUCAM score greater than six. They had mild to severe level symptoms in which fourteen patients were recovered with supportive care. It was noted that elderly females were affected commonly, in which one mortality case happened secondary to ACLF. The study observed no cases in the family even after the consummation of similar products with similar doses.

Conclusion: Tinospora Cordifolia (Gulvel/Guduchi) can cause mild to severe grade hepatotoxicity with high doses, most probably in genetically susceptible elderly patients. Additionally, the study also states that mortality is rare. However, to confirm this observation and to provide prompt details, more research must be carried out.

Keywords: Tinospora • Cordifolia • Gulvel • Guduchi • Hepatotoxicity

Introduction

Drug-induced liver injury (DILI) is defined as hepatotoxicity caused by various medications, herbs, or xenobiotics, leading to abnormalities in liver functioning, with or without clinical features after excluding other etiologies.1,2There are many herbal products, drugs, and chemicals that lead to DILI. 1, 2 Increase in liver enzymes, alanine aminotransferase (ALT) or aspartate aminotransferase (AST), alkaline phosphatase (ALP), or bilirubin, 3-5 times above their upper limit of normal (ULN) has been considered as DILI.2However, despite recent improvements, DILI remains unpredictable in the case of several drugs and herbs, leading to the prevalence and incidence of the majority of drug hepatotoxicities that are still only partially known. 3 Complementary and alternative medicine (CAM) is determined as the causative factor in 10% of DILI cases[1].

Plant products with their medicinal values are important in clinical research and practice as they are believed to have fewer adverse effects than allopathic drugs. For example, Tinospora cordifolia (Guduchi/Gulvel) has been used in Ayurveda to treat various diseases and symptoms. 5 Tinospora cordifolia is widely distributed in the Indian Subcontinent & China.6 That is grown as a wild plant in a hilly area, and therefore it is easily accessible. Tinospora cordifolia is a large climbing shrub with several number of long branches. The leaves are simple, alternate, roundish, and pulvinate, with petioles up to 15 centimeter. The lamina is seven nerved, broadly ovate, and deeply cordate at the basal region, 10 to 20cm long, 8 to 15 cm broad, and membranous. There exists a whitish tomentose with an upper pubescent region and a less prominent reticulum.7 Tinospora cordifolia family is Menispermaceae and is identified with common names-Guduchi, Moonseed, or Giloy.7Numbers of active constituents are extracted from the plant-like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides, which possess miraculous pharmacological functions. These components were isolated from different parts of the plant-like body, root, stem, and the plant's

***Address to correspondence:** Dadasaheb maindad, Department of Gastroenterology, Bharati Vidyapeeth University of Medical College and Hospital, Maharashtra,India,Ph: 9552993311 E-mail: dadasahebm98@gmail.co*

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starch.5 It is prescribed as a medication in many diseases in a readily available form as syrup, tablets, or powder [2].

Further, a considerable number of patients also consume the herb as self-medication in similar forms. It should be highlighted that there exists very scanty literature with regards to Guduchi-induced hepatotoxicity. In a study on Rasasindura, Ayurvedic mercurial preparation in which Guduchi is a component, mild hepatotoxicity was detected among the subjects .8There is another case report where probable etiology is the consumption of Tinospora crispa (TCP), which is hepatotoxic instead of Tinospora cordifolia (TCF), which is hepatoprotective.9The incidence of damage in a metabolically active organ is increased due to its consumption in raw form in large doses for prolonged periods without doctors consultation and monitoring. During the current COVID 19 pandemic, many individuals are known to have self-medicated themselves with Guduchi for its immune-boosting properties [3].

Materials and methods

Study area

The study was conducted at the Department of Gastroenterology, Bharati Vidyapeeth Deemed to Be University Medical College and Hospital, Pune, Maharashtra,India.

Study type

This observational hospital-based study is in the form of case series.

Study duration

The study duration included the period of Jun 2020 to January 2021. We encountered 16 cases of acute hepatitis-like illness in this duration where we did not found usual etiologies like viral, alcohol, autoimmune, metabolic, or vascular causes.

Study method

We advised to stop Guduchi intake and treated them as OPD patients with supportive treatment, ursodeoxycholic acid 300mg twice a day, nutritional support, and diuretics as per need. All patients followed every 15 days till LFT normalization or death. Patients have advised admission for liver biopsy and if there is any severe complication

Inclusion Criteria

The inclusion criteria for the study was the history of self-administration of Guduchi in variable forms, doses, and duration. Established causality by employing the RUCAM score where in all 16 patients had a score more than six (highly probable DILI).10

Exclusion Criteria

Patients having other etiologies for hepatic injury were excluded.

All patients evaluated with

1. Clinical history
2. History of alcohol or drug consummation
3. Detailed clinical examination
4. CBC, RFT, LFT
5. Etiological work up
6. Viral markers
7. Autoimmune workup
8. Ceruloplasmin & KF ring
9. Ferritin level and ferritin saturation
10. USG abdomen to rule out chronic liver disease, portal hypertension, and vascular disorder
11. Upper GI endoscopy to exclude portal hypertension
12. Ascitic fluid study (whenever applicable)

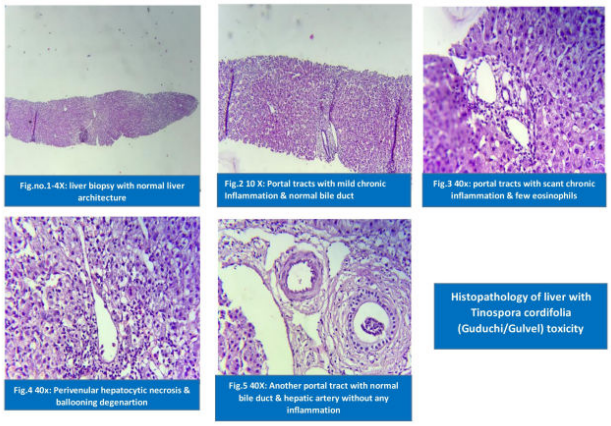

Figure 1: Tinospora Cordifolia (Gulvel/Guduchi) Induced hepatotoxicity.

Result

In our case, we have observed 16 patients between the age group 21-65yrs. who had deranged LFTs and a history of consuming Guduchi. The observations noted that females and elderly patients were affected more, and the male vs. female ratio was about 5:11. Further, 75% percent of cases (n=11) were patients more than 50 years. The elderly patients possess DM, hypertension, ischemic heart disease. However, none of our patients had a past history of liver diseases. RUCAM score was within 6-9 [4].

Moreover, the common complaints were jaundice, anorexia, nausea followed by vomiting, ascites, and pruritus. All 16 patients had the symptoms such as jaundice, anorexia, and nausea. And, six patients had Cholestatic features and ascites. The spectrum of the presentation was from mild symptoms, yellowish discoloration of eyes and urine with anorexia to more severe jaundice, ascites, and acute on chronic liver failure (ACLF). However, hepatomegaly, prodrome, or right upper quadrant pain was not seen in any patients. The average duration of Guduchi uptake was approximately three months (15days-4months) [5].

Seven patients have consumed leaves, juice, or boiled extract, five patients have consumed roots extract or crush, whereas four patients have consumed ready preparations.

Out of 16 patients, one patient had a history of repeat consummation of Guduchi, which led to a relapse of signs, symptoms, and laboratory abnormalities that subsided on intake stoppage. (Ref. table-1)

Case no.	Age	Sex	Presentation	Duration from Guduchi consummation to onset of symptoms	Past history of liver disease	Comorbidity	Clinical examination	Total duration of Guduchi consummation (approximate)	Form of Guduchi consummation	RUCAM Score
1	55	F	J,A, N,V, AS,	4 month	No	DM, HTN	J,A (mild)	6 month	Leaves	7
2	45	F	J,A, N,	2 month	No	No	J	3 month	Leaves	6
3	65	M	J,A, N,P	1 month	No	HTN	J,P	2 month	Roots	7
4	60	M	J,A, N,V, P	2 month	No	HTN, IHD, COVID Pneumonia	J,P	2 ½ month	Ready preparation	7
5	50	F	J,A, N,V	2month	No	DM	J	2 ½ month	Leaves	6
6	53	F	J,A, N,V, AS	3 ½ month	No	DM, HTN, IHD	J,A (moderate)	4 ½ month	Roots	6
7	40	F	J,A, N,V, P	1month	No	No	J,P	2month	Roots (developed same symptoms on repeat consummation)	9
8	46	F	J,A, N	1 month	No	No	J	2month	Roots	6
9	60	M	J,A, N,V, AS	2month	No	DM, HTN	J,A (moderate)	3 month	Ready preparation	7
10	62	M	J,A, N,V	2month	No	HTN	J,A (moderate)	2 ½ month	Leaves	7
11	61	F	J,A, N,AS ,P	3month	No	HTN	J,A,P (moderate)	4 month	Leaves	7
12	21	F	J,A, N	15days	No	No	J	1 month	Ready preparations	7
13	51	F	J,A, N,P	2 ½ month	No	HTN	J,P	3 month	Ready preparations	6
14	51	M	J,A, N,AS	2 ½ month	No	No	J,A	3½ month	Root	6
15	44	F	J,A, N	2 month	No	No	J	2 ½ month	Leaves	6
16	58	F	J,A, N,P	2 ½ month	No	DM, HTN	J,p	3 month	Leaves	7

J-Jaundice, A-Anorexia-Nausea, V-Vomiting, AS-Ascites, P-Pruritis **Table no.1:**Demography and clinical features.

Case no.	Hemogram			Sr. creat	Ascetic fluid study	HAV/ HBV/ HCV/ HEV	C/F	AIH panel	USG abdomen (liver)	OGD Scopy	Liver Biopsy		
	Hb (gm)	Total count (Cells/mm3)	Platelet count (mg/dl)		TC (Cells/mm3)	TP g/dl	Alb g/dl	SAAG					
1	10	4600	3.2	0.8	60	2.2	1.2	1.6	NR	N	Negative	Normal in size, shape, echotexture	Gastritis	Not done
2	9.3	5000	3	1.1	Not applicable				NR	N	Negative	Normal in size, shap	Normal	Not done

												e, echotexture		
3	8.2	5200	1.56	1.2	Not applicable				NR	N	Negative	Normal in size, shape, echotexture	Normal	Not done
4	9.3	6100	4.2	0.9	Not applicable				NR	N	Negative	Normal in size, shape, bright echotexture	Gastritis	Not done
5	7.8	3800	3.9	0.83	Not applicable				NR	N	Negative	Normal in size, shape, echotexture, dilated PV & multiple collaterals	Gastritis & esophagitis	Not done
6	10.2	6000	4.1	0.66	40	1.8	1	1.8	NR	N	Negative	Normal in size, shape, echotexture	Normal	Not done
7	11.2	5500	3.2	1.2	Not applicable				NR	N	Negative	Normal in size, shape, echotexture	Normal	Drug induced hepatitis
8	12	5200	1.89	0.89	Not applicable				NR	N	Negative	Normal in size, shape, bright echotexture	Normal	Drug induced hepatitis
9	9.1	4800	2.53	0.77	55	1.7	1.2	1.7	NR	N	Negative	Normal in size, shape, echotexture	Normal	Not done
10	7.7	3900	3.2	0.82	50	1.7	1.1	1.7	NR	N	Negative	Normal in size, shape, echotexture	Normal	Not done
11	8.6	4100	2	0.9	60	1.2	0.9	1.4	NR	N	Negative	Normal in size, shape, bright echotexture	Small Varices	Not done
12	11	5300	1.66	0.5	Not applicable				NR	N	Negative	Normal in size, shape, echotexture	Normal	Not done

13	10.5	4300	2.8	0.8	Not applicable				NR	N	Negative	Normal in size, shape, echotexture	Normal	Not done
14	9	4100	1.81	0.65	70	1.4	1	1.8	NR	N	Negative	Normal in size, altered, echotexture	Normal	Not done
15	10.2	7200	1.95	0.9	Not applicable				NR	N	Negative	Normal in size, shape, echotexture	Normal	Not done
16	8.5	6300	2.01	0.7	Not applicable				NR	N	Negative	Normal in size, shape, echotexture	Normal	Not done

NR-Non reactive, C-Ceruloplasmin ,F-ferritin

Table no.2 : Base line evaluation.

	On presentation LFT								After 15 days LFT								After one and half month LFT								
	TB (mg/dl)	DB (mg/dl)	IB (mg/dl)	AST (U/L)	ALT (U/L)	ALP (IU/L)	ALB (g/dl)	INR	TB (mg/dl)	DB (mg/dl)	IB (mg/dl)	AST (U/L)	ALT (U/L)	ALP (IU/L)	ALB (g/dl)	INR	TB (mg/dl)	DB (mg/dl)	IB (mg/dl)	AST (U/L)	ALT (U/L)	ALP (IU/L)	ALB (g/dl)	INR	Outcome
1	11.2	7.2	4.0	321	400	290	2.8	1.3	7.8	5.0	3.8	150	141	225	3.8	1.0	2.0	1.0	1.0	50	52	170	3.9	1.0	LFT normalized in 3 months
2	7.2	4.8	2.4	359	390	268	3.9	1.2	5.1	2.8	2.3	123	139	190	3.95	1.1	1.0	0.4	0.6	40	36	168	4.0	1.1	LFT normalized in 11/2 months
3	8.5	5.6	2.9	260	310	300	2.9	1.23	6.2	4.0	2.2	144	200	210	3.5	1.2	2.2	1.2	1.0	65	78	180	3.6	1.0	LFT normalized in 3 months
4	5.6	3.0	2.6	400	410	310	2.3	1.2	2.0	1.2	0.8	120	136	210	2.6	1.0	Pati								

																									ent expired due to COVID pneumonia
5	6.6	3.6	3.0	220	220	200	3.9	1.1	3.2	2.2	1.0	125	156	170	3.9	1.0	1.0	0.4		0.6	45	55	160	4.0	1.0	LFT normalized in 1½ months
6	10.2	7.8	2.4	210	300	206	2.8	1.36	7.4	5.8	1.6	160	182	166	2.8	1.23	3.8	2.0		1.8	112	142	160	3.2	1.1	LFT normalized in 3½ months
7	8.3	5.0	3.3	300	320	296	4.0	1.1	6.0	4.5	2.5	150	156	178	4.0	1.1	1.0	0.4		0.6	45	50	163	4.0	1.1	LFT norm
																									alized in 1½ months
8	6.1	4.2	1.3	220	230	190	3.9	1.0	3.2	1.9	1.3	120	132	176	4.0	1.0	1.1	0.5		0.6	45	55	160	4.1	1.0	LFT normalized in 1½ months
9	9.8	7.0	2.8	200	230	200	2.9	1.3	6.5	4.5	2.0	150	160	180	3.0	1.2	3.2	2.0		1.2	100	106	160	3.1	1.2	LFT normalized in 3 months
10	10.8	8.1	2.7	200	230	260	2.8	1.3	7.0	4.1	2.9	110	136	190	3.1	1.2	2.5	1.8		0.7	96	102	170	3.2	1.2	LFT normalized in 3 mont

11	188	66	22	190	180	170	23	15	66	50	16	189	175	177	20	19	Patient expired due to ACLF and multi-organ failure	
12	153	30	13	210	320	160	38	10	35	23	12	197	128	166	39	11	1.0	0.4	0.6	45	42	162	39	10	LFT normalized in 1½ months
13	10.1	70	30	310	340	210	32	213	65	40	5	200	182	192	32	16	3.0	1.8	12	68	78	178	35	10	LFT normalized in 3 months
14	184	60	24	300	346	189	28	156	55	35	11	210	235	180	31	13	2.4	14.1	10	75	82	170	34	11	LFT normalized in 3 months
15	75	52	23	250	278	180	34	121	43	30	31	110	162	170	34	11	1.5	0.8	07	60	65	170	38	11	LFT normalized in 2 months
16	182	50	32	222	238	230	32	15	45	30	15	152	168	200	33	13	2.3	13.1	10	60	74	180	35	12	LFT normalized in 3 months

Table no-3 : Laboratory data.

Fourteen patients were found to be anaemic, and the rest of the baseline evaluations seemed to be normal. Among those, four patients had modified echotexture of liver on USG abdomen in which the only one of these had small esophageal varices. However, the SAAG was higher in every ascetic patient.

Out of 16 patients, only two patients have given consent for liver biopsy. Further, one patient had drug-induced hepatitis, and the other patient had drug-induced hepatitis with underlying chronic liver diseases.

We observed increased concentrations of total bilirubin (mean 8.28mg/dl, range 5.3-11.2 mg/dl), direct bilirubin (mean 5.56 mg/dl, range 3-8.1mg/dl), indirect bilirubin (2.23mg/dl, range 1.3-4.0mg/dl), AST (mean 269.49U/L, range 190-400U/l) and ALT (mean 298.24U/L range 180-400U/L), ALP (228.68U/L range 160-310U/L) in all the 16 patients. Further, Hypoalbuminemia was observed in 9 patients (patients range - 2.3-3.2 gm/dl), and increased INR was observed in 10 patients with maximum 2.13.

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. The administration did not impact this disease.

Six patients had moderate ascites, and they were severely affected with highTB and hypoalbuminemia. Also, in these ascites patients, the recovery rate was significantly slower, with a duration of more than three months.

We treated them with ursodeoxycholic acid (300mg) twice a day, nutritional supplementation, and diuretic as required in ascites cases. Further, every patient was advised to stop the administration of Guduchi. In 14 patients, the LFT was normalized, and the average time required to recover was three months. The maximum time required was six months. One patient died due to liver-related multi-organ failure, and one patient died due to COVID pneumonia. In COVID pneumonia patients, the LFT was normalized before the death by stopping the intake of Guduchi.

The duration of recovery depends on the severity of the disease. For example, severe hepatotoxicity required more time to recover.

Discussion

There are several ingredients in Guduchi, which possess various properties that are widely used in Ayurveda as an immune-modulator. Further, Guduchi is easily accessible in Western Maharashtra, and it is consumed for preventing COVID 19.

We reported 16 cases of the hepatotoxic disease, followed by indiscriminate self-intake of Tinospora cordifolia (Guduchi). In these cases, the etiology were fairly established by the RUCAM score for DILI.

In addition to that, there are numerous beneficial properties; Guduchi has also been used as a hepatoprotective agent in alcohol, anti TB induced, and cyclophosphamide-induced hepatitis.11, 12, 13 Tinospora cordifolia was safe administered with 300 mg/kg orally in a study of immune-modulatory potential. 14, 15 Studies performed an experimental analysis in laboratory rats with different doses, found that it was safe when administered with 8 gm/kg16.

Wei-Te Huang et al. investigated about hepatotoxic impacts of intaking Guduchi and stated that there was only one case report of liver toxicity and acute liver failure. It may be next to Tinospora Crispa, which Tinospora cordifolia has misidentified since both plants possess similar leaves .9

Isolated cases of jaundice in families consuming T. Cordifolia can be elucidated by genetic predisposition. We could not quantify the dose aspect in our study, which required further research. The hepatoprotective or hepatotoxic effect could be dose-related. In an experimental study of paracetamol poisoning, the author found that Guduchi decreases AST, ALT, ALP, and total bilirubin at 200mg/kg but shows hepatotoxic activity at 400 mg/kg. This may be due to the toxic effect of Satwa at higher doses since T. cordifolia is growing on Neem tree.17 Also, underlying unknown liver disease predisposes hepatotoxicity. In an experimental study, one hepatic injury case was reported with Tinospora cordifolia consummation for 90days and recovered within a month after stopping of intake.18

The hepatic injury is self-limited and benign, with complete recovery of clinical and biochemical abnormalities in 14/16 patients and fatality in two patients. One case had evidence of prior CLD (Chronic liver disease) (hypoalbuminemia, altered hepatic echotexture, and small oesophagal varices) succumbed due to ACLF and the other fatality was secondary to COVID pneumonia. In COVID pneumonia patient, LFT is normalized on the stoppage of Guduchi before mortality. In addition, High SAAG ascites might be secondary to sinusoidal portal hypertension and hypoalbuminemia.

In our presented case series, 14 patients consumed a large quantity of Guduchi and had increased AST, ALT, ALP, and total bilirubin. Though two patients consumed a small amount of Guduchi, they developed hepatotoxicity.

According to our case series, aged people, females, high dose, genetic makeup, and liver disease are the predisposing factors for Guduchi induced hepatotoxicity. The disease course is benign, with good recovery on the stoppage of drug intake. However, the outcome is poor in patients with underlying CLD.

Conclusion

Tinospora cordifolia is used as an immunomodulator, to treat liver and other systemic diseases. Many people self-medicate with T.cordifolia to boost immunity in the COVID pandemic. However, the consummation of T.cordifolia in high doses and longer duration with or without the underlying liver disease can lead to hepatotoxicity. Variability in population may depend upon age, sex, doses, duration, liver status, and genetic makeup. Disease presentation is mild to moderate, and rare mortality can happen in patients with underlying liver disease. Further studies are required to understand Tinospora codifolia, induced DILI in detail.

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