Published online in http://ijam.co.in

ISSN No: 0976-5921

International Journal of Ayurvedic Medicine, Vol 15 (4), 2024; 911-916

A single-arm pilot study to analyse the hepatic safety of *Samshamani Vati* / *Guduchi Ghana Vati* (*Tinospora cordifolia* (Willd.) Miers) for the Prevention of COVID-19

Research Article

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Abstract

Background - The distribution of *Samshamani Vati / Guduchi Ghana Vati* (A preparation of *Tinospora cordifolia* (Willd.) Miers) to a large population as a prophylaxis medicine for COVID-19 was carried out by the Ministry of AYUSH. This drive was based on the promising clinical outcome in asymptomatic cases of COVID-19 infections. A small report has recently confused the public by showing an association between *Guduchi* (*Tinospora cordifolia* (Willd.) Miers) use and the development of herb-induced liver injury (HILI) with autoimmune features in some patients. There is no hepatic safety literature to clear up the confusion. Therefore, in the present pilot study, an attempt was made to create a primary database on the hepatic safety of *Samshamani Vati / Guduchi Ghana Vati* (*Tinospora cordifolia* (Willd.) Miers). Objectives- To create a primary database on the hepatic safety of *Samshamani Vati / Guduchi Ghana Vati* (*Tinospora cordifolia* (Willd.) Miers). Materials and Methods – *Samshamani Vati* was administered to subjects selected from the OPD of JSS Ayurveda Medical College, Mysuru, by pre-set inclusion and exclusion criteria, in the dose of four tablets in two divided doses after food with lukewarm water for one month for the assessment of hepatic safety clinically and bio-chemically. Study design – The study design was a single-arm, open-prospective, interventional study. Result- Fifty patients were approached for inclusion in the study. Thirty-one healthy persons fulfilled the criteria, and thirty subjects completed the study. The maximum number of studied participants were females between the age of 20 to 30 years. There is no significant change in liver function test (SGOT, SGPT, Alkaline Phosphatase), complete blood count (Hb% and PLT count) and Serum Creatinine before and after one-month of administration of *Samshamani Vati*. Conclusion- *Samshamani Vati / Guduchi Ghana Vati* (TC) has not induced any hepatic dysfunction in terms of clinical symptoms or abnormal liver function tests and is relatively safe.

Keywords: *Samshamani Vati, Guduchi Ghana Vati,* Hepatic safety, *Tinospora cordifolia* (Willd.) Miers.

Introduction

Samshamani Vati / Guduchi Ghana Vati (TC) is a classical formulation of *Siddhayoga samgraha,* indicated in different types of *Jvara* (Fever)(1). The Ministry of AYUSH launched a campaign to distribute *Samshamani Vati* to a large population as prophylaxis medicine for COVID-19 under its series of activities under the 'Azadi Ka Amrit Mahotsav''. There are two types of *Guduchi*, as per Dhanwantari Nighantu, identified as *Tinospora cordifolia* (Willd.) Miers and *Tinospora sinensis* (Lour.) Merr or *Tinospora malabarica (Lam.) Hook*. The aerial parts, mainly stem of *T. cordifolia, contains* various constituents, including phenyl propionic glycosides like cordifolioside A and B, syringin with diterpenoids, tinosporaside, neosporin, tinosporidine, tinocordifolioside, and alkaloids columbin, isocolumbin, berberine, magnoflorine have been reported(2). The important pharmacological properties are immune-modulatory, antipyretic, anti-inflammatory, hepato-protective, anti-stress, and anti-histaminic activities(3). *Samshamani Vati* is otherwise known as Guduchi Ghana Vati (Ghana Vati is a concentrated form of decoction). It is the secondary *Kalpana* (formulation) derived from the primary *Kwatha Kalpana* (decoction) and *Guduchi* has an excellent clinical outcome in asymptomatic cases of Covid-19 infections(4). Tinosporide, cordioside, cordiofolioside A, and candordiol have good immuno-stimulant and immunomodulatory properties. Guduchi has been shown to have immune-stimulating properties with the potential to increase Immunoglobulin G (IgG) in the serum in a small animal model(5-6). The reports of Ayurveda herb-induced Liver injury are not only creating a negative impact on society but also notices Ayurveda practitioners for judicious prescription(7-8). Case studies were reported on *Guduchi*-induced liver injuries (9-10). *Tinospora crispa* (L.) Miers ex Hook. f. & Thomson and *T. sinesis* are known to be hepato-toxic in animal study model(11-12). The chemical constituents responsible for liver injuries

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are *Borapetoside* and *Tinoseneside*, respectively. There is insufficient data to prove that *Guduchi* is safe for long-term administration in healthy persons as a preventive measure. Liver safety data is highly required even before a clinical trial(13). Therefore, this study was attempted to prepare preliminary data of hepatic safety analysis of healthy individuals taking *Samshamani Vati / Guduchi Ghana Vati* as preventive medicine for COVID-19.

Objectives

The objective was to analyse the hepatic safety of *Samshamani Vati / Guduchi Ghana Vati* used in a selected population as a preventive measure for COVID-19.

Materials and Methods

Study design and site

Healthy subjects are enrolled in a prospective open manner to observe the hepatic safety of *Samshamani Vati* (SV) used as prophylaxis medicine for COVID-19 for the duration of 30 days. The study was carried out at Out Patient Department of JSS Ayurveda Medical College and Hospital, Mysuru, Karnataka, India. Further, the patients were monitored clinically for another three months for any sign of hepatic dysfunction like- anorexia, jaundice, etc.

Ethical Consideration

The Institutional Ethical committee approved the clinical protocol vide its approval number JSSAMC01/22-23 dated 17/3/2022. The study was registered in the Clinical Trial Registry of India bearing registration no CTRI/2022/06/043050 dated 07/06/2022. Informed consent was obtained from each participant.

Enrolment of Patients

Healthy individuals interested in using SV as a prophylaxis medicine irrespective of the Vaccine dose were explained the possibility of derangement of Liver enzymes in those with a pre-existing Liver problem. The SV users who fulfilled the screening process and agreed through written informed consent to participate in the study were included in the trial. The study was carried out and reported adhering to the CONSORT statement.

Study duration and Visit

The total duration of the study was one month. The participants were asked to visit the OPD every 7th day for clinical examination and the 31st day. The outcomes were assessed on the completion of 30 days of treatment, and blood samples were taken.

Inclusion criteria

The subjects included in the analysis, irrespective of sex, between the ages of 20 to 60, have no disease. The subjects willing to come for regular follow-up visits were included in the study.

Exclusion criteria

The subjects having severe liver, kidney, and heart diseases were excluded from the study. Patients participating in any other clinical trial were also excluded from this study. Subjects with a history of alcohol consumption > 20 gm/week and drug abuse, known allergy, sensitivity, or intolerance to the study drug and its formulations were excluded from the study and any condition that, in the opinion of the investigator, does not justify the patient's inclusion in the study were excluded.

Subject withdrawal Criteria

Enrolled subjects can be withdrawn from the trial if they develop any adverse effect or non-compliance with the treatment regimen (a minimum of 80% Compliance is essential to continue the study). Subjects may themself withdraw from the study for any other reason. If subjects develop any other health ailments mentioned in the exclusion criteria during the trial. Suppose, if the Principal Investigator decides to withdraw a participant from the trial; in that case, it will be justified in terms of the actual reason, and further management will be suggested, if needed.

Laboratory Investigations

Liver function tests, Hb%, Total Platelet count, and Serum Creatinine were the Laboratory investigations carried out before using the SV and after the completion of 30 days of consumption of SV.

Assessment criteria

The hepatic safety assessment of the participants were subjected to physical examination, review of vital signs, clinical judgment, and laboratory investigations(14). Incidence of Hepatic toxicity can be given as the number of events per number of subjects exposed, or can incorporate during treatment exposure. Liver safety can be analysed by comparing the observation of the Hepatic enzyme panel before and after completion of treatment. Thrombocytopenia is a finding of chronic liver disease and a side effect of some herbal remedies, food supplements, and beverages(15). Therefore, total platelet counts and haemoglobin were used as safety assessment tools.

Sample size

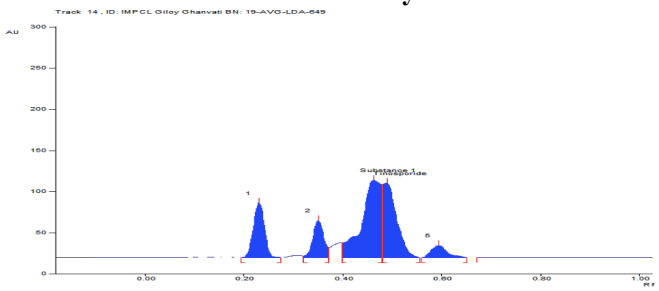
The sample size of the present study was decided by using the thumb rule for overall samples in the pilot study. It was agreed to be thirty to forty using the upper confidence limit(16). Therefore, it was decided to analyse the data for thirty patients.

Details of Intervention

Samshamani Vati was procured from Government supplied samples of IMPCL of the batch no 19 AUG/ LDA-649. The HPTLC fingerprinting of studied *Samshamani Vati* was carried out to maintain a standardised herbal medication intervention. (Figure no-1). Two tablets of *Samshamani Vati* (each tablet 250mg) were administrated twice after food with

lukewarm water for one month. Thus, each patient received 1000mg of SV in two divided doses(17).

Figure 1: HPTLC Chromatogram of Samshamani Vati manufactured by IMPCL



Outcomes

The primary outcome intended was to create a data base of Hepatic safety and address the evidence of *Samshamani Vati / Guduchi Ghana Vati* (TC) induced Liver injury, if occurred.

Secondary outcome was to detect the patient condition, morbid factors, gravity of Liver injury and dose of SV induced injury.

Statistical methods

The data found as quantitative measures were expressed as mean ± SD or SE or the mean with range. Qualitative variables were presented as counts and percentages. The variables are compared using a t-test. All P values were reported based on significant tests, and all statistical tests were interpreted at least up to 5%level of significance on 95% confidence levels.

Results

Demographic details

A total of fifty apparently healthy volunteers were interviewed to use SV as prophylaxis medicine for COVID-19 irrespective of prior vaccination with/ without a booster dose. Ten participants did not meet the inclusion criteria, and nine participants refused to participate in this study. Thirty-one were selected in a random fashion by following the pre-set inclusion and exclusion criteria. Thirty subjects completed the study, and one patient dropped out in this trial as the particular participant did not report for post-treatment screening (Flow chart no-1). The dropout participant was also absolutely healthy after completing of preventive dose of SV. Maximum subjects 20 (67%) were female and 10 (33%) were male (Table no-1). Maximum number of participants were between the age of 20-30 years, and Ayurveda medicos were predominant in this study.

Flow chart 1: Consort flow diagram of hepatic safety study of SV

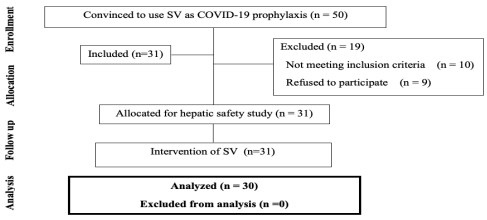


Table 1: Age and sex distribution of the studied thirty participants

Age in years	Male	Female	Total
20-30	10	16	26
31-40	0	2	2
41-50	1	1	2
51-60	0	0	0
TOTAL	11	19	30

Outcomes estimation

The individual laboratory data of participants before and after treatment are within the normal range (Tables no-2& 3). There is no significant change in mean values of the liver function test and complete blood count before administration of *Samshamani Vati* and after completion of therapy; values at 95% CI are insignificant (Table no-4). The participants did not report any adverse drug reactions or events during the treatment or observed period. The study shows the hepatic safety of *Samshamani Vati / Guduchi Ghana Vati* in the studied population. Our study found that Samshamani Vati/ Guduchi Ghana Vati is entirely safe in studied participants after thirty days of medication, and no sign of hepatomegaly and symptoms of anorexia, jaundice, itching, or other liver-related symptoms were observed in three months of observed periods.

Harms

No side effects and adverse drug reactions were noted in participants taking SV. No sign of hepatomegaly and symptoms of anorexia, jaundice, itching, or other liver-related symptoms were observed in three months of observation period.

Table 2: Various Hepatic safety Laboratory parameters before exposure to *Samshamani Vati*

S.N	Before treatment					
	Hb	PLT	SGOT	SGPT	ALP	S.CREA
	M=14-18 F=12-14	1.5-4.5	0-40	0-40	37-147	0.8-1.4
	gms/dL	lakh/µL	U/L	U/L	U/L	mg/dL
1	11	2.7	12	20	216	0.7
2	11.1	4.85	15	9	192	0.7
3	18.3	1.94	32	26	264	1
4	13.3	2.85	15	9	159	0.8
5	12.7	2.96	13	16	73	0.8
6	13	3.03	10	12	183	0.9
7	13.7	3	26	18	143	1
8	10	3.75	21	14	144	0.8
9	13.1	2.74	31	21	248	0.7
10	11.4	3.73	30	34	111	0.7
11	13.2	3.6	29	16	217	0.7
12	12.3	3.06	19	26	179	0.8
13	15.1	2.92	38	42	129	0.9
14	16	2.86	16	20	173	1
15	16.8	2.49	19	23	166	1.1
16	16.9	2.63	37	42	150	0.8
	12.3	3.64	21	27	166	0.9

17	11.9	3.29	14	21	147	0.7
18	17.4	2.77	21	32	216	1.1
19	12.6	3.69	12	18	165	0.7
20	11.4	3.19	19	25	149	0.6
21	16	3.53	22	29	137	1
22	11.8	3.31	16	22	90	0.7
23	15.6	1.9	28	32	184	1
24	12.4	4.06	27	34	168	0.6
25	12.2	2.16	38	42	153	0.6
26	16.1	2.94	12	18	162	1
27	13	3	38	42	185	0.7
28	15.8	3.33	50	58	195	0.9
29	13.1	3.82	34	38	164	0.6
30	13.5	4.13	21	30	206	0.7

Table 3: Various Hepatic safety Laboratory Parameters after the completion of Medication

S.N	AFTER 30 DAYS					
	Hb	PLT	SGOT	SGPT	ALP	S.CREAT
	M=14-18 F=12-14	1.5-4.5	0-40	0-40	37-147	0.8-1.4
	gms/dL	lakh/µL	IU	IU	IU	mg/dL
1	11.1	3.14	15	22	214	0.8
2	10.9	5.18	18	15	205	0.8
3	19.9	1.59	14	16	285	0.8
4	13.9	3.19	35	47	162	0.7
5	12.5	2.7	15	18	82	0.8
6	13	3.08	12	15	183	0.9
7	13.4	2.81	24	21	134	0.8
8	9.5	3.5	25	18	123	0.9
9	13.1	2.82	30	20	230	0.8
10	11.4	3.33	32	35	129	0.8
11	13.5	3.6	28	18	179	0.8
12	11.8	3.54	20	28	248	0.9
13	14.9	2.95	35	40	130	0.8
14	16.8	3.16	31	12	216	0.9
15	15	2.92	20	25	170	1.1
16	16.2	2.54	38	45	221	0.9
	DROPPED OUT					
17	12.4	3.21	15	22	150	0.8
18	17.1	2.56	31	12	216	0.9
19	12.5	3.34	26	35	158	0.7
20	11.2	3.55	20	30	152	0.7
21	15.6	3.38	25	38	140	1
22	11.5	3.34	15	23	95	0.8
23	14.8	1.89	16	19	171	0.8
24	12	3.67	24	16	142	0.6
25	12.1	2.33	29	36	180	0.7
26	15.8	3.14	15	20	178	1
27	12.8	2.7	31	40	186	0.6
28	15.4	3.26	56	48	217	1
29	13.2	4.09	36	31	179	0.8
30	13.3	4.07	18	31	226	0.7

Table 4: Statistical Analysis of Hepatic safety Parameters Before and After administration of *Samsamani Vati*

Parameter	Mean	Std. Deviation	Mean difference	95% CI for Mean diff		p
				Lower	Upper	
Pre_Hb	13.873	2.2011	0.136	-0.0751	0.3485	0.197
Post_Hb	13.737	2.2614				
Pre_PLT	3.1833	0.69045	0.011	-0.08859	0.11192	0.814
Post_PLT	3.1717	0.69086				
Pre_SGOT	24.13	10.122	-1.000	-3.808	1.808	0.472
Post_SGOT	25.13	9.612				
Pre_SGPT	26.53	11.599	-0.267	-4.193	3.659	0.890
Post_SGPT	26.80	10.949				
Pre_ALP	172.400	43.9871	-5.2333	-15.6402	5.1735	0.312
Post_ALP	177.63	45.410				
Pre_S.CREAT	0.810	0.1561	-0.0133	-0.0569	0.0302	0.536

Discussion

Limitation of this study

The major limitation is that, SV is exposed to healthy persons without the habit of consumption of alcohol, deranged liver enzymes, and other systemic diseases. Another limitation is the difficulty in interpreting or generalising the results because the studied population differs from those treated in everyday life.

Generalisability

Guduchi (TC) is identified as *Tinospora cordifolia* (Willd.) Miers, which is well-known to Ayurveda practitioners. Various properties are described in texts of Ayurveda, like *Rasayana, Sangrahi, Balya, Agnideepana, Tridoshshamaka, Dahnashaka, Mehnashaka, Kasa-swasahara, Pandunashaka, Kamla-Kushta-Vataraktanashaka, Jwarhara, Krimihara, Prameha, Arshnashaka, Kricch-Hridroganashak*, etc(18-20). But its *Virya* (potency) is *ushna*, so it should be judiciously used in *pitta prakruti* person in general. *Tinospora cordifolia* (Willd.) Miers was previously used as hepatoprotective. Liver dysfunction has not been observed in the apparent healthy participants after the administration of SV for one month.

Interpretation of Result

There is no significant change in mean values of liver function test and complete blood count before administration of *Samshamani Vati* and after completion of therapy. Previous reports of liver injuries after ingestion of Guduchi (TC) in different forms of formulations may be associated with self-medication and may be due to pre-existing liver diseases or adulteration of *Tinospora crispa* (L.) Miers ex Hook. f. & Thomson. Self-medication in Ayurveda is a challenging issue to address the Drug-induced Liver

toxicity(21) because general people assume Ayurveda drugs are safe to use. The toxicity of any herbal compound is dependent on dose, frequency, duration, type of formulation (whole plant versus parts), the final concentration of bioactive compounds, presence of other herbal components and herb–herb interactions that ultimately dysregulate immune homeostasis and promote liver injury in predisposed persons. Some herbal drugs have triggered Autoimmune Hepatitis(22-23). Guduchi is an important cause of autoantibody-mediated acute hepatocellular jaundice without other competing causes(24). Multicentric reports concluded that Guduchi (TC) is associated with acute hepatitis with autoimmune features and can unmask autoimmune hepatitis (AIH) in people with silent AIH-related CLD, and it was untested; this herb cannot be promoted by AYUSH in the interests of the public health and are especially important during this global health emergency(25). *Tinospora cordifolia* (Willd.) Miers is also used as hepatoprotective in Alcohol-induced liver toxicity(26). Therefore, it may be assumed that reported hepato-toxicity of *Tinospora cordifolia* (Willd.) Miers may have occurred by self-medication, the manner of intake, improper dose with a history of Chronic liver disease or autoimmune diseases but not in healthy individuals or when prescribed by registered Ayurveda practitioners. The entire study is not deviated from the protocol as registered in CTRI.

Further, it can draw the attention that, liver dysfunction has not been observed among thirty studied cases in three months of the observed period. So, *Guduchi* as an important cause of autoantibody-mediated acute hepatocellular jaundice in the absence of other competing reasons in previous studies, is found not correct. *Tinospora cordifolia* (Willd.) Miers as *Samshamani Vati* is found completely safe in studied participants after thirty days of medication. So, its safety is primarily tested by this study, and AYUSH Ministry can promote this herb in the interest of public health under medical supervision, which is an important issue during this global health emergency.

Conclusion

Samshamani Vati / Guduchi Ghana Vati (*Tinospora cordifolia* (Willd.) Miers) has not induced any hepatic dysfunction in clinical symptoms or abnormal liver function tests and is relatively safe. It can be prescribed to healthy individuals and those who have no pre-existing liver dysfunction. A larger population-based study is recommended.

Abbreviations

Samshamani Vati (SV), *Guduchi Ghana Vati* (GGV), *Tinospora cordifolia* (Willd.) Miers (TC), Liver Function tests (LFT)

Other information

Study Registration

The study was registered in the Clinical Trial Registry of India bearing registration no CTRI/ 2022/06/043050 dated 07/06/2022.

Availability of trial Protocol

The study protocol can be accessed from the Clinical Trial Registry of India. The authors can also provide the study protocol on request.

Source of Funding: Nil

Conflict of Interest: Nil

Acknowledgment

The authors acknowledge the participants, the Director, of JSS Ayurveda Medical College, Mysuru, and the Director General, of CCRAS, New Delhi, for their encouragement and comprehensive cooperation in conducting the study.

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