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Evaluation of Efficacy & Tolerability of Trisoliv® Syrup (Andrographolides + Tricholine Citrate + Sorbitol) in the Management of Various Liver Dysfunctions.

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ABSTRACT

Polyherbal drug formulations having hepatoprotective activity is the widely recognized and utilized therapy in the management of various liver dysfunctions. To evaluate efficacy and tolerability of Trisoliv® Syrup in the management of various liver dysfunctions. Open, non-comparative, multi-centre, post marketing study. 50 patients suffering from various liver dysfunction like were enrolled in this study, 46 patients completed the study. Patients were given hepatoprotective syrup containing Andrographolides + Sorbitol + Tricholine citrate (A + S + T) 10 ml 2 to 3 times in a day for 8 weeks. The subjective clinical improvement in (jaundice symptoms, fatigue, and loss of appetite) was assessed on a predefined 0 to 3 score scale. Total bilirubins (TB), SGOT/ AST, SGPT/ALT, serum alkaline phosphatase were assessed at baseline and end of 8 weeks. Secondary outcomes were patient's assessment about efficacy and tolerability of the hepatoprotective product Trisoliv. After 8 weeks of Trisoliv Syrup therapy 86.96% (40/46) of patients achieved the normal values for TB. As like TB, there was significant improvement in SGOT values after treatment with Trisoliv Syrup. 100 % of patients achieved normal values for SGPT/ALT and alkaline phosphatase (AP) values after 8 week of Trisoliv Syrup therapy. All the patients reported significant improvement in Jaundice, fatigue and loss of appetite on predefined 0 to 3 score scale. On the predefined scale of global efficacy 86.96% patients reported good to excellent efficacy rating for Trisoliv Syrup. Similarly, 82.61% patients reported good to excellent ratings for tolerability. The result of the study showed that A + S + T (Trisoliv syrup) is clinically effective and safe in the management of various liver dysfunctions.

KEYWORDS: *Hepatitis, liver, bilirubin, SGOT, SGPT, Andrographis paniculata, sorbitol*

INTRODUCTION

Liver disease or disorder (LD) is a global public health phenomenon that has continued to rise due to cases of excessive consumption of alcohol, inhaling of harmful gases, intake of contaminated food and drugs. While effect includes clinical symptoms like chills, fatigue, loss of appetite, dark urine, yellow sclera and conjunctiva, fever or right upper quadrant abdominal pain, Jaundice is not a disease but rather a sign that can occur in many different diseases[1].

Alcoholic liver disease is a major cause of morbidity and mortality worldwide. Mortality from alcoholic cirrhosis is higher than non alcoholic and survival is 5-10 years in 7-23% with 25% of patients dying within 1 year. Alcohol can cause liver damage in the form of fatty liver, hepatitis, fibrosis, and liver cirrhosis[2].

Infective hepatitis occurs endemically and sporadically throughout the world, depending on the endemicity of infection. Hepatitis A infection is common infection worldwide and human is thought to be its principal host. In developed countries, the incidence of Hepatitis A Virus (HAV) infection is low while in developing regions of the world, inadequate sanitation results in continuous transmission of HAV, especially to children and young individuals[3, 4, 5].

Hepatitis B Virus (HBV) is the second most common cause of acute viral hepatitis. Hepatitis B

is a potentially life-threatening liver infection caused by the HBV. It is a major global health problem and the most serious type of viral hepatitis. Approximately 5% of the world's population is chronically infected with HBV. Approximately 20% of these individuals will eventually develop HBV-related cirrhosis or hepatocellular carcinoma (HCC). According to the World Health Organization, these HBV-related complications lead to 0.5 to 1.2 million deaths each year, making HBV the 10th leading cause of death worldwide. In sub-Saharan Africa, the Pacific, and particularly Asia, HBV infection is highly endemic, with the majority of individuals becoming infected during childhood [6].

Drugs and chemicals can cause a wide spectrum of liver injury in several ways. Some drugs are directly injurious to the liver; others are transformed by the liver into chemicals that can be injurious to the liver directly or indirectly. It is common to find liver disorders in patients exposed to medications such as antitubercular drugs, paracetamol and statins[2].

Polyherbal drug formulations having hepatoprotective activity is the widely recognized and utilized therapy in the management of various liver dysfunctions.

Need of Study

No rational therapy is available for the cure of liver dysfunctions. At present ample studies on animals evaluating hepatoprotective effect of herbal drugs are available.

Andrographolide is one of the herbal drugs obtained from *Andrographis paniculata* (common name: Kalmegh) with proven efficacy in various liver dysfunctions.

In the present study we intend to evaluate the efficacy and tolerability of a herbal formulation Trisoliv Syrup containing andrographolides as one of the major ingredient besides Tricholine citrate and Sorbitol.

Objective

The present study was aimed to evaluate the efficacy and tolerability of Trisoliv® Syrup (Andrographolides + Tricholine citrate + Sorbitol) in the management of various liver dysfunctions.

Study design

This study was an open, non comparative, post marketing study conducted at 5 centers in India.

MATERIALS AND METHODS

Selection of subjects

Patients' suffering from liver dysfunctions like jaundice and hepatitis of varied etiology confirmed with biochemical examinations (liver function tests) mentioned as below:

- Serum Total Bilirubin: > 1.0 mg/dl
- SGOT/AST: > 45 IU/L
- SGPT/ALT: > 50 IU/L
- Serum Alkaline Phosphatase: > 125 IU/L

Inclusion criteria

A total of 50 patients suffering from various liver diseases & presenting with jaundice willing to give informed consent were included in the study.

Exclusion criteria

Pregnant and lactating women, known severe renal insufficiency, cardiac disease and patients with history of gastritis, peptic ulcer, bleeding ulcer were excluded from the study.

Follow up and monitoring

Patients were advised to follow up after every 14 days for monitoring of clinical symptoms and biochemical investigation.

There were 5 visits for each patient. The visit schedule was as follows.

Visit 1: Day 1 = Admission to the study.

Visit 2: After 2nd Week = First Follow up visit on 14th day.

Visit 3: After 4th Week = Second Follow up visit on 28th day.

Visit 4: After 6th Week = Third Follow up visit on 42nd day.

Visit 5: After 8th Week = Fourth Follow up visit on 56th day.

At the initial visit, informed written consent was obtained from all the enrolled patients, after explaining to them the nature of the study. A detailed medical history was obtained from all enrolled patients, which was followed by thorough clinical examination. All patients were subjected to liver function tests.

Trial drug and dosage administration

Trisoliv Syrup: Combination of Tricholine Citrate + Andrographolides + Sorbitol (Medley Pharmaceutical Ltd. Mumbai)

The patients were advised to take 2 teaspoonfuls (10 ml) of Trisoliv Syrup, orally, twice a day before meals, for 8 weeks.

Patients were not allowed to take any other medication, which would have any significant effect on LFT.

Concomitant medication

Patient will continue all the regular medication he has been prescribed for his associated disease except those mentioned in the exclusion criteria. Investigator may modify the drug therapy, if any modification of therapy is needed for chronic ailments.

Primary and secondary endpoints

Biochemical investigation

In each follow up visits patients were monitored for biochemical investigation of LFT by taking blood samples.

For biochemical tests we have fixed the standard normal values for each parameter as follows:

- Serum Total Bilirubin: 0.12 to 1.0 mg/dl
- SGOT/AST: 10 to 45 IU/L
- SGPT/ALT: 10 to 50 IU/L
- Serum Alkaline Phosphatase: 40 to 125 IU/L

The patients were monitored for the clinical symptoms of liver dysfunctions like chills, headache, malaise, anorexia, nausea, vomiting, diarrhea, upper abdominal pain, tender liver, enlarged spleen, dark urine, and yellow tint to sclera.

The subjective clinical improvement in (jaundice symptoms, fatigue, and loss of appetite) was assessed on a predefined 0 to 3 score scale (0=none, 1=mild, 2=moderate, 3=severe). Dark yellow urine and yellowish appearance of skin and conjunctiva were considered as jaundice symptoms. Improvement in all clinical symptoms were monitored and recorded by physician.

Global assessment of efficacy and tolerability by patients

The patients who successfully completed 8 weeks of treatments were asked to fill up the global assessment scale for efficacy and tolerability. Efficacy and tolerability were assessed on a predefined five points scale of scores 0 to 4 (0=none, 1=poor, 2=average, 3=good, 4=excellent).

Adverse events

Each subject was carefully monitored for adverse events. All adverse events either reported by patients or observed by physicians were recorded with information about severity, duration and action taken regarding the study drug. Severities of adverse events were recorded on a scale of scores 1 to 3 (1=mild, 2=moderate, 3=severe). Outcome of action taken on adverse events were recorded on a scale of scores 1 to 4 (1= Unchanged, 2=improved, 3=resolved, 4=worsened).

Subject dropout

Patients who have not completed the 8 week study were considered as drop out cases. The reason for the drop out was recorded in CRF.

Statistical analysis

Statistical analysis was done by "One-way Analysis of Variance (ANOVA)" followed by 'Dunnett's Multiple Comparison Test'. The minimum level of significance was fixed at 95% confidence limit and P<0.05 was considered as significant. All the bio-statistical data was performed by using Graph Pad Prism 5 version 5.03.

RESULTS

Out of 50 patients enrolled in this study, 46 patients completed the study. Others were considered as drop outs. Reason for drop out was lost to follow up. Out of 46 patients 30 were male 16 were females. Average age was 43.82 years.

Biochemical findings

Total Bilirubin

In biochemical investigation of Total Bilirubin we have found that with the use of Trisoliv Syrup there was significant improvement in the TB values. After 8 weeks of Trisoliv Syrup therapy 86.96% (40/46) of patients have achieved the normal values for TB, while in 13.04% (6/46) patients achieved the near normal value. Further continuation of Trisoliv Syrup therapy was recommended in those patients.

Mean TB at baseline was 6.34 ± 2.24 which reduced significantly to 0.72 ± 0.29 (p<0.001) at the end of therapy.

Table I: Effect of Trisoliv Syrup on Serum Total Bilirubin (mg/dl)

	Mean	SD	Mean Diff.	P < 0.05	Summary	95% CI of diff
Baseline	6.35	2.24	-	-	-	-
2nd week	4.09	1.36	2.26	Yes	***	1.62 to 2.90
4th week	2.41	0.82	3.94	Yes	***	3.29 to 4.58
6th week	1.51	0.44	4.84	Yes	***	4.20 to 5.49
8th week	0.72	0.29	5.63	Yes	***	4.99 to 6.27

*** = Highly Significant (p<0.0001)

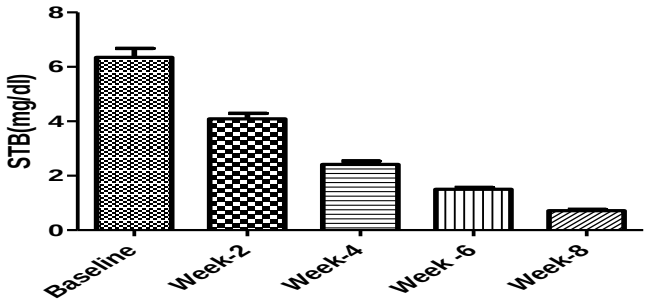

Figure 1 Effect of Trisoliv Syrup on Serum Total Bilirubin (mg/dl)

SGOT/AST

As like TB, there was significant improvement in SGOT values after treatment with Trisoliv Syrup. Only 2 patients (4.35%) did not achieve the normal values of SGOT after 8 week of treatment. Trisoliv significantly reduced SGOT to 28.67 ± 8.04 from a baseline of 122.5 ± 19.07 P<0.001

Table II: Effect of Trisoliv Syrup on SGOT/AST (IU/L)

	Mean	SD	Mean Diff.	P < 0.05	Summary	95% CI of diff
Baseline	122.5	19.07	-	-	-	-
2nd week	108.9	16.34	13.54	Yes	***	10.09 - 16.99
4th week	90.17	15.31	32.3	Yes	***	28.85 - 35.75
6th week	58.72	12.86	63.76	Yes	***	60.31 - 67.21
8th week	28.67	8.04	93.8	Yes	***	90.35 - 97.25

*** = Highly Significant (p<0.0001)

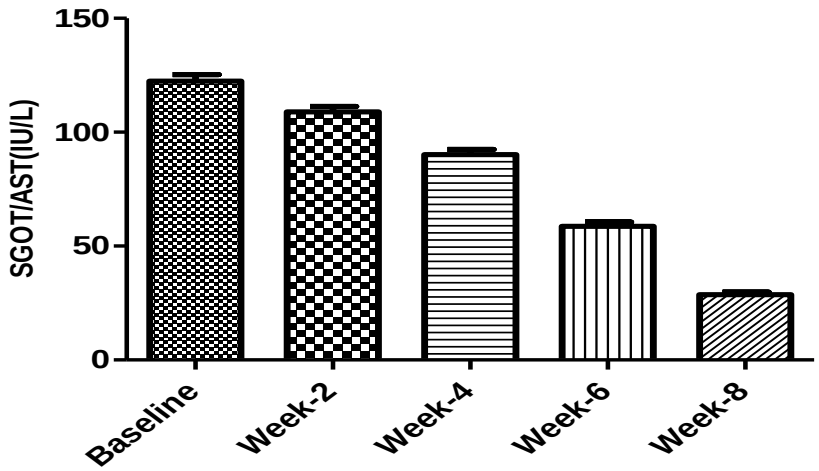

Figure 2 Effect of Trisoliv Syrup on SGOT/AST (IU/L)

SGPT/ALT

All 46 patients achieved normal values for SGPT after 8 week of Trisoliv Syrup therapy. There was a significant decrease in SGPT values in each follow up visit.

Table III: Effect of Trisoliv Syrup on SGPT/ALT (IU/L)

	Mean	SD	Mean Dif	P< 0.05	Summary	95% CI of diff
Baseline	151.4	37.13				
2nd week	124.2	29.99	27.17	Yes	***	20.91 - 33.44
4th week	89	25.48	62.39	Yes	***	56.13 - 68.66
6th week	54.46	18.29	96.93	Yes	***	90.67 - 103.2
8th week	27.43	8.65	124	Yes	***	117.7 - 130.2

*** = Highly Significant (p<0.0001)

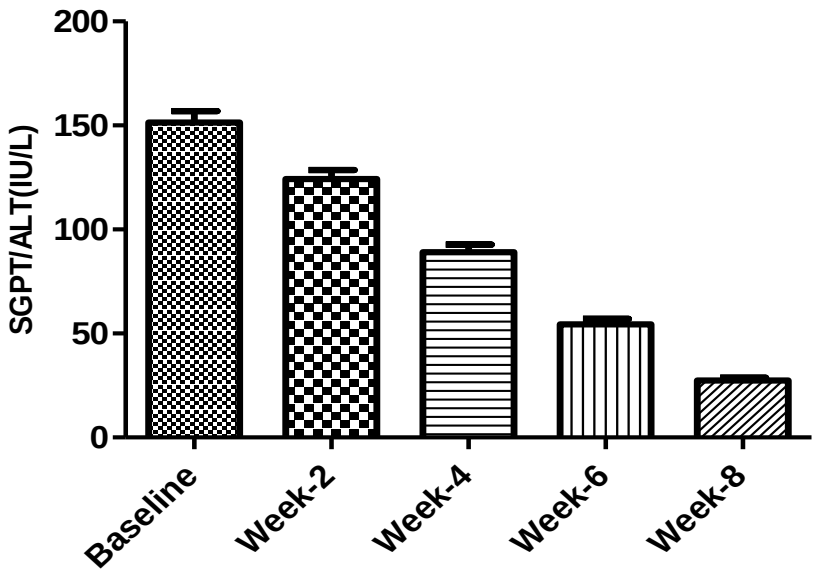

Figure 3 Effect of Trisoliv Syrup on SGPT/ALT (IU/L)

Serum Alkaline Phosphatase

There was significant improvement in the AP values after 8 weeks of treatment with Trisoliv Syrup and all 46 (100%) patients achieved the normal AP values.

Table IV: Effect of Trisoliv Syrup on Serum Alkaline Phosphatase (IU/L)

	Mean	SD	Mean Dif	P< 0.05	Summary	95% CI of diff
Baseline	214.5	33.3				
2nd week	176	25.75	38.5	Yes	***	26.47 - 50.53
4th week	147	19.91	67.52	Yes	***	55.49 - 79.55
6th week	117.9	18.1	96.61	Yes	***	84.58 - 108.6
8th week	89.09	15.42	125.4	Yes	***	113.4 - 137.4

*** = Highly Significant (p<0.0001)

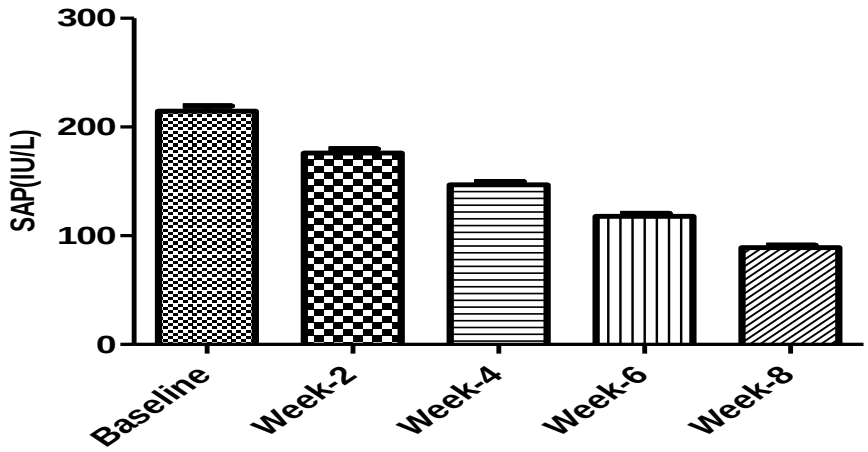

Figure 4 Effect of Trisoliv Syrup on Serum Alkaline Phosphatase (IU/L)

Clinical Monitoring

Jaundice symptoms score

All the patients (100%) who were enrolled in the study showed jaundice symptoms at the time of admission. After completion of 8 weeks of therapy with Trisoliv Syrup there was significant improvement in the jaundice scores from 2.70 to 0.22 as showed in the table V.

Table V: Effect of Trisoliv Syrup on Jaundice Symptoms score

	Mean	SD	Mean Diff.	P< 0.05	Summar	95% CI of diff
Baseline	2.70	0.47				
2nd week	1.28	0.46	1.41	Yes	***	1.19 - 1.64
4th week	1.13	0.34	1.57	Yes	***	1.34 - 1.79
6th week	0.33	0.47	2.37	Yes	***	2.15 - 2.59
8th week	0.22	0.42	2.48	Yes	***	2.26 - 2.70

*** = Highly Significant (p<0.0001)

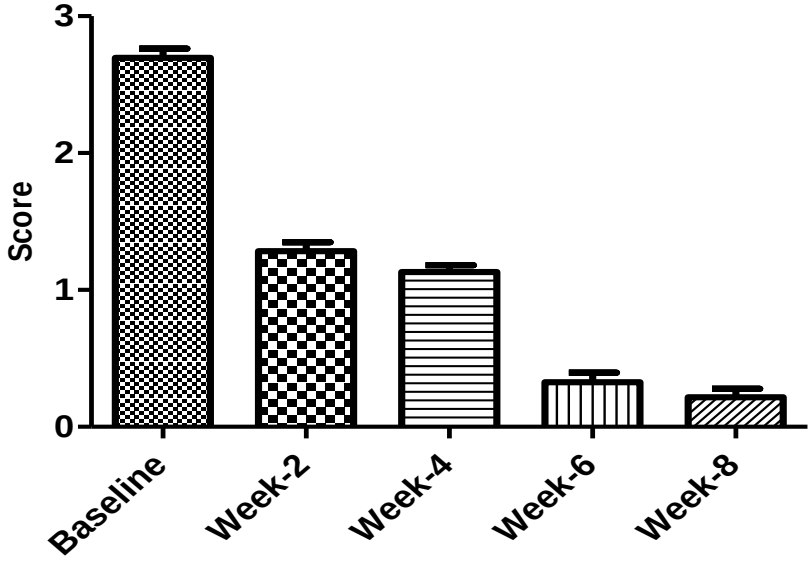

Figure 5 Effect of Trisoliv Syrup on Jaundice Symptoms Score

Fatigue Score

All the 46 (100%) patients showed fatigue at the beginning of the study. Mean score for fatigue on the time of admission was 2.35. After completion of 8 weeks of therapy all the patients (100%) were resolved completely from fatigue.

Table VI: Effect of Trisoliv Syrup on Fatigue score

	Mean	SD	Mean Dif	P < 0.05	Summary	95% CI of diff
Baseline	2.35	0.67				
2nd week	1.46	0.62	0.89	Yes	***	0.63 - 1.15
4th week	0.48	0.55	1.87	Yes	***	1.61 - 2.13
6th week	0.15	0.36	2.20	Yes	***	1.94 - 2.46
8th week	0	0	2.35	Yes	***	2.09 - 2.61

*** = Highly Significant (p<0.0001)

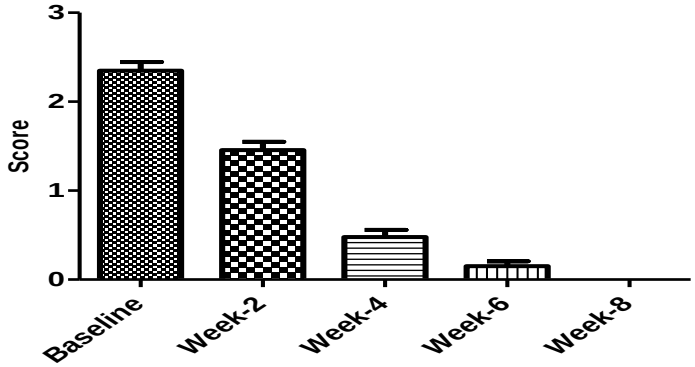

Figure 6 Effect of Trisoliv Syrup on Fatigue Score

Loss of Appetite score

All the 46 (100%) patients showed loss of appetite at the admission to the study. Mean score observed at the beginning was 2.74 indicating moderate to severe loss of appetite which resolved completely after 6 weeks of therapy with Trisoliv Syrup.

Table VII: Effect of Trisoliv Syrup on Loss of Appetite score

	Mean	SD	Mean Dif	P < 0.05	Significant Summary	95% CI of diff
Baseline	2.72	0.46				
2nd week	1.26	0.44	1.46	Yes	***	1.28 - 1.63
4th week	0.24	0.43	2.48	Yes	***	2.30 - 2.66
6th week	0	0	2.72	Yes	***	2.54 - 2.89
8th week	0	0	2.72	Yes	***	2.54 - 2.89

*** = Highly Significant (p<0.0001)

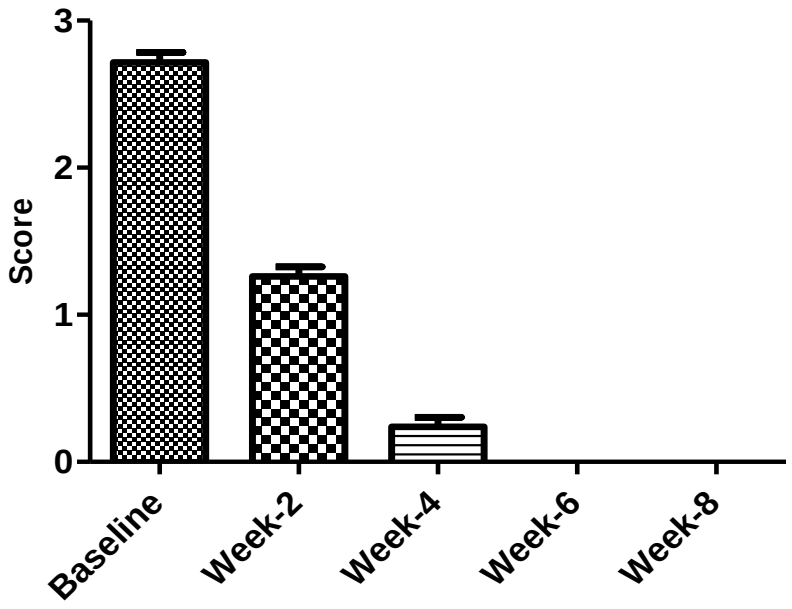

Figure 7 Effect of Trisoliv Syrup on Loss of Appetite Score

Global assessment of efficacy and tolerability

On the predefined scale of global efficacy 86.96% patients had given good to excellent efficacy rating for Trisoliv Syrup in the management of liver dysfunctions. Similarly, 82.61% patients had assessed good to excellent rating for tolerability. Only mild diarrhoea was reported by 2.17% (1/46) patients. No other adverse events were reported in the study and formulation was well tolerated.

Discussion

Liver dysfunctions are public global health problem responsible for millions of deaths per year. In the present study we evaluated the efficacy and safety of Trisoliv Syrup on various subjective (symptom score) and objective (LFT)

parameters. Trisoliv Syrup which has Tricholine citrate, andrographolide, and sorbitol helps not only in improving the LFT but also it improves the appetite and relieves symptoms associated with jaundice. These beneficial clinical effects of Trisoliv syrup in liver diseases might be due to the synergistic action of its ingredients, which had been well documented in various experimental and clinical studies by various researchers. The leaf extract of plant *Andrographis paniculata* i.e.Andrographolide has shown hepatoprotective effect on various models of drug and ethanol induced liver damage.[7, 8, 9, 10, 11]Andrographolide aids in digestion by exerting its choleretic action i.e. activity to stimulate the bile production by liver[12]. Andrographolide was found to be more potent than silymarin; a standard hepatoprotective agent in animal study to protect hepatocye against paracetamol induced damage [13]. The antioxidant effect of andrographolide could be due to its ability to activate antioxidant enzymes that catalyze the reaction of oxidants and are effective in severe liver damage[14]. Andrographolides are safe, non toxic and strong natural anti-oxidant in comparison with other phyto-antioxidant[15].Tricholine citrate offers lipotropic action because of its activity to remove excess fat from the liver and prevents excessive fat deposition in the liver[16]. The functions of choline which include methyl group metabolism, lipid transport, membrane phospholipids structure formation. Pathological consequence of choline deficiency includes fatty liver, liver cell death, liver cell proliferation, and liver cell cancer. Fatty liver due to choline deficiency appears to occur via interference with hepatic Very Low Density Lipoprotein (VLDL) production and output[17]. Sorbitol acts as a syrup base and also as a osmotic laxative to relieve constipation.

In this 8 week study Trisoliv Syrup significantly improved the LFT. Serum total bilirubin TB (used initially) gradually and significantly reduced from a baseline of 6.35 ± 2.24 to 0.72 ± 0.29 mg/dl ($p<0.0001$) over a period of 8 weeks. 86.95% patients achieved normal serum TB level at the end of study and 12.95% patients were required to continue Trisoliv Syrup till it comes within normal limits. Similarly SGOT reduced from a baseline of 122.5 ± 19.07 to 28.67 ± 8.04 IU/L ($p<0.0001$) gradually over a period of 8 weeks.

SGPT also showed a statistically significant reduction to 27.43 ± 8.65 from a baseline of 151.4 ± 37.13 IU/L ($p<0.0001$) at the end of trial. Similar finding was reported by Chaturvedi et al where andrographolide efficacy was evaluated in 20 patients suffering from infective hepatitis .80 % of patient reported to be cured and 20 % relieved after treatment with andrographolides [18].

As subjective improvement of the clinical symptoms is equally important, we evaluated the major clinical symptoms like loss of appetite, fatigue, and jaundice symptoms on a predefined scale of 0 to 3 score. At the end of 8 weeks study all the clinical symptoms score significantly reduced from baseline. 86.96% of patients reported good to excellent efficacy and 82.61% of patients reported good to excellent tolerability on global assessment scale.Thus the study proves that Trisoliv Syrup is significantly efficacious and safe in patients suffering from various liver dysfunctions.

Abbreviations

LFT	Liver Function Test
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
SAP	Serum Alkaline Phosphtase
SD	Standard Deviation

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