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A Randomized Clinical End Point Study to Evaluate the Safety and Efficacy of Polyherbal Tablets in Patients with Alcoholic Liver Disease

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ABSTRACT

Objective: To evaluate and compare the hepatoprotective effect of herbal tablets with silymarin in patients with alcoholic liver disease. **Material and methods:** This was a prospective, randomized, multicenter, open-label, parallel group, interventional clinical end point study (Phase IIa). Patients attending General Medicine outpatient department were screened for alcoholic liver disease by using the serum biochemical liver function test, ultrasonogram (USG) abdomen. Investigators tested whether they satisfied the selection criteria and 24 patients were then enrolled in the study. The study drug was administered to Group A and tablet silymarin was administered to Group B from Day 1 to Day 56. Patients were reviewed once in 2 weeks. Liver function test was repeated, and patients were enquired of their well-being and any adverse events. **Results:** The demographic characters and body weight of the subjects showed no significant difference between the groups. There was a significant improvement ($p < 0.05$) in the aspartate transaminase (AST), alanine transaminase (ALT) and total bilirubin (TB) levels on 28th day and 56th day in both silymarin and herbal tablet groups. Out of the two groups, there was higher significance of improvement in herbal tablet group ($p < 0.001$), compared to silymarin group. The herbal tablet group started showing a significant reduction in AST and ALT levels in the first 14 days of study period. On comparing the mean percentage reduction in the levels of AST (35.7% vs. 35%), ALT (26.7% vs. 24.3%) and TB (26.7% vs. 25%), it was found that the herbal tablets showed a better percentage of reduction of the above parameters compared to silymarin. There were reports of adverse effects like loss of appetite and gastritis in both the groups. **Conclusion:** This clinical study proves that the herbal tablets used functioned as a hepatoprotective drug. They offered better hepatoprotection compared to silymarin. These tablets can be indicated for the management of liver dysfunction, which occurs due to alcoholic liver damage. It may also be used in similar manner in cases of viral hepatitis, drug-induced liver damage, as well as acute and chronic hepatitis.

Keywords: Alcoholic liver disease, hepatoprotective, herbal medicine, silymarin

In the year 2010, the global burden of alcoholic liver diseases was large and resulted in 4,93,000 deaths and 14,544,000 disability-adjusted life years. This burden represented 0.9% of all deaths and 0.6% of all disability-adjusted life years in 2010.[1] Alcoholic liver disease encompasses a clinical-histologic spectrum including fatty liver, alcoholic hepatitis and cirrhosis with its complications.[2] The World Health Organization (WHO) estimates that alcohol is now the third highest risk factor for premature mortality, disability and loss of health worldwide.[3] There is a growing incidence of hepatocellular carcinoma (HCC) worldwide. The annual global incidence of HCC is over 5,00,000 cases. The highest incidence of HCC is observed in Asia and Africa, associated with the high prevalence of hepatitis in these regions.[4] The hallmark of therapy in alcoholic liver diseases has been abstinence from alcohol and nutritional therapy. Role of steroids has been accepted in the treatment; however, the effectiveness of therapy should be assessed after 1 week of treatment. Pentoxifylline has been equally effective, especially in patients with renal dysfunction or hepatorenal syndrome. The use of biologics has been disappointing in the treatment of alcoholic liver diseases.[5]

India is the largest producer of medicinal plants. Medicinal plants have a very important role in the

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health of human beings as well as animals. According to the WHO estimates, about three-quarters of the world's population currently use herbs and other traditional medicines to cure various diseases, including liver disorders.[6]

The herbal medicine used in this study is a research product Polyherbal Formulation* developed by Apex Laboratories Limited for hepatoprotection. It is composed of: *Ricinus communis* - 42.85 mg, *Phyllanthus niruri* - 25 mg, *Eclipta alba* - 15 mg, *Boerhavia diffusa* - 12.5 mg, *Tinospora cordifolia* - 10 mg, *Tribulus terrestris* - 14.28 mg, *Tephrosia purpurea* - 11.11 mg, *Indigofera tinctoria* - 9.37 mg, *Andrographis paniculata* - 6.25 mg, *Rubia cordifolia* - 5 mg, *Terminalia chebula* - 12.5 mg, *Curcuma longa* - 3.5 mg and *Aconitum heterophyllum* - 10 mg. The formulation has been validated scientifically and traditional claims have been supported by scientific data. Standardization of all the extracts has been established without losing the essence of the Ayurvedic tradition. In an animal study conducted by Kumar et al, it was shown that this herbal medicine, in doses of 800 and 1,000 mg/kg, has a significant hepatoprotective action against various hepatotoxicant-induced liver necrosis and injury.[7] These tablets are formulated in such a way that it offers three clear benefits in liver care, i.e., conserves the liver, controls the liver damage and corrects the liver function. This tablet is indicated for the management of liver dysfunction which may occur due to alcoholic liver damage, viral hepatitis, drug-induced liver damage and acute and chronic hepatitis. This tablet can also be prescribed during pregnancy for intrahepatic cholestasis (ICP) and associated constipation.

Herbal medicines have been used in the treatment of liver diseases for a long time; however, standardization of herbal medicines has been a problem. Hence, the rationale behind this study is that we have standardized an herbal medicine for liver disease and if it is efficacious without any side effects, then it can be useful for the population suffering from liver disease at a cheaper cost, compared to the current treatments available. Prospective, randomized, controlled clinical trials are also lacking to support their efficacy.[8] Hence, with an aim to evaluate the efficacy and safety of these herbal tablets in patients with liver dysfunction like alcoholic liver disease in comparison with standard drug like silymarin, the present study was conducted.

MATERIAL AND METHODS

This was a prospective, randomized, multicenter, open-label, parallel group interventional clinical end point study (Phase IIa). The study was conducted at two centers in India - Mahatma Gandhi College and Hospital, Pondicherry and PM Medical Centre, Walajapet, Tamil Nadu, according to Good Clinical Practice. The study was initiated after obtaining proper ethical committee approvals. The study was registered in Clinical Trial Registry of India (No: CTRI/2018/03/012644) and Drug Control General of India (DCGI) (AYUSH) was notified (Notification No: 2730). Informed written consent was obtained from the patients attending General Medicine outpatient department. They underwent general and systemic examination followed by laboratory tests for hematology, blood biochemistry, blood microbiology, urine analysis, electrocardiogram and chest X-ray for initial evaluation and were screened for alcoholic liver disease by using serum biochemical liver function test, and ultrasonogram (USG) abdomen. Investigators tested whether they satisfied the selection criteria and 24 patients were then enrolled in the study. The following patients were recruited in the study:

- Patients of either sex, 18-70 years of age, with chronic alcohol intake.
- Patients in whom serum aspartate transaminase (AST) and alanine transaminase (ALT) were typically elevated to a level of 2-6 times the upper limit of normal, patients who tested negative for human immunodeficiency virus (HIV), hepatitis B and C.
- Female patients who tested negative for pregnancy (up to 2 weeks prior to the study), were included.

Patients who were excluded from the study included:

- Those who had liver disease with a cause different from that of alcohol-induced liver disease.
- Patients who were suffering with hepatic failure, hepatic cirrhosis, Wilson's disease, malignant tumor, serious metabolic disease, severe renal disease, severe pulmonary disease, severe cardiovascular disease, severe nervous disease/psychiatric disorder and muscular disorders.
- Pregnant or lactating women.
- Patients with comorbidities, reduced life expectancy, patients known to be dependent on drugs and patients with any known hypersensitivity or allergy to any component of the drugs involved in the study.
- Patients who were on medications that may affect treatment such as colchicine, penicillamine, corticosteroids, ursodeoxycholic acid, pentoxifylline, long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), statins, neuroleptics, anticonvulsant medications, high-dose acetaminophen (>2.5 g/day).

- Patients who may have participated in recent past (past 3 months) in a clinical trial.

Eligible subjects were randomly selected via computer-generated randomization using simple randomization and were divided into Groups A and B. The study drug, polyherbal tablet (2 tablets twice-daily postprandial), was administered to Group A and silymarin tablet (70 mg twice-daily postprandial) was administered to Group B from Day 1 to Day 56 at the specified time of the day. The drugs were provided to the patients at each visit (once in 2 weeks) along with a patient diary to monitor the compliance. The patients were reviewed on Days 14, 28, 42 and 56. Liver function test was repeated, patients were enquired of their well-being, adverse events and compliance. Patients were strictly advised not to consume alcohol throughout the study period. Counseling for alcohol abstinence was given at each visit. Further course of the treatment for the test subjects was based upon the discretion of the investigator. The reports were compiled. Continuous data was reported using the descriptive statistics using mean and standard deviation. For analyzing continuous data, Student's *t*-test followed by Mann-Whitney 'U' test and two-way analysis of variance (ANOVA) was applied. P value <0.05 was considered as statistically significant. All the statistical analysis was performed using SPSS 23.0 software.

RESULTS

All the 24 patients selected for completed the study. There were no dropouts. Complete disposition of the study participants is given in Table 1.

The efficacy of both control and test drugs was found to be similar and there was no statistically significant difference observed between the two. The efficacy was observed as an improvement in AST, ALT and TB levels from the baseline as a result of the treatment with the two drugs. Table 2 enumerates the comparison of mean percentage improvement between the control and the test group (Figs. 1 and 2).

Gastritis and loss of appetite were the two adverse events observed during the study period. None of the patients experienced nausea, vomiting, diarrhea, cardiovascular side effects or neurological side effects. Among 12 subjects in the treatment group, 4 subjects reported loss of appetite and 5 subjects reported symptoms of gastritis, which resolved on their own. Among the 12 subjects in the control group, 6 reported decrease in appetite and 8 subjects reported symptoms of gastritis, which resolved on their own. No other

Table 1. Baseline Demographic Parameters

Parameter*	Silymarin group (Control group) (n = 12)	Herbal tablet group (Test group) (n = 12)
Gender (%) male	100	100
Age	39.08 ± 7.76	36.3 ± 4.3
Body weight	76.8 ± 7.87	78.03 ± 7.04
AST level (IU)	141 ± 19.04	142.58 ± 22.73
ALT level (IU)	68.2 ± 11.09	69 ± 12.22
Total bilirubin (mg/dL)	1.8 ± 0.48	1.87 ± 0.30

*Two-way ANOVA followed by Bonferroni post-test. P value was not significant for baseline parameters.

Table 2. Comparison of Percentage Reduction in AST, ALT and Total Bilirubin Levels at Various Follow-up Visits

Parameter*	Mean (%) Improvement		P value	Significance
	Control group	Test group		
AST				
Day 14	28	34	P > 0.05	NS
Day 28	39	38	P > 0.05	NS
Day 56	38	35	P > 0.05	NS
ALT				
Day 14	28	30	P > 0.05	NS
Day 28	18	20	P > 0.05	NS
Day 56	27	30	P > 0.05	NS
TB				
Day 14	45	45	P > 0.05	NS
Day 28	10	9	P > 0.05	NS
Day 56	20	26	P > 0.05	NS

*Two-tailed student *t*-test followed by Mann-Whitney 'U' test was performed. P value < 0.05 is considered statistically significant.

NS = Not significant.

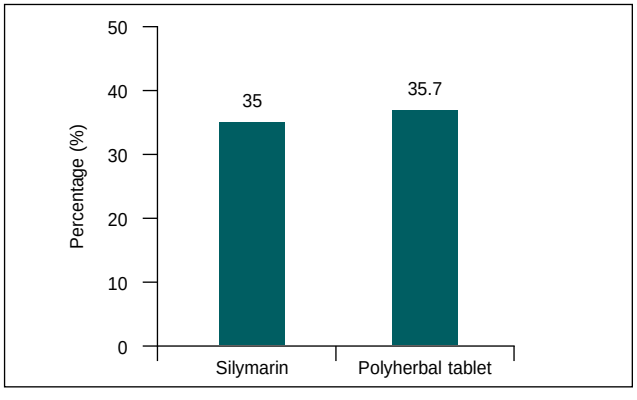

Figure 1. Comparison of mean percentage reduction in AST levels (n = 12 subjects per group).

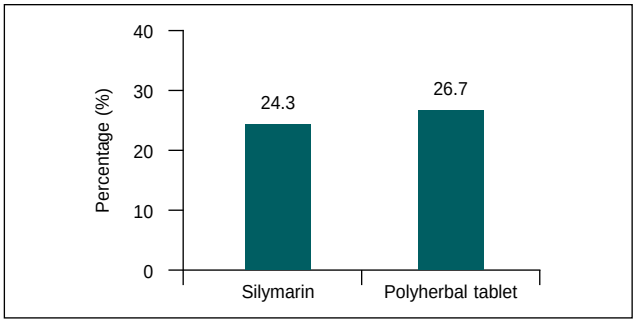

Figure 2. Comparison of mean percentage reduction in ALT levels (n = 12 subjects per group).

Table 3. Adverse Events during the Study Period

Type of adverse events	Number of subjects in control group (n = 12)	Number of subjects in test group (n = 12)
Gastritis	8	5
Nausea	0	0
Vomiting	0	0
Diarrhea	0	0
Loss of appetite	6	4
Cardiovascular side effects	0	0
Neurological side effects	0	0

serious adverse events were reported during the study period. Table 3 enumerates the adverse events recorded during the study period.

DISCUSSION

There was no significant difference between the demographic characteristics of the two groups. None of the patients showed any discomfort in the usage of the herbal tablet. As is observed from the measurement of primary outcome, there is an extremely significant improvement in the AST, ALT and TB levels on 28th day and 56th day of the treatment, both in the silymarin and herbal tablet groups. However, it is noticeable that the patients in the herbal tablet group started showing a significant reduction in AST and ALT levels in the first 14 days of the study period, which was not seen in the silymarin (control) group. A comparison of the percentage reduction in the levels of AST, ALT and TB (Table 2) showed that both silymarin and herbal tablet were equally effective, but herbal tablet demonstrated a better overall reduction in percentage values of these parameters. There was a remarkable overall improvement in the well-being of the study subjects, both in the test and the control group. But the improvement was better in the test group.

Thus, the polyherbal tablet showed a hepatoprotective action. The main component of this formulation, *R. communis* or castor plant, has shown hepatoprotective activity in previous studies done by Pingale et al[9] and Visen et al,[10] where the extract of *R. communis* leaves was used against hepatosuppression induced by carbon tetrachloride and galactosamine-induced hepatic damage, respectively. The hepatoprotective activity may be due to the important phytochemical constituents like flavonoids, saponins, glycosides, alkaloids and steroids in this herb. It was also found out that there were two active intermediate products from the herb namely, ricinine and N-demethyl-ricinine, which showed hepatoprotective activity.

The other major component, namely *P. niruri*, which originated in India, usually occurring as a winter weed throughout the hotter parts, has been shown to have hepatoprotective properties because of the presence of active phytochemicals, flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins and saponins. Extracts of this herb have been proven to have therapeutic effects in many clinical studies.[11,12] The hepatoprotective effects of other components namely *E. alba*, *A. paniculata*, *T. cordifolia*, *T. purpurea*, etc., have been proved in previous studies, by doing biochemical and histopathological assay of liver specimens.[13-15]

All the herbs included in this polyherbal formulation* have antioxidant property. The hepatoprotective activity of this polyherbal formulation* is evident from the normalization of AST, ALT and bilirubin levels. Hence, it can be postulated, that the hepatoprotective effect of these polyherbal tablets is due to the inhibitory effect of the active phytochemicals of each herb upon the free radical formation.

CONCLUSION

The results of the clinical study have shown that this polyherbal formulation* is an effective hepatoprotective drug offering comparatively better hepatoprotection as compared to silymarin. A significant reduction in the AST, ALT and TB levels was observed from 14th day onwards in the polyherbal formulation* treated group. Both the polyherbal formulation* and silymarin treatment groups showed a better reduction in the above parameters from baseline at 28th and 56th days of the treatment.

Hence, it can be concluded that these polyherbal tablets can be indicated for the management of liver dysfunction, which occurs due to alcoholic liver damage. It may also be used effectively in case of viral

hepatitis, drug-induced liver damage, as well as acute and chronic hepatitis. We can clearly say that this polyherbal formulation* is not only an effective but also a safe drug to be used in patients with alcoholic liver disease, which may be evaluated further by doing large-scale clinical studies on liver dysfunction caused due to factors other than alcoholic liver disease.

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"If you have zest and enthusiasm you attract zest and enthusiasm.
Life does give back in kind."

—*Norman Vincent Peale*

"One resolution I have made, and try always to keep, is this:
To rise above the little things."

—*John Burroughs*