

The efficacy of Liv-52 on liver cirrhotic patients: A randomized, double-blind, placebo-controlled first approach

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Abstract

Cirrhosis is the irreversible sequel of various disorders that damage liver cells permanently over time. Presently, the use of herbal medicines for prevention and control of chronic liver diseases is in the focus of attention for both the physicians and the patients; the reasons for such shift toward the use of herbals include the expensive cost of conventional drugs, adverse drug reactions, and their inefficacy. In the present study, the efficacy of herbal medicine Liv-52 (consisting of *Mandur basma*, *Tamarix gallica* and herbal extracts of *Capparis spinosa*, *Cichorium intybus*, *Solanum nigrum*, *Terminalia arjuna* and *Achillea millefolium*) on liver cirrhosis outcomes was compared with the placebo for 6 months in 36 cirrhotic patients referred to Tehran Hepatic Center. The outcome measures included child-pugh score, ascites, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, prothrombin time, platelet and white blood cells counts. The indices were recorded in all patients before and after 6 months of drug or placebo treatment. The results demonstrated that the patients treated with Liv-52 for 6 months had significantly better child-pugh score, decreased ascites, decreased serum ALT and AST. In placebo administered patients all the clinical parameters recorded at beginning of the study were not significantly different than after 6 months. We conclude that Liv-52 possess hepatoprotective effect in cirrhotic patients. This protective effect of Liv-52 can be attributed to the diuretic, anti-inflammatory, anti-oxidative, and immunomodulating properties of the component herbs.

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Introduction

Cirrhosis is the common outcome or complication of viral hepatitis, alcohol abuse, drug toxicity, hereditary

metabolic diseases (e.g. alpha-1-anti-trypsin deficiency, Wilson disease), that has no effective treatment yet (Chung and Podolsky, 2001). The current treatment is directed at the management of the complications of cirrhosis and prevention of further liver damage. Several medicinal plants have been used worldwide in various traditional herbal recipes for the prevention and

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treatment of liver disease (Patrick, 1999). Many patients with liver disease use these herbal preparations without the advice or even knowledge of their caring physician. The effectiveness of some of these herbal medicines has been recently investigated. Silymarin, a natural product isolated from the seed extract of *Silybum marianum* has been investigated clinically and found useful in the treatment of liver disease (Ferenci et al., 1989; Saller et al., 2001).

Liv-52 is a herbal medicine commonly used in Indian traditional herbal recipes. Liv-52 formulation consists of *Capparis spinosa*, *Cichorium intybus*, *Solanum nigrum*, *Terminalia arjuna*, *Achillea millefolium*, *Tamarix gallica* and Mandur basma. It is a hepatotonic and has been used traditionally in the treatment of various liver disorders (Mehrotra, 1973; Kalab and Krechler, 1997; De Silva et al., 2003). Experimental studies have reported that Liv-52 offers significant protection against carbon tetrachloride, alcohol, and beryllium-induced hepatic damage (Kataria and Singh, 1997; Sandhir and Gill, 1999; Mathur, 1994). Liv-52 markedly improves liver function by acting as a stimulant. Previous clinical studies also indicate that Liv-52 has liver protective effect against alcohol-induced hepatic damage and hepatitis B virus infection without any side effects (Kalab and Krechler, 1997; Galitskii et al., 1997). The present study was undertaken to investigate the efficacy of 6-months Liv-52 and placebo administration in chronic liver cirrhotic patients.

Materials and methods

For conducting this interventional (randomized double-blind clinical trial) study, 36 cirrhotic patients of both sexes (32 males and 4 females) were selected using systematic random sampling method (Pocock, 1999) out of 554 patients, who were registered in Tehran Hepatic Center registry. As inclusion and exclusion criteria, all the patients who were older than 20 years, had no present or previous addiction to alcohol and did not have active variceal bleeding were included in the study. The patients were admitted by investigators and informed about the rationale and main aims of the study. A written informed consent was obtained from each patient in presence of member of the ethics committee. The patients were then randomly allocated in two groups of 18 patients (16 males and 2 females) each using blocked randomization method. The average ages of patients for treatment group was 52.7 yrs (min. 29 yrs, max. 76 yrs) and for placebo group, 46.39 yrs (min. 21 yrs and max. 69 yrs). The protocol of this study was approved by the ethics committee of the Tehran Hepatic Center.

Liv-52 tablets were purchased from Himalayan Co. India and the placebo tablets with same shape and color were formulated at the Institute of Medicinal Plants in Tehran. Each Liv-52 tablet contains extracts of *Capparis spinosa* 65 mg, *Cichorium intybus* 65 mg, *Solanum nigrum* 32 mg, *Cassia occidentalis* 16 mg, *T. arjuna* 32 mg, *A. millefolium* 16 mg, *Tamarix gallica* 16 mg. It also contains 'Mandur bhasma' (33 mg/tablet) which is prepared from ferric oxide. One group of patients received Liv-52 and the placebo group received three placebo tablets thrice daily. The conventional supportive treatment such as diuretics, vitamins and lactulose continued in two groups. The compliance of patients with treatment was observed indirectly using pill count method.

The diagnosis of cirrhosis was confirmed by the liver biopsy, biochemical, pathological and clinical findings as well as abdominal examination.

The patients visited every 3 months and the clinical parameters such as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, prothrombin time, platelet and white blood cells were determined using standard reagent kits purchased from Boehringer Mannheim, Germany. The blood samples were drawn after an overnight fast and were analyzed immediately. The data at the beginning of the study and after 6 months was selected for the statistical analysis.

All the patients underwent clinical examination (according to a prepared check list) for the child-pugh score and ascites. The child-pugh score comprises of five parameters including degree of ascites, encephalopathy, serum levels of albumin and bilirubin and blood prothrombin time. Each of the parameters were given 1–3 score according to their severity. The combination of above five parameter scores were graded and named as score 5–6 = A, score 7–9 = B and score >9 = C. Ascites was graded as without, mild, moderate and severe according to the degree of accumulation of serous fluid in the peritoneal cavity.

The patients and the staff who carried out assessment of clinical and practical parameters were unaware of treatment groups and type of medication.

Statistical analysis

The statistical analysis of the recorded data at the starting and after 6 months was performed using paired student *t* test of SPSS statistical software for quantitative variables. The nonparametric analysis was used for child-pugh score and ascites; and parametric analysis was used for all other tests. The average data in each group recorded at the end of the study were compared to the data recorded at the beginning of the study. A value of $p < 0.05$ was considered as statistically significant.

Results

All the 36 patients completed the study and there were no dropouts.

Ascites

The results of clinical findings of ascites in both of the groups at the beginning and after 6 month of the study are summarized in Table 1.

The results indicate that in placebo group at the beginning of the study out of 18 patients 8 (44.4%) had no ascites whereas 6 (33.3%) mild, 3 (16.7%) moderate and 1 (5.6%) had severe ascites. After 6 months of placebo administration out of 18 patients, 5 (27.8%) had no ascites, 5 (27.8%) had mild, 4 (22.2%) moderate and 4 (22.2%) had severe ascites. The statistical analysis indicated that the severity of ascites at 6 month of placebo administration was not significantly different as compared to beginning of the study.

In Liv-52 group at the beginning of the study, out of 18 patients, 4 (22.2%) had no ascites, 6 (33.3%) mild, 5 (27.8%) moderate, and 3 (16.7%) had severe ascites. In this group at the end of the study out of 18 patients 6 (33.3%) without, 10 (55.6%) mild, 2 (11.1%) moderate and none of the patients had severe ascites. The statistical analysis indicated that the severity of ascites in Liv-52 treated patients was significantly lower ($p < 0.032$) as compared to beginning of the study.

Child-pugh score

The results of clinical findings of child-pugh score in both the groups at the beginning and after 6 month of the study are summarized in Table 2.

In the placebo group at the beginning of the study out of 18 patients 8 (44.4%) had score *A*, 8 (44.4%) score *B* and 2 (11.1%) had score *C*. This range changed to 5 (27.8%) score *A*, 7 (38.9%) score *B* and 6 (33.3%) score *C* after 6 months of placebo administration. The difference was not significant. In Liv-52 group at the beginning of the study out of 18 patients 4 (22.2%) had score *A*, 6 (33.3%) score *B* and 8 (44.4%) score *C*. These values changed to 6 (33.3%) score *A*, 7 (38.9%) score *B* and 5 (27.8%) score *C* after 6 month of Liv-52 administration. The severity of child-pugh score in Liv-52 treated patients at 6 month was significantly ($p < 0.001$) better as compared to beginning of the study.

Serum analysis

The average serum values before and after 6 months of Liv-52 and placebo administration in two groups are summarized in Table 3.

The average serum levels of ALT and AST after 6 months of Liv-52 treatment were found to be significantly ($p < 0.044$ and $p < 0.029$, respectively) lower as compared to beginning of the study. In placebo administered group, the average serum level of AST and ALT after 6 months did not show any significant changes when compared to the beginning of the study.

The average serum levels of total bilirubin, albumin, platelets and white blood cells and serum prothrombin time, in both the groups were not significantly different after 6 months as compared to the beginning of the study.

Table 1. Degree of ascites at beginning and after 6 months of the study in placebo and Liv-52 treated group

Group	Without ascites		Mild ascites		Moderate ascites		Severe ascites		Total	
	0 month	6 month	0 month	6 month	0 month	6 month	0 month	6 month		
Placebo	8 (44.4%)	5 (27.8%)	6 (33.3%)	5 (27.8%)	3 (16.7%)	4 (22.2%)	1 (5.6%)	4 (22.2%)	4 (22.2%)	18
Liv-52	4 (22.2%)	6 (33.3%)	6 (33.3%)	10 (55.6%)	5 (27.8%)	2 (11.1%)	3 (16.7%)	0	0	18

Table 2. Degree of child-pugh score at beginning and after 6 months of the study in placebo and Liv-52 treated group

Group	Child-pugh score at 0 and 6 months						Total
	<i>A</i> ''		<i>B</i> ''		<i>C</i> ''		
	0 month	6 month	0 month	6 month	0 month	6 month	
Placebo	8 (44.4%)	5 (27.8%)	8 (44.4%)	7 (38.9%)	1 (5.6%)	6 (33.3%)	18
Liv52	4 (22.2%)	6 (33.3%)	6 (33.3%)	7 (38.9%)	5 (27.8%)	0	18

Table 3. Average serologic parameters in cirrhotic patients at the beginning of the study and after 6 months of Liv-52 and placebo treatment

Serologic parameters (n = 18)	Placebo Mean \pm SD		Liv-52 Mean \pm SD		p-Value
	Beginning	After 6 months	Beginning	After 6 months	
ALT (U/L)	76.33 \pm 13.65	51.11 \pm 10.20	89.0 \pm 24.56	38.5* \pm 3.79	<0.044*
AST (U/L)	92.78 \pm 13.36	72.00 \pm 12.59	89.2 \pm 14.24	57.2* \pm 5.60	<0.029*
Bilirubin (mg/dl)	2.38 \pm 0.37	3.43 \pm 0.72	2.20 \pm 0.36	4.27 \pm 2.08	
Albumin(g/dl)	3.52 \pm 0.14	3.47 \pm 0.11	3.22 \pm 0.17	3.66 \pm 0.22	
Protrombin time (s)	15.3 \pm 0.53	16.4 \pm 0.76	16.0 \pm 0.61	16.1 \pm 0.86	
Platelet (mm ³)	133,617 \pm 24,055	132,722 \pm 23,043	126,611 \pm 24,726	119,889 \pm 17,047	
White blood cell (mm ³)	5802.2 \pm 530.5	5508.8 \pm 875.3	5505.5 \pm 975.3	6050.0 \pm 1260.0	

* $p < 0.05$. The average serum level ALT and AST were significantly lower in Liv-52 treated patients after the 6 month as compared to the beginning of the study.

Discussion and conclusion

Cirrhosis is a chronic disease due to liver cell damage and proliferation of fibrous tissue. The damage eventually becomes extensive and normal structure of the liver is distorted and its function becomes impaired. This abnormality affects almost every physiologic process including digestion, endocrine, circulatory and other metabolic functions. These changes themselves slowly aggravate liver damage. The aim of the medication in cirrhotic patients is to prevent metabolic abnormalities and the progression of the liver cell damage.

The traditional healers approach to management of the chronic liver disease is to regulate and strengthen the liver, gastrointestinal and immune system (Seeff et al., 2001). The regulation of gastrointestinal system may improve the general well being of the patients as well as improvement of the constipation may prevent the absorption of harmful substances and indirectly decrease ascites (Langmead and Rampton, 2001). The protection of liver cells against toxic materials including drugs, lipid peroxidation and free radical injury may decrease inflammation, improve liver blood flow and ultimately help in reduction of ascites and blood pressure (Yang et al., 2000). Immune dysfunction is component of liver disease and thus immunomodulation by herbal therapy prevent oxidative stress, inflammation and strengthens the detoxifying power of liver cell (Jiang et al., 1997). All these effects strengthen liver and regulate body metabolism and ultimately inhibit further liver cell damage in the favor of their regeneration (Bean, 2002).

In present study, the efficacy of herbal medicine Liv-52 medication on liver cirrhosis was investigated. In cirrhotic patients treated with Liv-52 for 6 months, the serum ALT and AST levels were significantly decreased. This decrease in serum ALT and AST levels in Liv-52 treated patients in part may be due to the protective effect of this drug on liver cells following restoration of liver cell membrane permeability (Kalab and Krechler, 1997). This protective effect indicates reduction in

enzymes present in the extra cellular milieu as elevated serum level of ALT and AST is attributed as damage to the structural integrity of liver (Chenoweth and Hake, 1962). Liver cell protective effect of Liv-52 has also been observed in several experimental studies (Kataria and Singh, 1997; Sandhir and Gill, 1999; Mathur, 1994).

Furthermore, in present study, in Liv-52 treated cirrhotic patients, the child-pugh score and ascites were found to be significantly decreased. The observed effects of Liv-52 on serum ALT and AST levels, child-pugh score and ascites demonstrates the favorable effect of this drug on liver function. Although the exact mechanism of the Liv-52 on liver function as well as body metabolism is not yet clearly known, it can be stated that since Liv-52 contains *Tamarix gallica*, *Mandur basma* and crude herbal extracts of *Capparis spinosa*, *Cichorium intybus*, *Solanum nigrum*, *T. arjuna*, and *A. millefolium*, these medicinal herbs alone or in combination can influence the cellular functions and body metabolism. The diuretic effect of *T. arjuna* and anti-inflammatory and anti-immunotoxicity effect of *Cichorium intybus* have been shown in clinical and experimental studies (Bharani et al., 1995; Tubaro et al., 1988; Kim et al., 2002). The anti-oxidative and anti-hepatotoxic property of esculetin and *p*-methoxybenzoic acid the main constituent of *Cichorium intybus* and *Capparis spinosa*, respectively, have been reported in chemically induced hepatotoxicity in experimental animals (Gilani et al., 1998a, b; Germano et al., 2002). *Achillea millefolium*, another component of Liv-52 contains several bioactive constituents including flavonoids and terpenoids with anti-oxidative and anti-inflammatory properties (Glasl et al., 2002; Candan et al., 2003; Goldberg et al., 1969). The curative and hepatoprotective effect of *Mandur basma* and *Cassia occidentalis*, the other two components of Liv-52 were observed against chemically induced liver damage in experimental animals (Kanase et al., 1997; Jafri et al., 1999). Furthermore anti-oxidative property of flavonoid content of *Tamarix gallica* and inhibitory effect *Solanum nigrum*

crude extracts on free radical-mediated DNA damage increase the hepatoprotective effect of Liv-52 (McPhail et al., 2003; Sultana et al., 1995). In addition, the anti-oxidative, anti-lipoperoxidative and increase in glutathione content of the liver cells was observed with arjunolic acid and flavonoids present in *T. arjuna* (Sumitra et al., 2001; Munasinghe et al., 2001).

In support to above studies on live-52 component, the anti-oxidative, anti-inflammatory and increase in cellular glutathione level effect of Silymarin induces protective effect on liver disease in several experimental and clinical studies (Vogel et al., 1975; Ferenci et al., 1989; Saller et al., 2001).

We conclude that Liv-52 possess hepatoprotective effect in cirrhotic patients and this effect may be due to its diuretic, anti-inflammatory, anti-oxidative, immunomodulating as well as restorative effects. All these activities directly or indirectly influence the cellular and body metabolism and play favorable and protective role in maintaining liver integrity and restoring its function. Liv-52 is thus beneficial in the treatment of cirrhotic patients.

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