Role of Liv.52 in Non-Infectious Chronic Liver Disease

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Abstract

Background: Chronic liver diseases (CLDs) are a group of illnesses characterized by hepatic insufficiency associated with abnormal liver function tests (LFTs). Although plethora traditional pharmacological drugs are available, they have many limitations either in their efficiency or adverse effects.

Aims: To investigate the effectiveness and safety of herbal Liv.52 supplement in the treatment of chronic liver disease.

Patients and Methods: An interventional randomized blind clinical trial was conducted on a total of 200 patients with chronic liver disease. Patients were randomly divided into two equal groups. Group A, 100 patients who received Liv.52 supplement alongside their usual therapy regime. Group B, 100 patients with no Liv.52 supplement and restricted for their usual therapy regime. Patients were followed up for 6 months for clinical assessment, with laboratory investigations to assess routine blood chemistry and liver function tests were done after 1, 2 and 6 months of therapy.

Results: After 6 months of treatment, the mean alanine transaminase (ALT) in treated group was 56.54 ± 24.32 U/L which was significantly lower than that of controls (70.39 ± 27.74 U/L). On the other hand, the mean serum albumin after six months' treatment was 3.54 ± 0.52 g/dL in treated group compared with 2.96 ± 0.36 g/dL in controls with highly significant difference. After two month's treatment, the mean total leukocyte (WBC) count in treated group was $7.37\pm1.49 \times 10$ /ml which was significantly lower than that of controls ($8.11\pm1.38 \times10^3$/ml). In contrast, hemoglobin (Hb) was significantly higher in treated group than controls at one, two- and six-months' post treatment with significant differences.

Conclusions: Liv.52 has a hepato-protective effect in patients with chronic non-infectious hepatitis as well as having extrahepatic effects through reducing total leukocyte count and increasing the hemoglobin. There was no evidence of short-term adverse effect of Liv.52.

Keywords: Liv.52, chronic liver disease, non-infectious

List of Abbreviations

Abbreviation	Term
ALD	Alcoholic liver disease
ALP	Alkaline phosphatase

ALT	Alanine transaminase
AST	Aspartate transaminase
ATT	Antitubercular treatment
BMI	Body mass index
CAM	Complementary and alternative medicine
CBC	Complete blood count
CLD	Chronic liver disease
ER	Endoplasmic reticulum
ESR	Erythrocyte sedimentation rate
Hb	Hemoglobin
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HSC	Hepatic stellate cell
IL	Interleukin
LFT	Liver function test
MCH	Mean corpuscular hemoglobin
MCV	Mean cell volume
NAFLD	Non-Alcoholic fatty liver disease
NO	Nitric oxide
PBMC	Peripheral blood mononuclear cells
PCV	Packed cell volume
PLT	Platelet
PT	Prothrombin time
SD	Standard deviation
SPSS	Statistical package for social sciences
TB-DILI	Antituberculosis drug-induced liver injury
TNF-α	Tumor necrosis factor alpha
TSB	Total serum bilirubin
WBC	White blood cell
WHO	World Health Organization

1. Introduction

1.1 Definition

Chronic liver disease (CLD) is defined as progressive degeneration of the liver parenchyma lasting more than 6 months, resulting in deterioration of liver function and subsequent fibrosis and cirrhosis. Cirrhosis of the liver and hepatocellular carcinoma (HCC) are the leading causes of liver- related death and impairment in quality of life. The onset and progression of CLD are influenced by a variety of factors, including environmental and genetic factors (Poynard et al., 2003), with alcohol consumption, hepatitis B (HBV) and C (HCV) virus, and obesity being the most common. These factors can cause the entire spectrum of chronic liver damage, from simple hepatocellular damage (indicated by an increase in serum transaminases) to end-stage diseases like cirrhosis and HCC (Ramakrishna et al., 2013).

1.2 Etiology and Epidemiology

1.2.1 Hepatitis Viruses

The chronic hepatitis C virus infects about 3% of the world's population and is one of the most common causes of chronic liver disease in Western countries (Lavanchy, 2011). Chronic liver disease affects the vast majority of HCV-infected people (80%). Twenty percent of individuals infected will develop liver cirrhosis 20 years after infection, and 25% of those with HCV-related cirrhosis will acquire end-stage liver disease sequelae such as hepatocellular carcinoma.

Effective HCV treatment appears to decrease the evolution of cirrhosis but not the beginning of HCC (European Association for Study of Liver, 2014).

Cirrhosis caused by a virus is the most common reason for liver transplantation in Europe today. The mechanisms of HCV-induced liver damage have received a lot of attention. The virus is a slow- replicating RNA virus that infects the hepatocytes of the host. HCV produces chronic inflammation in the liver, which is linked to the formation of reactive oxygen species (ROS) on a constant basis, resulting in increased oxidative stress (Ivanov et al., 2013). HCV also interacts directly with the endoplasmic reticulum (ER) and disrupts protein transport, causing ER stress (Asselah et al., 2010). The virus or the intricate interplay between the virus and the host could cause cellular death. In the liver of HCV-infected people, the expression of Fas antigen, an apoptotic marker, is higher. T-lymphocytes also release a range of cytokines that can trigger pro-apoptotic pathways when stimulated by the virus (Wang, 2014).

Around 2 billion people worldwide are infected with the Hepatitis B virus, with 350 million of them being chronic carriers (Aspinall et al., 2011). HBV infection was the tenth leading cause of death, accounting for almost half of all fatalities due to liver cancer (Lozano et al., 2012).

The virus replicates in hepatocytes during the first phase of HBV infection, which is immunological tolerant. After that, the immune system reacts against the infected hepatocytes, resulting in an immune reactive phase (Chisari, Isogawa, & Wieland, 2010). If the immune response to persistent HBV infection is insufficient, subjects may develop more severe illness, such as cirrhosis and HCC. Over a 5-year period, 67 percent of chronic HBV infected persons develop cirrhosis. HBV-related HCC is thought to be caused by a combination of host and viral mechanisms, including viral DNA integration, production of oncogenic proteins, and chronic immune-mediated inflammation (An et al., 2018).

1.2.2 Alcoholic Beverages

Alcohol consumption is a major cause of morbidity and mortality, accounting for 4.6 percent of global illness and injury burden and 3.8 percent of global deaths. It is likely the oldest type of chronic liver disease because fermented 14 beverages were around thousands of years ago. It's now one of the most common causes of liver disease all across the world (Gao & Bataller, 2011). It represents one-third of the causes of cirrhosis in patients who have received a liver transplant in Europe (Marroni et al., 2018). The term "alcoholic liver disease" refers to a wide range of liver problems induced by excessive alcohol intake (ALD). ALD is characterized by steatosis, inflammation (i.e., hepatitis), fibrosis (the ultimate stage of which is liver cirrhosis), and carcinogenesis. Although more than 90% of at-risk drinkers have steatosis, not all of them move to a more severe stage of the disease. If alcohol intake is sustained, 20-40% of steatosis patients will develop steatohepatitis, with 16% of these developing cirrhosis (An et al., 2011). Cirrhosis risk rises dramatically with steatohepatitis, with 16 percent of individuals with steatohepatitis developing cirrhosis after five years, compared to only 7% of those with simple steatosis (Deleuran, Grønbaek, Vilstrup, & Jepsen, 2012).

1.2.3 Genetic influences

There have been reports of ethnic differences in the susceptibility to chronic liver disease. Non- alcoholic fatty liver disease (NAFLD) is more common in Mexican-Americans (24%) than in non- Hispanic whites (18%) and non-Hispanic blacks (14%), for example (Lazo et al., 2013). The prevalence of alcoholic cirrhosis is more concordant in monozygotic twins than in dizygotic twins. Furthermore, only a subset of people with mild chronic liver disease progress to a more severe disease (An et al., 2018). The most recent genetic analysis technologies have resulted in the discovery of new genetic loci involved in the susceptibility to chronic liver disease over the last decade.

One study on Europeans looked at the impact of genetic variants on NAFLD prevalence and histological features. The study found that the TM6SF2 rs58542926 variant is linked to NAFLD and advanced fibrosis/cirrhosis, and that this link is independent of other known risk factors (Dongiovanni et al., 2015).

1.2.4 Obesity

Obesity is defined by the World Health Organization (WHO) as an abnormal or excessive fat buildup that may be harmful to one's health and corresponds to a body mass index (BMI) of 30 or more. Obesity has been more common in the United States during the previous three decades, affecting 35 percent of the adult population (Ogden, Carroll, Kit, & Flega, 2014). A population study of over 83,000 people found that obese people had a higher risk of death (from any cause) than those who were normal weight. Furthermore, obese subjects who remain obese have a 24% higher risk of death than obese subjects who lose weight after bariatric surgery (Sjöström et al., 2007).

In general, lipid accumulation in the liver (i.e., steatosis) can be caused by one of two factors (Fabbrini et al., 2008): increased lipid production or decreased lipid catabolism. However, not all people who have steatosis will progress to a more severe stage (de Alwis et al., 2008). Recently, a multiple parallel hits model (Tilg & Moschen, 2010) was proposed, in which dyslipidemia causes insulin resistance, which leads to steatosis. The steatotic liver is more vulnerable to a cascade of insults (e.g., oxidative stress, adipokines), which can cause damage, inflammation, and, eventually, fibrosis.

Obese people have hyperinsulinemia and high serum free fatty acids (FFAs), which can lead to an increase in the production of ROS and ER stress, which causes liver damage and inflammation (Sanyal et al., 2001). Some cytokines, including adiponectin, tumor necrosis factor- (TNF-), and interleukin-6 (IL-6), have also been implicated in the progression of liver damage (Tomita et al., 2008).

1.3 Pathophysiology

A constant and progressive process of hepatic fibrosis, architectural deformation of liver tissue, and regenerative nodule formation characterize CLD. While fibrosis is normally irreversible, it can sometimes be reversed in its early stages. The exact timing when reversible fibrosis becomes irreversible fibrosis is uncertain. If CLD is not treated, permanent fibrosis, regeneration nodules, and the development of liver cirrhosis are the most common outcomes. The underlying etiologies govern the rate of fibrosis development (Schuppan & Afdhal, 2008). The progression of hepatic fibrosis was evaluated in 4852 patients with varied underlying etiologies in one research.

Patients with HIV-HCV coinfection developed fibrosis at the quickest rate, while those with primary biliary cirrhosis developed fibrosis at the slowest rate. In all but alcoholic liver illness, the rate of fibrosis progression increased with age, whereas females showed a more gradual progression of liver fibrosis (Poynard et al., 2003). In another investigation, genetic polymorphism was found to be an underlying reason for variances in fibrosis rate advancement and the development of more severe disease in some people with the same underlying etiology as others (Bataller, North, & Brenner, 2003).

Hepatic fibrosis is the buildup of extracellular matrix (ECM) in the liver as a result of persistent liver damage from any source. The common pathway is started by hepatic stellate cells (HSC), which are vitamin A-storing latent cells situated between sinusoids and hepatocytes. HSCs proliferate into proliferative fibrogenic myofibroblasts in response to chronic liver injury, which release chemokines and other leukocyte chemoattractants, which upregulate expression of inflammatory receptors such as chemokine receptors, intracellular adhesion molecule (ICAM-1) and other inflammatory mediators (Sharma & Nagalli, 2021). The pro-inflammatory or initiation phase also alters the gene and phenotypic expression of liver cells, making them more susceptible to inflammatory cytokines, and the persistence of activated HSC cells leads to extracellular matrix formation and progressive fibrosis (Tsuchida & Friedman, 2017).

1.4 Management

Prior to treatment, evidence must be gathered to demonstrate that the diseased liver is altered in structure, function, or both. To treat liver diseases with structural abnormalities, surgical and ablative therapies are recommended (Alqahtani, 2012). Medication is critical for all patients with structural or functional problems in order to achieve a positive outcome (Safdar, Bartolome, & Sussman, 2012).

The treatment of chronic liver disease is determined by the underlying cause. To treat specific disorders, medications such as corticosteroids, interferon, antivirals, bile acids, and other medicines may be employed. Supportive therapy for cirrhosis problems includes diuretics, albumin, vitamin K, blood products, antibiotics, and nutritional therapy (Nusrat et al., 2014). When medicinal and interventional therapy have failed to cure the condition and the patient's life expectancy is between 6 and 12 months, a liver transplant is an option.

Congenital liver disorders, cancer, end-stage cirrhosis, and acute or subacute liver insufficiency are among the conditions that necessitate a liver transplant (Shiffman et al., 2006).

Unresectable liver cancer can be made resectable or transplantable by transcatheter arterial chemoembolization and radiofrequency ablation (Tesdal, Wikström, & Flechtenmacher, 2006). Transjugular intrahepatic portosystemic stent shunting is used to treat portal hypertension in patients awaiting liver transplantation (Saad et al., 2013).

Medication for the liver is used to treat underlying liver illness, supplement nutrients that aren't adequately absorbed owing to poor liver function, and prevent or relieve symptoms (Li et al., 2012). Infectious organisms such as viruses, bacteria, and parasites are all treated with drugs (Bunchorntavakul and Chavalitdhamrong, 2012).

Others are used to lower serum aminotransferase, cure jaundice, prevent intoxication, and preserve the plasma membrane of hepatocytes (Kuo, Chang, Tsai et al., 2012).

1.5 Complementary and Alternative Medicine

Herbs are effective in the treatment of CLD, such as fibrosis, steatosis, and hepatitis viruses, as well as in liver cell protection (X. B. Wang, Feng, N. Wang, et al., 2012). A Saudi Arabian study looked at the incidence of alternative medicine use and attitudes toward it in patients with liver illness. More than half of the patients acknowledged to using alternative and complementary medicine, and more than two-thirds of the patients thought that alternative and complementary treatments provided various health benefits, according to the data. The bulk of these research (Al-Zahim et al., 2013) found surprising extensive use and a generally favorable view about it.

Alternative medicine refers to the use of non-traditional medicine in place of mainstream medicine. When herbs and conventional medications are taken together, the chance of adverse effects is reduced. Despite this, there has long been a contentious discussion over its legal standing. As previously stated (Jeong et al., 2012), complementary medicine refers to the use of non-traditional medicine in addition to conventional treatment. As a result, the risk of unpleasant reactions may increase. Integrative medicine is a branch of medicine that incorporates all suitable treatment modalities, both conventional and unconventional, into a framework that prioritizes health, the therapeutic relationship, and the full person. A hallmark of this method is the emphasis on evidence as a critical aspect in therapeutic decision-making. One study looked at the safety and efficacy of using a mix of Chinese and Western therapy to treat infantile CMV hepatitis. The integrated medicine group had a total effective rate of 95.0 percent, which was significantly greater than the conventional treatment alone group (77.5 percent) (Hu et al., 2012). Another study interviewed ten leading experts in the fields of complementary and alternative medicine and integrative medicine in Western countries and came to the conclusion that integrated medicine can help in removing barriers and 19 opening up medical practice and research toward new visionary health care delivery and is concerned with changing conventional medical practice (Holmberg, Brinkhaus, & Witt, 2012).

Curcumin, emodin, and quercetin, among other active components of various herbs, have been found to have pharmacological actions against liver disorders on a molecular level (Vinod, Maliekal, & Anto, 2012). Clinical experiments further indicated that these phytochemicals operate as chemosensitizers by influencing key participants in the death receptor pathway and limiting DNA repair and apoptosis, leading to anti-cancer actions (Yu, Bao, & Lei, 2013). Herbal medications are available in many different forms, including ointment, pellet, ball, powder, and fluid decoction (Halberstein, 2004).

More standardized therapies include extracts from single plants and formula injections (Wu et al., 2006).

Both medical professionals and individuals should be more vigilant about drug safety while utilizing herbal injections. Adverse effects, including death, were reported in some patients who received herbal injections (Bate et al., 2013). Here, things get a lot more difficult. The quality of medications and their proper clinical administration are currently key concerns.

Falsified and substandard pharmaceuticals are commonly available in the private marketplaces of low- and middle-income countries (Bate et al., 2013). Potential safety hazards arise from insufficient extensive chemical analysis and research into associated technologies in traditional Chinese medicine (Wu et al., 2006).

1.6 Liv.52

Liv.52 is an herbal medicine that is commonly used in traditional Indian herbal recipes.

Capparis spinosa, Cichorium intybus, Solanum nigrum, Terminalia arjuna, Achillea millefolium, Tamarix gallica, and Mandur basma make up the Liv.52 formulation. It is a hepatotonic and has traditionally been used in the treatment of various liver disorders (De Silva et al., 2003). 20 Liv.52 has long been used to treat liver disorders due to its potential hepatoprotective effects. Several epidemiological and toxicological studies suggest that the Liv.52 formulation plays an important role in the detoxification of xenobiotics from the liver in both humans and animal models (Mitra et al., 2008; Vidyashanka, Mitra, & Nandakumar, 2010). This preparation contains a high

concentration of active pharmacological substances, the most important of which are phenolic compounds.

These compounds, in particular, are thought to be responsible, at least in part, for the majority of the beneficial effects of this herbal preparation. However, many other compounds do have effects in specific conditions (Vidyashanka, Mitra, & Nandakumar, 2010).

Experiments have shown that Liv.52 provides significant protection against carbon tetrachloride, alcohol, and beryllium-induced hepatic damage (Sandhir & Gill, 1999). By acting as a stimulant, Liv.52 significantly improves liver function. Previous clinical studies have also shown that Liv.52 has a liver protective effect against alcohol-induced hepatic damage and hepatitis B virus infection with no side effects (Galitskii et al., 1997).

1.7 Study Objectives

This study will investigate the efficacy and safety of Liv.52 in the treatment of chronic liver disease.

2. Patients and Methods

2.1 Design and Configuration

This is an interventional randomized clinical trial that took place at the internal medicine outpatient clinic at Baghdad Teaching Hospital from June 2017 to December 2019. (2.5 years). A total of 200 patients with chronic liver disease participated in the study. The diagnosis of each disease was based on clinical, laboratory, and radiological examinations (as needed) under the supervision of a gastrointestinal hepatologist. The Arab Council of Medical Specializations approved the study.

2.2 Inclusion Criteria

All patients with chronic hepatitis for at least one year.

2.3 Exclusion Criteria

- Viral Hepatitis
- Malignancy
- Pregnancy

2.4 Ethical Consideration

After explaining the purpose of the study, each participant signed a written consent form prior to data collection. Each patient was given the unconstrained right to withdraw at any time. The confidentiality of data was ensured throughout the study, and patients were assured that their data would only be used for research purposes.

2.5 Study Groups

Patients were divided into two equal groups at random (based on days of attainment). Group A consisted of 100 patients who received the Liv.52 supplement (two tablets thrice daily) in addition to their usual therapy regimen. 22 Group B consisted of 100 patients who did not receive the Liv.52 supplement and were restricted from their usual therapy regimen.

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 (32mg), A. millefolium (16mg), and Tamar ix gallica (16 mg). It also includes 'Mandur bhasma' (33mg/tablet), which is made from ferric oxide.

Patients were monitored for 6 months for clinical evaluation and therapy compliance (by tablet counting), as well as laboratory tests to examine routine blood chemistry and liver function after 1, 2, and 6 months of treatment.

2.6 Data Gathering

Direct interviews were used to collect demographic data such as age, gender, family history, residence, body mass index (BMI), and smoking status. Clinical characteristics such as the type and duration of liver disease, as well as the type of treatment, were obtained from patient records.

2.7 Laboratory Investigations

Serum alanine and aspartate aminotransferase (ALT and AST), alkaline phosphatase (ALP), albumin, and total serum bilirubin (TSB) levels were determined using methods described in commercially available reagent kits purchased from Randox/UK. The total leukocyte count (WBC), hemoglobin (Hb), platelet count (PLT), and prothrombin time (PT) were also extracted from the complete blood count (CBC).

2.8 Statistical Analysis

Data were expressed as mean and standard deviation for continuous and normally distributed variables, median

and range for continuous variables that did not have a normal distribution, and frequencies (percent) for categorical variables. The Chi square 2 -test was used to compare categorical variables, while the Student's t-test was used to compare the continuous 23 variables between the two study groups. The statistical significance level was set at p-value 0.05. The Statistical Package for Social Sciences, version 25, was used for statistical analysis (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1 Patients' Demographic and Clinical Characteristics

The mean age of treated patients was 31.779.6 years, which did not differ significantly from that of controls (29.68.7 years). In terms of gender distribution and BMI, the two groups were also compatible, with no significant differences. NAFLD was the most common liver disease, accounting for 45 percent and 39 percent of the treated group and controls, respectively. The next most common disease was alcoholic liver disease, which affected 22% and 26% of the treated and control groups, respectively. PBC, Wilson, and AIN are examples of uncommon diseases. In general, there were no significant differences in the distribution of these diseases between the two groups (Table 1).

Table 1. Patients' characteristics and clinical data

Variables	Treated group (n=100)	Controls (n=100)	p-value
Age (years)			
Mean ± SD	31.77 ± 9.6	29.6 ± 8.7	0.189
Range	8 – 38	10 - 34	
Gender			
Male	62(50%)	64(50%)	0.770
Female	38(50%)	36(50%)	
Liver Disease			
NAFLD	45 (45%)	39 (39%)	0.788
Alcoholic	22 (22%)	26 (26%)	
Autoimmune hepatitis	12 (12%)	13 (13%)	
PBC	7 (7%)	9 (9%)	
Wilson	5 (5%)	4 (4%)	
AIN	3 (3%)	6 (6%)	
Unknown	6 (6%)	3 (3%)	
BMI (kg/m^2)			
Mean ± SD	6.71 ± 4.7	27.14 ± 6.12	0.289
Range	18.31 - 32.9	19.44 - 34.21	

SD: standard deviation, BMI: body mass index.

3.2 Clinical Evaluation

There was a highly significant and rapid symptomatic improvement regarding loss of appetite, weight loss, fatigue and jaundice in the Liv.52 group as compared to the placebo group.

3.3 Liver Functions Tests

The time trends of ALT, AST, TSB, ALP and serum albumin are depicted in Figures 1–5. At baseline, all tests were comparable between the two groups with no significant differences. However, ALT and serum albumin showed a significant variation between treated group and controls in some time point. After 6 months of treatment, the mean ALT in treated group was 56.54±24.32 U/L which was significantly lower than that of controls (70.39±27.74 U/L). On the other hand, the mean serum albumin after one, two and six months' treatment were 2.94±0.4 g/dl, 3.25±0.38g/dl and 3.54±0.52 g/dl, respectively in treated group compared with 2.57±0.32 g/dl, 2.75±0.36 g/dl and 2.96±0.36 g/dl, respectively in controls with highly significant differences (Table 2).
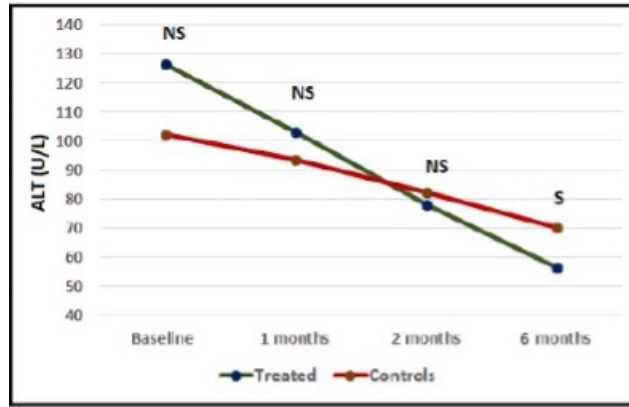
Figure 1. Time trend of ALT in treated group and controls. S: significant, NS: non-significant
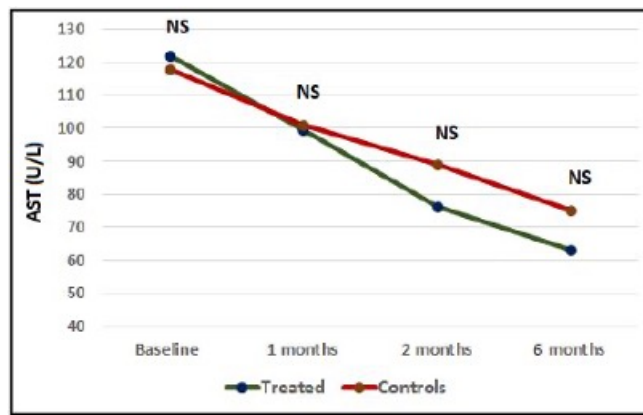

Figure 2. Time trend of AST in treated group and controls, NS: non-significant difference

Figure 3. Time trend of TSB in treated group and controls, NS: non-significant difference
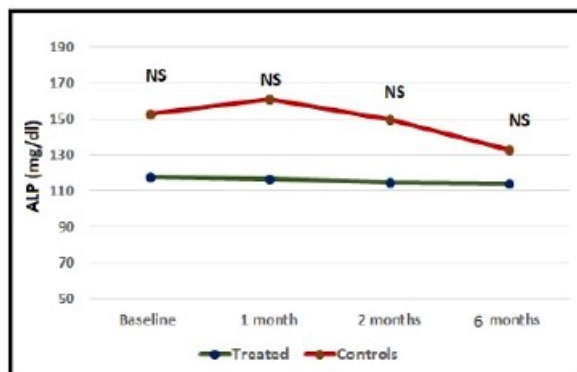
Figure 4.Time trend of ALP in treated group and controls, NS: non-significant difference
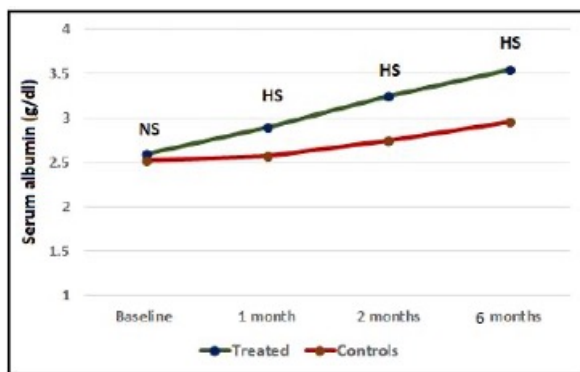
Figure 5. Time trend of serum albumin in treated group and controls, HS: highly significant

Table 2. Liver functions tests in treated and control patients

Variables	Time post- treatment	Treated (n = 100)	Controls (n = 100)	p value
ALT (U/L)	Baseline	126.55±82.07	102.56±55.68	0.116
	1 month	103.06±60.2	93.67±51.68	0.424
	2 months	78.27±39.77	82.39±35.2	0.599
	6 months	56.54±24.32	70.39±27.74	**0.019**
AST (U/L)	Baseline	122.0±76.45	118.56±52.19	0.789
	1 month	99.35±48.09	100.67±35.37	0.885
	2 months	67.14±35.04	89.17±28.62	0.055
	6 months	63.16±58.7	75.22±18.0	0.231
TSB (mg/dL)	Baseline	3.71±4.35	4.54±5.71	0.236
	1 month	3.11±3.28	3.81±4.54	0.267
	2 months	2.47±2.37	2.9±2.52	0.151
	6 months	2.05±1.92	2.35±1.78	0.148
ALP (mg/dL)	Baseline	118.0±122.29	153.06±214.93	0.407
	1 month	117.28±117.77	161.22±217.8	0.329
	2 months	115.31±128.25	149.5±185.84	0.386
	6 months	114.58±11.39	132.67±117.88	0.359
Albumin (g/dL)	Baseline	2.62±0.41	2.52±0.35	0.244
	1 month	2.94±0.4	2.57±0.32	**<0.001**
	2 months	3.25±0.38	2.75±0.36	**<0.001**
	6 months	3.54±0.52	2.96±0.36	**<0.001**

3.4 Hematological Parameters

At baseline, all these parameters were comparable between the two groups with no significant differences. With exception of platelet count, all other included hematological parameters were significantly differed between treated group and controls. After one and two month's treatment, the mean WBC count in treated group was $7.44 \pm 1.37 \times 10^3$/ml and $7.37 \pm 1.49 \times 10^3$/ml, respectively which was significantly lower than that of controls ($8.43 \pm 2.95 \times 10^3$/ml and $8.11 \pm 1.38 \times 10^3$/ml, respectively). In contrast, Hb was significantly higher, while PT was significantly lower in treated group than controls at one, two and six months' post treatment with significant differences (Table 3, Figures 6, 7, 8, and 9).

Table 3. Hematological parameters in treated and control patients

Variables	Time post- treatment	Treated (n =100)	Controls (n =100)	p value
WBC ($x10^5$/mL)	Baseline	7.51±2.88	8.33±5.79	0.129
	1 month	7.44±1.37	8.43±2.95	**0.018**
	2 months	7.37±1.49	8.11±1.38	**0.014**
	6 months	7.45±1.68	7.59±1.47	0.653
Hb (g/dL)	Baseline	13.14±1.67	12.68±1.81	0.192
	1 month	13.69±1.0	13.21±1.47	**0.047**
	2 months	13.89±1.13	13.09±1.04	**0.001**
	6 months	13.88±0.8	13.31±1.07	**0.002**
PLT ($x10^3$/mL)	Baseline	212.7±89.78	191.72±71.13	0.073
	1 month	212.47±73.56	199.56±68.4	0.379
	2 months	213.71±68.53	210.89±69.42	0.841
	6 months	215.84±46.43	209.0±66.71	0.734
PT (seconds)	Baseline	16.32±3.19	16.63±2.81	0.439
	1 month	15.71±2.82	17.57±2.83	**0.002**
	2 months	15.3±2.64	17.32±2.78	**<0.001**
	6 months	14.87±2.63	16.83±2.66	**<0.001**
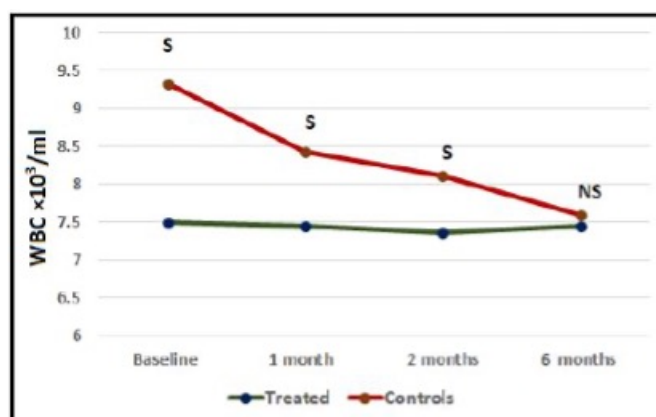
Figure 6. Time trend of total WBC in treated group and controls, S: significant difference, NS: non-significant difference
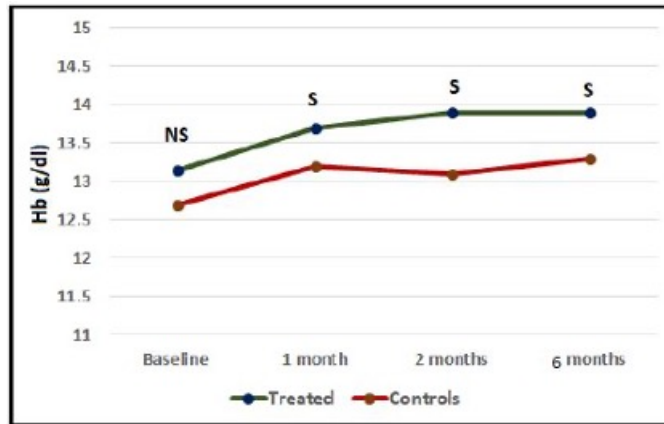
Figure 7. Time trend of Hb in treated group and controls, S: significant difference, NS: non- significant difference
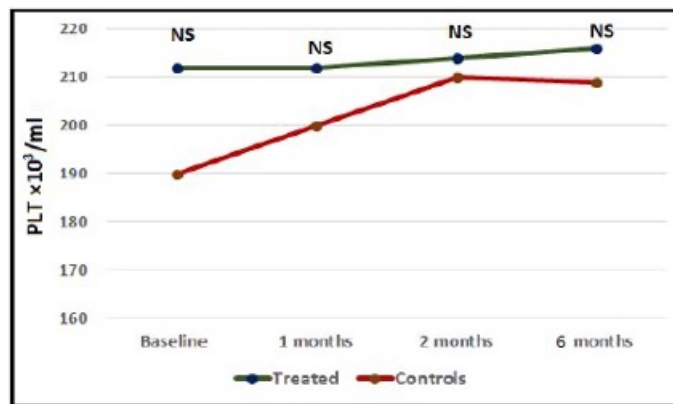
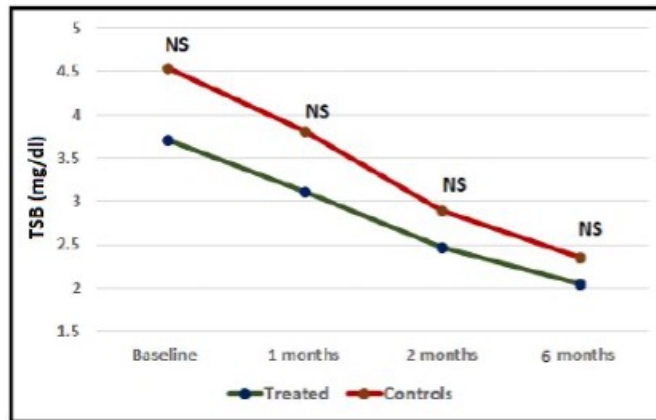Figure 8. Time trend of platelets in treated group and controls, NS: non-significant difference
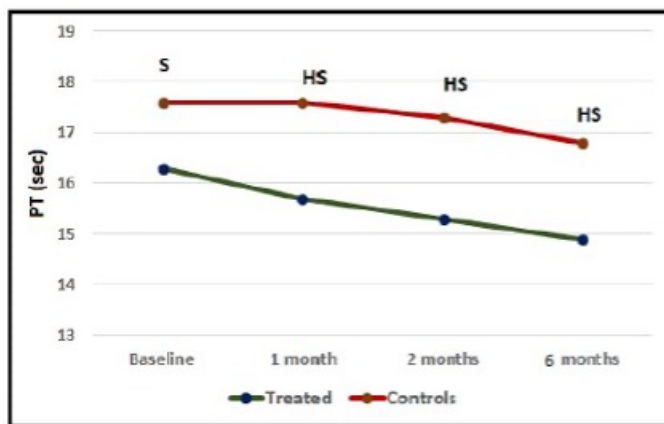
Figure 9. Time trend of prothrombin time in treated group and controls, S: significant difference, HS: highly significant difference

4. Discussion

The purpose of this study was to look into the efficacy of Liv.52 in the treatment of chronic liver disease. In terms of age, gender, BMI, and type of liver disease, there were no significant differences between treatment groups. As a result, variation in outcomes could be attributed to the treatment protocol. According to the study's findings, there was a significant improvement in liver function, as measured by liver enzymes and protein, in the treated group when compared to controls at various time points after treatment.

Such outcomes were common as Huseini et al. (2005) conducted a similar study in which they compared the efficacy of Liv-52 versus placebo on liver cirrhosis outcomes in 36 cirrhotic Iranian patients. ALT, AST, TSB, and albumin were among the outcomes measured. "The results showed that patients who were treated with Liv-52 for 6 months had significantly lower serum ALT and AST levels". The researchers concluded that "Liv-52 has a hepatoprotective effect in cirrhotic patients".

Choijamts et al. (2012) tested Liv.52 for hepatoprotective activity in 90 cases of antituberculosis drug- induced liver injury (TB-DILI) in a double blind placebo controlled design over 6 months. Their findings revealed an improvement in Hb, serum protein, and TB-DILI signs and symptoms. In addition, significant reductions in liver enzymes such as AST, ALT, ALP, and TSB were observed.

A meta-analysis of eight clinical studies on tubercular patients receiving antitubercular therapy (ATT) in addition to Liv.52 or placebo. "Improvement in the various parameters of hepatotoxicity, such as hepatomegaly, anorexia, weight gain, general well-being, and liver function tests, as well as improvement in the hepatobiliary ultrasonographic findings." Furthermore, in treated patients, there was a significant improvement in hepatotoxicity, associated symptoms such as anorexia, weight gain, hepatomegaly, and general well-being (Yew et al., 1995).

Not only is Liv. 52 effective in non-infectious hepatic diseases, but it is also effective in virally infected liver disease. Baijal et al. (2004) enrolled 50 patients with acute viral hepatitis who underwent hematological and biochemical testing, including CBC, LFTs, and ESR. "When compared to the placebo group, treated patients with Liv.52 showed a highly significant and rapid symptomatic improvement in the mean scores for loss of appetite, weight loss, fatigue, and jaundice." More importantly, when compared to controls, there was a significant renormalization of LFTs after 2 months of treatment.

Ghosh et al. (2014) obtained nearly identical results, demonstrating that Liv.52 is effective and safe in the treatment of non-alcoholic steatohepatitis. Despite the fact that the authors of one small study on patients with alcoholic liver disease did not report a significant effect of this preparation (de Silva, Saparamadu, & Thabrew, 2003), This variation in results may be related to the type of disease, implying that Liv. 52 is ineffective in alcohol-induced liver diseases due to fibrosis or cirrhosis associated with these diseases.

These effects of Liv.52 are attributed to the supplement's various components. Capparis spinosa, for example, has potent hepatoprotective activity against chemically-induced hepatotoxicity, preventing elevations of malondialdehyde levels (plasma and hepatic) and enzyme levels (AST and ALT) (Mantawy et al., 2004). "It improves the functional efficiency of the liver and spleen, with a protective effect on the liver's histological architecture and a beneficial effect on liver glycogen and serum proteins (Huseini et al., 2005)." Cichorium intybus has hepatoprotective activity by inhibiting oxidative DNA degradation (Gazzani, Daglia, Papetti, & Gregotti, 2000). It also has strong antioxidant properties, as evidenced by free radical scavenging, hydrogen peroxide inhibition, and iron chelation (Buso et al., 2020). Solanum nigrum protects DNA against oxidative damage, and also acts as a potent scavenger of hydroxyl and diphenylpicrylhydrazyl radicals (Heo & Lim, 2004). Finally, Terminalia arjuna has strong antiviral activity, inhibiting viral attachment and penetration (Cheng, C. C. Lin, T. C. Lin, 2002).

The other most intriguing finding in this study was the reduction in WBC and PT time, as well as an increase in Hb concentration in the treated group compared to controls at various time points during treatment. According to these findings, the study of Baijal et al. (2004) found a highly significant reduction in ESR and WBC in Liv.52 treated patients when compared to the placebo group. El-Azhary et al. (2017) found that Capparis spinosa extracts, one of the most important components of Liv-52, had significant anti-inflammatory activity in a mouse model. Similarly, Moutia et al. (2016) found that this component had anti-inflammatory activity in vitro on human peripheral blood mononuclear cells (PBMC) from healthy people. The authors also discovered that PBMC treated with Capparis spinosa extract aqueous fraction had a significant increase in IL-4 gene expression (an anti-inflammatory cytokine) and a significant decrease in IL-17 gene expression (pro-inflammatory cytokine). This explains the lower WBC count in treated patients compared to controls in the current study. An in vivo study, on the other hand, revealed that oral administration of Solanum nigrum (the third most abundant component of Liv 52) to anemic rats significantly increased the packed cell volume (PCV), Hb, red blood cells, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), but was associated with a decrease in the WBC and neutrophils within three weeks. These effects were attributed by the authors to the free radical scavenging activity that reverses anemic conditions (Aduwamai, Abimbola, & Ahmed, 2018). Also in accordance with the present study is a recent study by Moloudi et al. (2020) in which the authors used the hydroalcoholic extract of C. intybus (the first component of Liv.52) in the treatment of bile duct ligated experimental rats. The extract significantly decreased PT as well as the serum levels of AST, ALT, TNF-α and nitric oxide (NO) compared with the control group. On the other hand, the serum albumin

levels were increased in the extract-treated groups compared with the control group. This component's anti-inflammatory and antioxidant properties may be to blame for this effect.

5. Conclusions and Recommendations

5.1 Conclusions

1) Liv.52; a polyherbal supplement, has a hepatoprotective effect in patients with chronic non- infectious hepatitis.

2) This effect is attributed to the different components of this supplement which have anti- inflammatory, anti-oxidative, immunomodulation as well as restorative effects, and is reflected by improvement of liver function tests.

3) Liv.52 can also have extrahepatic effects through reducing total leukocyte count and prothrombin time and increasing the erythropoiesis.

4) There was no evidence of short term adverse effect of Liv.52.

5.2 Recommendations

1) Liv.52 is safe and effective in improving liver function in patients with chronic liver disease, and should be regularly prescribed for those patients.

2) Study the efficiency of this supplement on specific types of chronic hepatitis to further specify its use.

5.3 Study Limitations

1) The small sample size especially for particular types of chronic hepatitis did not allow evaluation of Liv.52 efficiency in each type.

2) The relatively short follow up period cannot exclude the possible long term effect of the supplement.

Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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