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Review

Hepatoprotective Effects of Liv.52 in Chronic Liver Disease Preclinical, Clinical, and Safety Evidence: A Review

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Abstract: Chronic liver disease (CLD) is a growing concern worldwide. The common etiological factors include infection, alcohol abuse, exposure to hepatotoxic drugs, autoimmune disorders, and metabolic diseases. The chronic liver disease progresses to liver cirrhosis and its consequent complications. It is routinely managed by a combination of various therapies in combination with lifestyle modifications. The current literature supports the growing importance of the usage of herbal medicines in the management of CLD due to their efficacy and very low incidence of adverse effects. Liv.52 is a known polyherbal formulation and has been used for over 50 years in India and other countries. The evidence collected from preclinical and clinical studies supports the use of Liv.52 in symptomatic improvement and supportive treatment due to hepatitis (including Hepatitis B), alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH) and hepatotoxicity due to drugs used in the treatment of tuberculosis. Liv.52 has also shown some preliminary hepatoprotective effects in patients with liver cirrhosis due to its potential antioxidant and anti-inflammatory effects. Both the syrup and tablet formulations are well tolerated and have shown a good safety profile. Liv.52 may be a favorable herbal choice for the management of CLD due to various etiologies.

Keywords: chronic liver disease; hepatoprotective; herbal; liver cirrhosis; Liv.52

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1. Introduction

Chronic liver disease encompasses a wide gamut of conditions and is a major cause of morbidity and mortality globally. Chronic liver disease leads to progressive deterioration of liver function. The process includes destruction, inflammation, and regeneration of liver parenchymal cells, leading to fibrosis and cirrhosis. Chronic liver disease is one of the frequent causes of death due to liver dysfunction, especially in developing countries. A wide spectrum of aetiologies is responsible for the occurrence of chronic liver disease, including infection, autoimmune diseases, metabolic disorders, toxins, and the use of hepatotoxic drugs as well as alcohol abuse for a prolonged time [1].

Liver cirrhosis is the final stage of chronic liver disease, where there is disruption of liver architecture, vascular reorganization, formation of widespread nodules, and deposition of an extracellular matrix. It is estimated that approximately 1.5 billion people have chronic liver disease worldwide. The age-standardized incidence of chronic liver disease and cirrhosis is 20.7/100,000. Overall, there has been a 13% surge in cases of chronic liver disease since the year 2000. According to the national vital statistics report 2017 by the Center for Disease Control and Prevention, about 4.5 million adults in the United States

(1.8%) were affected by chronic liver disease and cirrhosis. It is estimated that approximately 7% to 20% of non-obese Asians with a body mass index (BMI) below 25 kg/m^2 have non-alcoholic fatty liver disease (NAFLD) [2].

Anorexia, fatigue, and weight loss are some of the common symptoms experienced by patients with chronic liver disease. The symptoms depend on one or more of the complications developed. In complications like esophageal varices, ascites develop due to portal hypertension subsequent to the disease [1]. Prevention of the progression of the disease and its complications is the primary goal of the treatment of patients with chronic liver disease [1]. Several biomarkers are used to measure liver function. The important biomarkers include serum alanine transaminase (ALT), aspartate transferase (AST), bilirubin, alkaline phosphatase (ALP), albumin, total protein, and NAFLD score. The disease causes significant morbidity and mortality, largely owing to the complications [3].

The components in Liv.52 have strong hepatoprotective properties against chemically induced hepatotoxicity [4]. Liv.52 is indicated in the management of ALD, viral hepatitis, pre-cirrhotic conditions, early cirrhosis of the liver, anorexia, appetite loss, and liver damage from radiation therapy [5,6]. Liv.52 also shows improvement in anorexia and helps gain weight in pediatric cases of simple protein-calorie malnutrition of dietetic origin [7].

Additionally, Liv.52 is used as an adjuvant to hepatotoxic medications (chemotherapeutic agents, statins, anti-tubercular drugs, and antiretrovirals) and during extended sickness and convalescence [5,6].

Over many years, natural therapy with herbal medicines has been considered effective for the treatment of chronic liver disease mainly because of the low side effect profile. Herbal formulations may provide a natural way of healing with long-lasting effects compared to conventional medicines. Some of the natural medicines used for the treatment of chronic liver disease include silymarin, glycyrrhizin (licorice root extract), bitter-kola (*G. kola*), TJ-9 (*sho-saiko-to*), compound 861, CH-100, Liv.52, AO-8, HD-03, and extracts of Plantago asiatica seed, Phyllanthus amarus (*bhumiamalki*), and *Eclipta alba* [8].

Liv.52, a polyherbal ayurvedic formulation, is composed of eight constituents, including seven herbs; *Capparis spinosa* (65 mg), *Solanum nigrum* (32 mg), *Cichorium intybus* (65 mg), *Terminalia Arjuna* (32 mg), *Achillea millefolium* (16 mg), *Tamarix gallica* (16 mg), *Cassia occidentalis* (16 mg), and *Mandur Bhasma* (33 mg) [9].

These potent constituents of Liv.52 are reported to have a wide spectrum of hepatoprotective properties. The literature suggests that Liv.52 (both tablet and syrup formulation) taken two or three times a day is effective for liver protection against various hepatotoxins [10].

The current review focuses on preclinical, clinical, and safety evidence of Liv.52 in hepatic dysfunction and chronic liver disease.

2. Liv.52 Formulation

2.1. Hepatoprotective Effect of Individual Component of Liv.52

Liv.52, a polyherbal formulation of several plant principles prepared according to Ayurvedic concepts, is widely prescribed in India as a hepatotonic. The selection of constituents of Liv.52 was based on their reported traditional uses [11].

2.1.1. *Cichorium intybus*

The hepatoprotective effect of *Cichorium intybus* was observed by Aktay et al. and Zafar et al. against carbon tetrachloride-induced hepatotoxicity. The researchers reported a significant reduction in the elevation of AST and ALT enzymes and malondialdehyde formation [12,13]. In a study conducted by Ahmed et al., comparable hepatoprotective activity to silymarin was observed. The hepatoprotection was accompanied by nearly full tissue normalization, wherein neither necrosis nor fatty acid accumulation occurred [14].

According to the work of Gurbuz et al., a significant cytoprotection was observed in ethanol-induced lesions in rats [15]. The ethanol-induced immunotoxicity in mice was significantly prevented or restored by the ethanolic extract of *Cichorium intybus* [16].

2.1.2. *Capparis spinosa*

It was studied that p-methoxy benzoic acid from *Capparis Spinosa* had strong hepatoprotective properties against carbon tetrachloride-induced hepatotoxicity in experimental animals [17]. As per the work of Al-Said et al., *Capparis spinosa* showed a potent anti-inflammatory property that is comparable to oxyphenbutazone [18,19].

Capparis spinosa and *Cichorium intybus* containing esculetin and p-methoxy benzoic acid have been shown to have antioxidant and hepatoprotective effects in different animal models [20–22].

2.1.3. *Solanum nigrum*

Solanum nigrum was investigated for its hepatoprotective activity against carbon tetrachloride-induced hepatic damage. Raju et al. observed remarkable hepatoprotective activity that was confirmed by the evaluated biochemical parameters (AST, ALT, ALP) [23].

The hepatoprotective activity of *Solanum nigrum* was also studied by Moundipa et al., wherein it was reported that the activity of uridine diphosphate glucuronyltransferase, aminopyrine N-demethylase, and glutathione-S-transferase was increased and levels of aspartate aminotransferase, gamma-glutamyl transferase, and alkaline phosphatase were not altered [24]. In another study conducted by Sultana et al., *Solanum nigrum* was markedly protected from the DNA damage caused by free radicals [25].

2.1.4. *Cassia occidentalis*

A significant hepatoprotective effect of *Cassia occidentalis* in paracetamol and ethyl alcohol-induced liver damage was reported by Jafri et al. [26]. The anti-inflammatory activity of constituents of the roots and stem of *Cassia occidentalis* was shown by Kuo et al. [27]. *Cassia occidentalis* and *Achillea millefolium* showed antioxidant and hepatoprotective effects [26–28].

2.1.5. *Terminalia arjuna*

In a study conducted by Doorika P et al., the aqueous extract of bark of *Terminalia arjuna* significantly decreased the elevated levels of biochemical ALT, AST, ACP, ALP, and bilirubin. The extract increased the levels of antioxidant enzymes SOD and GSH [29]. Arjunolic acid and flavonoids, isolated from arjuna, increased the glutathione levels as per the results of a study conducted by Sumitra et al. [30].

2.1.6. *Achillea millefolium*

Antioxidant and antimicrobial effects of *Achillea millefolium* were studied by Candan F et al. The essential oil from *Achillea millefolium* showed antimicrobial activity against mycobacterium smegmatis, candida albicans, candida krusei clostridium perfringens, streptococcus pneumoniae, and acinetobacter lwoffii, whereas the methanolic extract did not show significant activity [28].

2.1.7. *Tamarix gallica*

The extract of leaves of *Tamarix gallica* was investigated by Urfi et al. for its hepatoprotective potential against rifampicin and isoniazid-induced liver injury in rats. The levels of elevated serum bilirubin, ALT, AST, ALP, LDH, and cholesterol were found to decrease, whereas the levels of albumin and total protein increased in the treatment group, indicating a hepatoprotective effect of the extract. The histopathological results also supported the study findings [31].

2.1.8. *Mandur bhasma*

Devarshi et al. conducted a study on *Mandur bhasma* wherein carbon tetrachloride-induced hepatitis was prevented by *Mandur bhasma,* indicating its hepatoprotective activity [32].

2.2. Mechanism of Action of Liv.52

Oxidative stress coupled with decreased enzymatic and non-enzymatic antioxidant levels is a major cause of liver injury and consequent damage [33]. Several mechanisms are proposed and worked out for the ingredients of Liv.52 and the whole formulation. Liv.52 may exert its effect through various mechanisms that collectively contribute to its hepatoprotective efficacy. The published literature indicates that Liv.52 acts on various arms of cellular processes and reduces oxidative stress and inflammation. Liv.52 also reduces the de novo lipid synthesis (by inhibiting the expression of a carbohydrate-responsive element-binding protein (ChREBP), improves mitochondrial beta-oxidation of fatty acids (by enhancing the activity of 3-hydroxyacyl CoA dehydrogenase), and inhibits extracellular matrix (ECM) accumulation [34]. The formulation also inhibits the up-regulation of markers of stellate cell activation, such as α-smooth muscle actin (α-SMA) and desmin. The levels of collagen and lumican also drop down upon usage of Liv.52, leading to inhibition of fibrinogenesis [34].

Liv.52 also offers protection against oxidative damage and aids in stabilizing cell membrane networks by inhibiting the formation and expression of inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukins (IL-8). It also abrogates the ethanol-induced suppression of peroxisome proliferator-activated receptor (PPARγ), suggesting its hepatoprotective activity [35]. The formulation also prevents GSH depletion and significantly decreases lipid peroxidation, suggesting its ability to reduce oxidative stress [36].

Liv.52 has been found to be effective in treating liver cirrhosis. The formulation significantly improves the Child-Pugh score, decreases ascites, and decreases serum *alanine aminotransferase* (ALT) and aspartate aminotransferase (AST). The overall effect is seen due to the diuretic, antioxidant, anti-inflammatory, and immunomodulatory properties of the component herbs [37] (Figure 1).

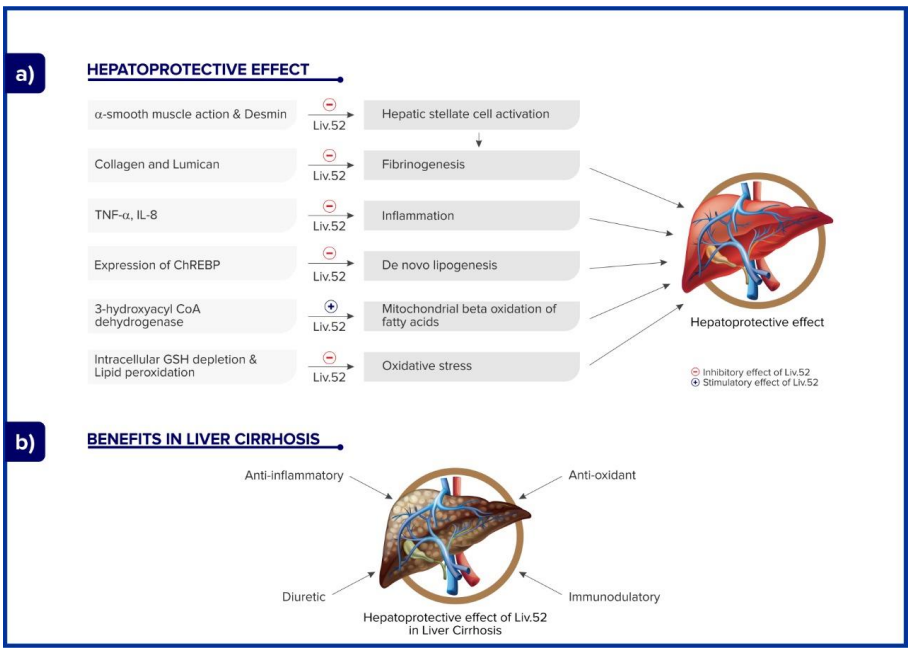

Figure 1. Mechanism of action of Liv.52.

2.3. Preclinical Studies: Hepatoprotective Effects of Liv.52

2.3.1. Hepatoprotective Effect

In a study conducted by Vidyashankar et al. (Table 1) on the effect of hydro-alcoholic extract of Liv.52 (50 µg/mL) on oleic acid-induced hepatic steatosis in HepG2 cells, the authors found that Liv.52 could circumvent oleic acid-induced steatosis. The proliferation of cells was increased by 3.81 folds with a decrease in levels of triacylglycerol (55%) and

cytokines. They also reported an increase in intracellular glutathione content by 8.9 folds along with an increase in antioxidant levels (superoxide dismutase, glutathione peroxidase, and catalase activities were increased by 88%, 64%, and 128%, respectively). The study demonstrated that Liv.52 formulation decreased IL-8 and TNF-α levels by 6.5% and 51% folds, respectively, lipid peroxidation by 65%, and DNA fragmentation was inhibited by 69%. Further, they also found that Liv.52 increased the enzymatic and non-enzymatic antioxidants and reduced molecular perturbations associated with non-alcoholic fatty liver disease (NAFLD) in HepG2 cells [38]. In yet another study by Vidyashankar et al. (Table 1), Liv.52 was found to be effective against oxidative damage (oxidative stress) induced by tert-butyl hydroperoxide in HepG2 cells. The formulation prevented GSH depletion and significantly decreased lipid peroxidation in these cells. Study findings suggest that Liv.52 formulation reduced oxidative stress, possibly by preventing intracellular glutathione depletion and reducing lipid peroxidation, indicating its hepatoprotective effect [36].

The long-term effect of carbon tetrachloride exposure in male albino rats was studied by Mitra et al. (Table 1). The results demonstrated carbon tetrachloride-induced elevated activities of hepatic enzymes and NADPH-dependent lipid peroxidation. Significant reversal of these effects was recorded following treatment with a daily dose of Liv 52 formulation (0.2 mL) for six weeks. Liv.52 formulation also helped in maintaining the normal levels of circulating thyroid hormones in the experimental animals [35]. Dhawan et al. demonstrated that Liv.52 significantly reversed liver ischemia-reperfusion damage in male albino Wistar rats. The increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, malondialdehyde, and myeloperoxidase were found to be reduced. Liv.52 also increased the levels of superoxide dismutase and glutathione-related enzyme activities in the study animals, thus preventing the oxidant-antioxidant disequilibrium and the ischemia-reperfusion associated with the hepatic dysfunction [39]. Studies conducted by Cimen et al. and Sandhir et al. (Table 1) demonstrated that 0.1 mL/kg body weight treatment with Liv.52 for four weeks inhibited the ethanol-induced increase in activity of gamma-glutamyl transpeptidase enzyme in male Wistar rats. Following treatment with Liv.52, a decrease in ethanol-accentuated lipid peroxidation in the liver was reported. Further, it was also reported that Liv.52 reversed the reduction in the activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase in the study animals following ethanol ingestion. The results obtained from both studies highlight the hepatoprotective effect of Liv.52 against alcohol-induced liver injury [9,40].

Kataria and Singh, in another study, demonstrated that Liv.52 treatment reversed the activity of hepatic arginase, acid phosphatase, cathepsin-B, and ribonuclease in rats exposed to carbon tetrachloride [41]. Several other preclinical studies have further confirmed the hepatoprotective nature of Liv.52 [42–45].

2.3.2. Antioxidant Effect and Radiation Hazard

Irradiation leads to a decrease in the cellular antioxidant level and an increase in the reactive oxygen species posing oxidative stress. The strength of Liv.52 inhibiting the generation of radiation-induced free radicals was evaluated by Jagetia et al. (Table 1) [46]. Pre-treatment of mice with Liv.52 (500 mg/kg body weight daily for seven days) significantly decreased the frequency of gamma radiation-induced micronucleated polychromatic erythrocytes as well as micronucleated normochromatic erythrocytes [46]. Liv.52 also reduced the symptoms of radiation sickness and increased the survival of mice 30 days post-irradiation. An increase in the activity of glutathione peroxidase, glutathione reductase, glutathione transferase, superoxide dismutase, and catalase was observed. The lipid peroxidation and the activities of ALT and AST were reduced. The effects were observed 30 min after exposure and persisted for one month post-exposure. The results of the study indicated that pre-treatment with Liv.52 lowered the genotoxic and lethal effects of gamma irradiation in experimental animals [46].

The evidence clearly supports the antioxidant activity of Liv.52, which is considered highly beneficial in hepatoprotection.

2.4. Clinical Studies: Hepatoprotective Effect of Liv.52 in Different Clinical Conditions

2.4.1. Tuberculosis

Tuberculosis and its treatment with various anti-tubercular drugs may result in liver damage. Commonly used anti-tubercular drugs, such as isoniazid, rifampicin, pyrazinamide, etc., are all known to be hepatotoxic [47,48]. There is an increased risk of drug-induced hepatitis in patients where hepatic reserves are already depleted. The efficacy of Liv.52 in preventing drug-induced hepatotoxicity due to anti-tubercular therapies has been well-documented in the literature [49,50]. In a double-blind placebo-controlled study conducted on 90 patients having tuberculosis and taking anti-tubercular therapy, treatment with Liv.52 DS tablets (two tablets twice daily for six months) demonstrated significant relief from symptoms of liver damage (appetite loss, indigestion, fatigue, weight loss) caused due to anti-tubercular drugs. An improvement in serum levels of protein, hemoglobin, ALT, AST, alkaline phosphatase, and bilirubin was also seen (Table 1) [51]. In a meta-analysis with eight controlled clinical studies and 689 patients taking anti-tubercular therapy and presenting with hepatotoxicity, a significant improvement was reported with respect to hepatomegaly, weight gain, anorexia, general well-being, symptoms related to hepatitis and gastrointestinal symptoms in patients treated with Liv.52. No adverse effects were reported with Liv.52 treatment in tuberculosis [52]. In another clinical trial, rifampicin and Liv.52 were investigated for drug–drug interactions, comparing the initial and subsequent levels of rifampicin in control and treated groups. The serum rifampicin levels on days 1, 15, and 30 were found to be comparable and not significant, suggesting that the process of enzymatic induction with rifampicin metabolism is not affected by the addition of Liv.52. Furthermore, Liv.52 (2 tablets twice daily) reduced gastrointestinal symptoms and deranged liver function in patients receiving ethionamide and pyrazinamide as a second line of anti-tubercular therapy [53].

In a separate double-blind, placebo-controlled trial, the effectiveness of Liv.52 DS was assessed for hepatoprotective activity in 90 cases of TB-DILI (drug-induced liver injury) in Mongolia over a period of six months. Statistics revealed improvements in hemoglobin, serum protein, and signs and symptoms of TB-DILI. Additionally, a significant decrease in the liver enzymes SGOT, SGPT, serum alkaline phosphatase, and serum bilirubin was seen. The results were encouraging for the utilization of the Liv.52 DS formulation in TB-DILI [51].

2.4.2. Alcoholic Liver Disease

In an open, nonrandomized, and non-comparative clinical study conducted on 50 patients with early alcoholic cirrhosis, the evaluation parameters were ALT, AST, total bilirubin, ALP, albumin, and prothrombin time. Significant improvement was seen in clinical symptom scores of asthenia, anorexia, nausea, tiredness, easy fatigability, abdominal pain, abdominal discomfort, frequency of stool, and muscle cramps subsequent to six months of treatment with Liv.52 DS tablets (1 tablet twice daily). Improvements in symptoms were observed from the first month of treatment. Physical sign scores of muscle wasting, edema, anemia, jaundice, ascites, and hepatomegaly were also significantly reduced at the end of the six-month treatment. Improvement in liver function tests was also reported suggesting a favorable and protective role of Liv.52 in maintaining liver integrity and restoring its function in alcoholic cirrhosis [54] (Table 2). A study conducted by Kalab et al. in 1997 evaluated the hepatoprotective effects of Liv.52 on patients with liver damage primarily due to alcoholic steatosis and observed improvement of clinical symptoms as well as laboratory parameters within one year of administration [55]. Mahto et al., in another phase 3 randomized, prospective study conducted on 25 patients with ultrasound-confirmed alcoholic hepatitis, noted a marked improvement in sonographic echogenicity and ascites. There was an improvement in liver function tests done before and after treatment. Liv.52 treatment was given for eight weeks (two tablets twice daily) and was well tolerated [56]. (Table 2). A comprehensive review of the clinical and safety evaluation of Liv.52 in alcoholic liver disease is well-documented in the review journal authored by Ganesh Subramanian et al. [57] (Table 3).

2.4.3. Viral Hepatitis

The goal of clinical treatment of viral hepatitis is early normalization of liver function and quicker symptomatic as well as clinical recovery. Most of the drugs used in the treatment of viral hepatitis have limited efficacy and have severe adverse effects. Furthermore, these antiviral drugs are expensive [58].

A double-blind study was conducted to evaluate the efficacy of Liv.52 in the treatment of acute viral hepatitis. Out of the 50 study participants, 25 were given Liv.52 two tablets thrice a day until total biochemical recovery. The other 25 participants were given a placebo. The Liv.52 group took an average of 2.4 weeks for the complete biochemical recovery, whereas the placebo group took 3.8 weeks. The total time required for both clinical and biochemical recovery was significantly shorter in the Liv.52 group [59].

Gupta et al. (Table 2) studied infectious hepatitis in 36 patients aged up to twelve years. Liv.52 was found to reduce the duration as well as the course of the disease with certain improvements in liver function [60].

Results of the other two studies exhibited improvement in hepatic histology and uniform improvement in clinical symptomatology and liver function test in viral hepatitis after treatment with Liv.52 [61].

Kolhapure et al. conducted a meta-analysis including 50 clinical trials evaluating the efficacy and safety of Liv.52 tablets and syrup in infective hepatitis caused by the hepatitis A virus. A significant decrease in the mean SB, SGOT, SGPT, AP levels, PT, and mean period needed for complete (symptomatic, clinical, and biochemical) recovery was seen in the cumulative data analysis. In all pertinent investigations, the reduced SA and SG levels were also considerably elevated compared to the pre-treatment values. In all trials, there were no serious adverse events that were either reported or seen, and there was overall good compliance [49].

Several studies have been conducted to assess the safety and efficacy of Liv.52 HB (a different of Liv.52) on chronic hepatitis B. Premashish Kar et al. (Table 2) conducted a clinical study to assess the safety and efficacy of Liv.52 in chronic hepatitis B where after six months of therapy, significant reduction of ALT values and significant loss of HBeAg and HBV DNA was observed [62]. Similar promising results were also observed by JS Rajkumar et al. (Table 2) [63]. A comprehensive review of the Role of Liv.52 HB capsules in the management of hepatitis B infection is conducted by Asim Maji et al. [64] (Table 3).

2.4.4. Non-Infectious Chronic Liver Disease

Al-Khazraji et al. (Table 2) conducted an interventional randomized blind clinical trial to investigate the effectiveness and safety of the Liv.52 supplement in the treatment of chronic liver disease. This study was conducted independently in Iraq, which reported beneficial effects of Liv.52. Liv.52 two tablets thrice daily showed hepato-protective effects in patients with chronic non-infectious hepatitis as well as extrahepatic effects through reducing total leukocyte count and increasing the hemoglobin. This effect is attributed to the components of Liv.52 supplement having anti-inflammatory, anti-oxidative, immunomodulation, as well as restorative effects [65].

2.4.5. Liver Function in Pregnancy

The rate of morbidity and mortality due to liver diseases during pregnancy is high in developing countries like India [66]; malnutrition coupled with inversion of T and B lymphocytes in early pregnancy have been postulated to be the contributing factors [67,68]. Mortality is in the range of 30% to 45%, and it may be as high as 70%. The majority of cases die undelivered [68,69].

In a study conducted on 84 cases of liver disorders in pregnancy, Liv.52 treatment reduced the earlier reported mortality from 26.7% to 1.1% in pregnant patients with jaundice. There was definite alleviation of symptoms like anorexia, pruritus, and nausea in 70% to 80% of patients. The liver enlargement was reduced in 60% of patients within six weeks, whereas yellow discoloration of the conjunctiva was lessened in 67% of patients. Significant

diminution was seen in the bilirubin value, with a mean decrease of 6 mg in six weeks. The albumin/globulin ratio demonstrated beneficial changes. The levels of ALT and AST enzymes also showed a significant decrease in six weeks. Out of 84 patients, relief was noted in 69 patients, whereas no relief from symptoms was noted in 14 patients, and 1 patient died. There were no adverse effects reported with the six-week Liv.52 treatment (Table 2) [70].

2.4.6. Liver Cirrhosis

Liver cirrhosis and hepatocellular carcinoma are the end stages of chronic liver disease. Worldwide, infectious hepatitis and alcohol consumption have been the leading causes of cirrhosis. Lately, modern lifestyles, the growing prevalence of obesity, and metabolic syndrome has resulted in a growing incidence of cirrhosis secondary to non-alcoholic fatty liver disease (NAFLD), especially in developed countries. A study conducted on 36 patients with cirrhosis and treated with Liv.52 for six months demonstrated a significantly improved Child–Pugh score, reduced ascites, and reduced serum ALT and AST compared to a placebo. The hepatoprotective action of Liv.52 has been found due to the anti-inflammatory, antioxidant, diuretic, and immunomodulatory properties of the constituent herbs [39]. In another study conducted by Malik et al., five patients out of eight with liver cirrhosis exhibited improvement in functioning hepatocytes with noticeable improvement in symptomatic and biochemical parameters following a twelve-week treatment with Liv.52. The signs of hepatic failure and symptoms of hematemesis and clinical jaundice also disappeared in all cases of liver cirrhosis within four weeks of Liv.52 therapy [41]. A randomized, double-blind, placebo-controlled, preliminary study conducted by Fallah et al. on 36 patients with cirrhosis found statistically significant improvement of symptoms like ascites, serum ALT, AST levels, Child-Pugh Score after six months, and these improvements were found to be statistically significant compared to the placebo [37].

2.4.7. Non-Alcoholic Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver Disease (NAFLD)

NASH is hepatic steatosis with or without hepatitis in the absence of alcohol use. The prevalence of NASH is 2% to 6% in the general population and can rise from 9% to 40% in obese people with a body mass index of 30 kg/m^2 or more. The disease occurs mainly in people between 40 and 60 years of age, although children over 10 years of age have also been reported to have it.

In a study conducted for 12 weeks of treatment with Liv.52 DS, individuals with non-alcoholic steatohepatitis showed significant improvement in hepatoprotective effects with respect to the clinical response and a decline in biochemical markers (Table 2) [71]. Another study was conducted in Indonesia by Siregar G et al. (Table 2) on patients with confirmed NAFLD. The Liv.52 DS was given as two tablets twice daily for two months. It was observed that treatment with Liv.52 resulted in significant improvement in hepatomegaly and liver enzymes. No progression of liver fibrosis due to NAFLD was observed during the study period. During the course of the trial, no adverse events or abnormal lab results were noted [6]. A study conducted by Shantanu Ghosh et al. (Table 2) showed that Liv52 had a beneficial effect in improving clinical and liver function parameters as well as ultrasonographic and NAFLD parameters in NASH [72]. A comprehensive review of preliminary trends identified from a cumulative efficacy analysis of Liv.52 in non-alcoholic fatty liver disease is well-documented in the review journal authored by Sharad C. Shah et al. [73] (Table 3).

2.4.8. Hepatomegaly Syndrome

Marginean et al. (Table 2) conducted an open-label clinical trial in children diagnosed with hepatomegaly syndrome. Liv.52 syrup, a pediatric formulation (2.5 mL twice daily for children below 12 years of age and 5 mL twice daily for children above 12 years) given for four months, showed a decrease in the size of the liver and spleen with improvements in clinical symptoms (like relief from nausea and appetite) and normalized readings for biochemical parameters indicating a protective effect on liver cells [74].

2.4.9. Safety

Overall, the clinical studies indicate that there was no evidence of clinically significant adverse effects or serious side effects, or adverse drug reactions that have been reported in the studies referred to in this review.

Table 1. Preclinical studies supporting Liv.52 actions.

Sr. No.	Author	Year	Type of Study	Aim	Findings Description	Reference
	Hepatoprotective effect					
1	Vidyashankar et al.	2012	In vitro study	Evaluate Liv.52 in oleic acid-induced non-alcoholic fatty liver disease (NAFLD) in HepG2 cells.	• Liv.52 can deceive oleic acid-induced steatosis and increase insulin-mediated glucose uptake and cell proliferation along with intracellular glutathione content by 8.9 folds. • Liv.52 also increases antioxidant levels (superoxide dismutase, glutathione peroxidase, and catalase activities were increased by 88%, 64%, and 128%, respectively). • Liv.52 also decreases IL-8 and TNF-α levels by 6.5% and 51% folds, respectively, lipid peroxidation by 65%, and DNA fragmentation was inhibited by 69%.	[38]
2	Vidyashankar et al.	2010	In vitro study	Evaluate the hepatoprotective effect of Liv.52 against oxidative damage induced by tert-butyl hydroperoxide (t-BHP) in HepG2 cells.	• Liv.52 significantly decreases toxicity induced by t-BHP in HepG2 cells and lipid peroxidation. • It also prevents GSH depletion in HepG2 cells induced by t-BHP.	[36]
3	Mitra et al.	2008	In vitro study	Determine whether ethanol and Liv.52 can modulate PPARc and TNFα induction in human hepatoma cells, HepG2.	Liv.52 is capable of attenuating ethanol-induced expression of TNFα and abrogating ethanol-induced suppression of PPARc in liver cells, suggesting its immunomodulatory and hepatoprotective effect. Liv.52 reverses the effects of carbon-tetrachloride-induced elevated activities of hepatic enzymes and NADPH-dependent lipid peroxidation.	[35]
4	Cimen et al.	2020	In vivo study	Evaluate effect of Liv-52 on liver ischemia-reperfusion damage in rats	Liv-52 is effective in reducing markers of liver damage and improving the histopathological condition of the liver tissue in the context of liver I/R injury.	[9]
5	Sandhir et al.	1999	In vivo study	Evaluate hepatoprotective effects of Liv-52 on ethanol-induced hepatic damage in rats.	Liv-52 prevents ethanol-induced increase in the activity of the enzyme gamma-glutamyl transpeptidase and decreases ethanol-accentuated lipid peroxidation.	[40]
6	Kataria et al.	1997	In vitro study	Evaluate effect of Liv.52 and Kumaryasava on growth and hepatic enzymes of CCl4 treated rats	Liv.52 and Kumaryasva both provide a certain amount of protection and correct liver dysfunction due to CCl4-induced hepatotoxicity. Also, the combination stimulates regeneration of hepatic and microsomal enzyme decreased due to CCl4 toxicity.	[41]
	Antioxidant effect and radiation hazard					
1	Jagetia et al.	2006	In vivo study	To evaluate radioprotective activity of Liv 52 in mice	• Liv 52 significantly reduces the frequency of radiation-induced MPCEs and MNCEs. • It also reduces the symptoms of radiation sickness and increases mouse survival, elevates the levels of reduced glutathione (GSH), increases the activities of glutathione transferase, GSH peroxidase, GSH reductase, superoxide dismutase, and catalase, and lowered lipid peroxidation and the activities of alanine aminotransferase and aspartate aminotransferase.	[46]

Abbreviations: NAFLD: non-alcoholic fatty liver disease; t-BHP: tert-butyl hydroperoxide; GSH: glutathione; PPARc: proliferator activator receptor gamma; TNFα: tumor necrosis factor-alpha; CCl_4: carbon tetrachloride.

Table 2. Clinical studies supporting hepatoprotective effect of Liv.52.

Sr No.	Study and Origin	Study Design	Treatment Duration	Country	Participant	Sample Size (Commenced, Completed)	Intervention	Outcome Measures	Results	References
Drug-induced hepatotoxicity: tuberculosis										
1	Choijamts et al.; 2018	Double Blind Placebo Controlled Study	6 months	Mongolia	Patients aged between 18 years to 60 years under ATT.	Liv 52 DS (47,47), Placebo (43,43)	Liv 52 DS-2 tablets twice daily.	LFT (SGOT, SGPT, serum alkaline phosphatase, and serum bilirubin), hemoglobin, serum protein	Compared to placebo, significant reduction was observed in LFT (SGOT, SGPT, serum alkaline phosphatase, and serum bilirubin) ($p < 0.05$). Hemoglobin improved from 13.17 ± 1.70 to 13.29 ± 1.21 with a significance of $p < 0.004$.	[51]
Non-alcoholic fatty liver disease										
1	Siregar et al., 2021	Prospective, interventional study	2 months	Indonesia	Patients aged between 18 and 65 years with NAFLD	Liv.52 (60,60)	Liv.52 DS-2 tablets twice daily for 2 months.	LFT (SGOT, SGPT), ultrasound, NAFLD Fibrosis Score.	Compared to placebo, Liv.52 group showed greater reduction in the fibrosis score for NAFLD. Hepatomegaly decreased to 42% of the participants. SGOT and SGPT levels significantly decreased ($p < 0.0339$ and $p < 0.0022$, respectively.)	[6]
Non-alcoholic steatohepatitis (NASH)										
1	Maity et al., 2015	Randomized controlled study	12 weeks	India	Patients aged between 18 and 65 years with non-alcoholic steatohepatitis	Liv.52 DS group (19,19); UDCA (16,16).	Liv.52 DS-2 tablets twice daily; 600 mg of UDCA thrice daily for 12 weeks	SGPT, SGOT, ALT, serum bilirubin, total protein, albumin and globulin	Compared to UDCA, Liv.52 showed faster clinical and biochemical recovery. Significant decrease was noted in the levels of SGPT($p < 0.004$), SGOT ($p < 0.033$), and ALP ($p < 0.008$).	[71]
2	Ghosh et al., 2014	Open clinical study	3 months	India	Patients suffering from steatohepatitis.	Liv.52 DS (50)	Liv.52 DS-2 tablets twice daily for a period of 3 months	ALP, total protein, total cholesterol, random blood sugar, TSH, serum triglyceride	Liv.52 showed improvement ($p < 0.0001$) in clinical and liver function parameters along with ultraso-nographic and NAFLD scores.	[72]
Viral hepatitis										
1	Kar et al., 2009	Open-labeled clinical trial	6 months	India	Patients aged 18–60 years with hepatitis B infection	HD-03/ES (51,51)	HD-03/ES-2 capsules twice daily for 6 months.	LFT, serum HBsAg, HBeAg and HBV DNA	Liv.52 showed significant reduction of ALT values from 71.2 ± 16.3 to 36.4 ± 6.8 ($p < 0.01$) and a significant HBeAg loss (27.4%) and HBV DNA loss (27.4%) ($p < 0.01$).	[62]
2	Rajkumar et al., 2007	Open prospective controlled clinical trial	6 months	India	Patients aged 18–60 years with hepatitis B infection	HD-03/ES(25)	HD-03/ES-2 capsules twice day for 6 months	ALT, AST, total bilirubin, serum protein	HD-03/ES showed significant reduction in ALT values from 66.5 ± 11.1 to 39.1 ± 5.2 ($p < 0.01$), significant HBsAg loss (52%, $p < 0.001$), HBeAg loss (60%, $p < 0.05$) and HBV DNA loss (60%, $p < 0.05$).	[63]
3	Habibullah et al., 1978	Double-blind study	Till total biochemical recovery	India	Patients suffering from viral hepatitis	Liv.52 group (25,25); Placebo (25,25)	Liv.52-2 tabs three times daily	SGPT, ALP, serum albumin, serum globulin, serum cholesterol, prothrombin time, serum bilirubin	Compared to placebo, Liv.52 showed faster biochemical recovery (2.4 weeks in Liv.52 group versus 3.8 weeks in placebo group).	[59]

Table 2. *Cont.*

Sr No.	Study and Origin	Study Design	Treatment Duration	Country	Participant	Sample Size (Commenced, Completed)	Intervention	Outcome Measures	Results	References
4	Gupta et al., 1972	Controlled clinical study	Follow up at intervals of 15 days/one month	India	Patients of infectious hepatitis from infancy to twelve years	Liv.52 (55, ND); control (30, ND)	Liv.52-1 tablet or 10 drops three times a day (up to 2 years); 1 tablet three times a day (up to 2–5 years); 1 tablet four times a day (above 5 years)	LFT, Urine examination; Haemogram, Liver biopsy, Radiological examination	Compared with control, serum bilirubin levels, albumin/globulin ratio, SGOT, and SGPT levels were normal in Liv.52 group. Total serum protein, serum alkaline phosphatase, and prothrombin time values were not affected. Also, biopsies clearly showed receding phase of infectious hepatitis in the group treated with Liv.52 tablets.	[60]
7	Singh et al., 1977	Controlled study	8 weeks	India	Patients with infective hepatitis of varying age groups	Liv.52 (25, 25); Control (25, 25)	Liv.52-6 tablets in divided doses along with B-complex and corticosteroids daily	SGOT, SGPT, Serum bilirubin, serum alkaline phosphatase, thymol turbidity	Compared with placebo, serum bilirubin values reduced by 86%(66% in placebo). The values in the Liv.52 group after 4 weeks and 8 weeks of treatment were reduced by 23% and 42% over the initial values. The percentage decline in thymol turbidity after 4 and 8 weeks of treatment in the control group was 24% and 29% as against 37% and 66% in the Liv.52 group. SGPT and SGOT values also showed reductions.	[61]
8	Jha et al., 2021	Comparative study	18 months	India	Patients with hepatitis B	Tenofovir(35,35); Liv.52 HB (32,32); Tenofovir plus Liv.52 HB (37,37)	-	ALT, AST, Serum bilirubin, ALP, serum creatinine, HbeAg, blood urea, INR, Hb	Tenofovir plus Liv.52 group showed significant reductions in Serum Bilirubin, serum ALT, AST, and ALP levels compared to tenofovir alone or Liv52 HB alone. There was a statistically significant reduction in HbsAg after 12 months within the tenofovir + Liv52Hb group, and also the outcome was statistically better when compared to other two groups. HbeAg positivity was also significantly better in the tenofovir + Liv52 HB group in both inter and intra-group comparisons.	[75]
					Non-infectious chronic liver disease					
1	Al-Khazraji et al., 2022	Interventional randomized blind clinical trial	6 months	Iraq	Patients with liver damage	Liv.52 (100, ND; Control (100, ND)	Liv.52-2 tablets thrice daily	ALT, AST, total serum bilirubin, ALP serum albumin	Compared to control, Liv.52 showed significant reduction in ALT ($p = 0.019$), AST ($p = 0.231$), total serum bilirubin ($p = 0.148$), ALP ($p = 0.359$), and serum albumin ($p < 0.001$).	[65]
					Alcoholic liver disease					
1	Kalab et al., 1997	Retrospective study	1 year	Prague	Patients having liver damage caused by alcohol, steatosis and persistent hepatitis.	Liv.52 (19, ND)	Liv.52-2 tablets (b.i.d.) for 1 year	ALT, AST, ALP, serum bilirubin, TZR, GMT	Liv.52 showed significant reduction in ALT, AST, GMT levels. There was no influenced on the value of TZR.	[76]
2	De Silva et al., (84)	Prospective, double-blind, randomized, placebo-controlled trial	6 months	Srilanka	Patients with alcoholic liver disease.	Liv.52 (40, 19); Placebo (40, 19)	Liv.52-3 capsules twice daily for 6 months	ALT and AST, gamma-GT, albumin, and bilirubin	Compared to placebo, there were no significant outcome measures observed in Liv.52 treated group. No subject complained of adverse effects attributable to the drug.	[11]

Table 2. *Cont.*

Sr No.	Study and Origin	Study Design	Treatment Duration	Country	Participant	Sample Size (Commenced, Completed)	Intervention	Outcome Measures	Results	References
					Liver dysfunction in pregancy					
1	Mitra et al., 2008	-	6 weeks	India	Pregnant women with severe viral hepatitis	Liv.52 (84, ND)	-	Liver biopsy	Liv.52 brought reduced the earlier reported mortality from 26.7% to 1.1% in patients of jaundice with pregnancy. All the patients recovered completely after 6 weeks of treatment except one patient.	[70]
					Liver cirrhosis					
1	Huseini et al., 2004	Randomized, double-blind, placebo-controlled	6 months	Iran	Subjects with liver cirrhosis were selected	Placebo (18,18); Liv.52 (18,18)	Liv.52—3 tablets twice daily for 6 months	ALT, AST, Child–Pugh score, ascites	Significant reduction in ALT (Mean 89 to 38), AST values (mean from 89 to 57) along with reduction in ascites and child-pugh scores.	[37]
					Hepatomegaly syndrome					
1	Marginean et al., 2002	Open clinical trial	6 months	Romania	Children (2–17 years) diagnosed with hepatomegaly syndrome.	Liv.52 (51,51); control (20,20)	Liv.52 syrup-2.5 mL ($\frac{1}{2}$ teaspoon), twice daily (children under 12 years of age); 5 mL (1 teaspoon) twice daily (children above 12 years)	AST, ALT, lactic-dehydrogenase, immunoglobulins, and serum proteins.	Compared to control, Liv.52 group showed significant decrease in AST and ALT values. Liv.52 group stimulated the synthesis of gammaglobulin. Liv.52 also improved protein synthesis.	[74]

ATT: anti-tubercular therapy; B.S.P: bromsulphthalein test; UDCA: ursodeoxycholic acid.

Table 3. Summary of review articles related to the hepatoprotective role of Liv.52.

Sr No.	Study and Origin	Study Design	Country	Indication	Study Size (N), Duration	Intervention	Outcome Measures	Results	References
1	Ganesh et al. 2022	Review	India	Alcoholic liver disease	N = 19 to 50, upto 1 year	Liv.52 DS	Liver parameters like ALT, AST, prothrombin, clinical symptoms like ascites, USG	Improvement in liver parameters, clinical symptoms, and USG findings.	[57]
2	Sharad C et al., 2022	Cumulative efficacy analysis	India	Non-alcoholic fatty liver disease	N = 35 to 50, up to 3 months	Liv.52 DS	Liver parameters like ALT, AST, clinical symptoms, USG (fatty liver grading, hepatomegaly), NAFLD fibrosis score	Improvement of hepatic parameters and clinical symptoms	[73]
3	Maji et al., 2013	Review	India	Hepatitis B infection	N = 14 to 51 (up to 6 months)	Liv.52 HB	LFT paramters, HbsAg, HbeAg, HBV DNA	Improvement in LFT paramters and lss of HbsAg, HbeAg, HBV DNA	[64]

3. Discussion

In this systematic review, over 35 clinical studies were identified examining the effects of Liv.52 on various chronic liver diseases. The hepatoprotective effect of Liv.52 was studied on clinical symptoms and liver parameters for the following conditions: tuberculosis (six studies), alcoholic liver disease (five studies), viral hepatitis (nine studies), non-infectious chronic liver diseases (one study), liver function in pregnancy (one study), liver cirrhosis (three studies), non-alcoholic fatty liver disease (six studies), and hepatomegaly syndrome (one study). Results from these studies indicated a positive trend of Liv.52, although the treatment duration, dose, and exact product type varied. Three products identified were: Liv52, its higher dose variant Liv.52 DS, and another variant Liv.52 HB, for hepatitis B. Although many of the studies were randomized and placebo-controlled, the robustness of the findings of some of them was limited by the small sample size. Many of the studies were conducted in India, with some notable studies conducted outside, like in Indonesia [6], Iran [37], Iraq [65] and Mongolia [51]. Most of the studies show improvement in clinical symptoms and liver parameters in various hepatic disorders. However, these findings have limited robustness due to the absence of histological assessments like ultrasound, fibroscan, or liver biopsy and in showing the long-term effect of Liv.52. Most of the studies show rapid improvement of liver parameters and clinical symptoms (within 4 to 12 weeks) of administration of Liv.52 indicating its hepatoprotective action, which may be attributed to reducing oxidative stress and inflammation in the hepatocytes. Our understanding is limited about the possible additional mechanism by which Liv.52 may show a long-term beneficial effect as a hepatoprotective agent in clinical populations with chronic liver diseases. Although the findings from these studies generally look promising, further studies are required with larger sizes and specific endpoints related to chronic liver diseases.

Apart from the above multiple positive trend studies, one study conducted by H.A. de Silva et al. in 2002 in Srilanka on 38 subjects with a history of chronic alcoholism (>2 years) and known alcoholic liver disease found limited efficacy of Liv.52 on reducing liver parameters after six months. Here, it is also important to note that this study mentioned a very high dropout rate (only 38 out of 80 subjects completed the study), which might have attributed to such types of results and cannot be deemed conclusive [11]. Another old study by W.E. Fleig et al. (1997) showed the negative effect of Liv.52 in increasing survival rates for patients with advanced alcoholic cirrhosis [76]. However, Liv.52, as per the information available, is probably not indicated in patients with critical and severe liver conditions, especially in those patients with higher degrees of other comorbidities. Moreover, the veracity of the results of this study is not well established as this study was only referred to in a conference proceeding and was never published for unknown reason. Therefore, these findings cannot be validated.

4. Conclusions

Overall, the results derived from this systemic review suggest that Liv.52 may be beneficial for improvement in symptoms and hepatic parameters in a wide variety of liver diseases like drug-induced hepatotoxicity, hepatitis, liver dysfunction in pregnancy, alcoholic liver disease, non-alcoholic fatty liver disease. Liv.52 has demonstrated potential hepatoprotective effects and has shown marked improvement in liver function and quality of life. The polyherbal formulation is well-tolerated, and no serious or drug-related side effects were reported in any of the patient groups studied. A further collection of data in a large population with robust study designs is warranted to corroborate our findings and validate the role of Liv.52 in the treatment of specific clinical conditions.

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