


Review

Clinical and Safety Evaluation of Liv.52 in Alcoholic Liver Disease: A Review

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Abstract: Alcoholic liver disease (ALD) has been a growing concern in developed and developing nations. Oxidative stress and lipid peroxidation are the most common cause of the development and progression of ALD. Due to paucity in the number and efficacy of hepatoprotective drugs currently available, and with the easy availability of natural therapy and herbal medicines, ALD is managed using a combination of pharmaceutical interventions and herbal medications. However, the effectiveness of these hepatoprotectives is controversial. Preclinical and clinical studies have demonstrated that Liv.52 modulates the lipotropic activity of hepatocytes, reduces inflammation, enhances alcohol and acetaldehyde metabolism, and protects the hepatic parenchyma by restoring the antioxidant levels of hepatocytes. Clinical studies further support that there is improvement in the subjective symptoms of patients as well as improvements in liver function test parameters. Studies suggest that Liv.52 is well tolerated and has no reported side effects.

Keywords: alcoholic liver disease; hepatoprotective; herbal preparation; liver function; Liv.52



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1. Introduction

Alcoholic liver disease (ALD) is the leading cause of death due to alcohol in adults worldwide [1]. The International Classification of Diseases (ICD-11) has recognized various forms of ALD (often referred to as stages), ranging from mild to reversible alcoholic hepatic steatosis (ASH, fatty liver) and alcoholic hepatitis to alcoholic fibrosis. Furthermore, ALD includes severe and irreversible stages such as alcoholic liver cirrhosis and alcoholic hepatic failure [2–4]. About 1% to 2% of all ALDs progress to hepatocellular carcinoma (HCC). While steatosis and inflammation can be reversed and managed upon abstinence, severe ASH, decompensating cirrhosis, and HCC are concerning due to their adverse prognosis. According to the World Health Organization (WHO) mortality database, in the European Union, excessive drinking is the cause of more than two-thirds (60–80%) of liver disease-related deaths [5]. The WHO further mentions that “morbidity attributable to alcohol in developed countries accounts for 10.3% of disability-adjusted life years and comes second only to that of tobacco (11.7%), with liver cirrhosis primarily responsible for 70% to 80% of alcohol-related mortality” [5]. Globally, alcoholic liver cirrhosis has caused 493,300 deaths (47.9% of all liver cirrhosis deaths) and 80,600 deaths have been due to alcohol-related HCC [1].

Alcohol is one of the most frequent causes of end-stage liver disease, and it is directly or indirectly responsible for 50% of cirrhosis-related deaths [6]. ALD is responsible for 4% of mortality and 5% of DALYs globally, with Europe suffering the most. Cirrhosis caused by alcohol accounts for one in ten alcohol-related deaths, while liver disease accounts for

nearly half of all alcohol-related deaths. This results in a loss of 22 million DALYs each year [1,7]. Alcohol is the leading cause of cirrhosis in India (34.3%), and over 20% of all liver disease patients (regardless of the etiology) are currently alcohol consumers [8].

As a result, alcohol contributes significantly to the global burden of liver disease. Further, a significant proportion of liver-related mortality of unknown etiology may well be attributable to alcohol as patients may withhold their history of alcohol use, and doctors may not mention alcohol use in the death certificates because of various socio-cultural and insurance-related issues [9]. Furthermore, several studies have only considered ALD in patients with no other liver disease etiologies. Over 50% of people with other liver illnesses, such as Hepatitis C, NAFLD, and hemochromatosis, may consume alcohol significantly [10,11]. Because of these many circumstances, it is hypothesized that the burden of ALD-related mortality is roughly twofold [12].

The majority of severe ALD patients require liver transplantation. About 40% of primary liver transplants in Europe and about 25% in the United States are attributed to alcohol consumption [13]. In the United States (1999–2013), middle-aged white non-Hispanic men and women's all-cause mortality increased significantly due to rising death rates due to drug and alcohol poisoning, chronic liver diseases, and cirrhosis.

Abstinence from alcohol is the gold standard for treating the initial stages of ALD, which depends on patient compliance. Both the American Psychiatric Association DSM criteria (DSM-IV) and ICD-10 describe ALD as "drinking behavior leading to physical, psychosocial and mental disadvantages requiring therapeutic intervention" [14,15]. Psychosocial intervention and pharmacological therapy are effective treatment strategies for ALD [16].

1.1. Risk Factors for ALD

1.1.1. Alcohol

The quantity and frequency of alcohol consumption are the two most significant risk factors for developing ALD. Early French studies claimed that the cirrhotogenic dose of alcohol was 80 g/day, but recent research, notably in women, has revealed a substantially lower threshold [17,18]. Northern Italian community-based studies showed a linear relationship between alcohol consumption and the risk of cirrhosis and liver disease [19]. Data from several epidemiological studies together indicate that at least 30 g of alcohol per day for women and 50 g per day for men over five years can cause clinically severe liver damage [20]. There is no conclusive evidence to support a safe alcohol consumption limit, despite the fact that a dose–effect link between alcohol use and liver disease has been well proven. The type of alcohol consumed also affects the risk of ALD, with wine drinkers having a decreased risk [21,22]. It is unclear, nevertheless, whether this is a result of wine's inherent antioxidant properties or other complicating lifestyle elements. The recent UK Million Women Study showed that daily intake without meals increases the chance of developing cirrhosis by twofold [20]. There is debate over whether binge drinking increases danger because recent research has shown contradictory findings. In the Danish Cancer, Diet, and Health research cohort, daily drinking was associated with the highest risk of cirrhosis [12].

1.1.2. Diet

Diet may also affect the risk of ALD, and in animal models, low-calorie diets high in iron and polyunsaturated fatty acids have been linked to more pronounced inflammation [12,23].

1.1.3. Gender

Although men experience an incidence of alcohol-related cirrhosis that is higher than that of women (0.2% vs. 0.03% annually), women have a higher relative risk of ALD for any given level of alcohol consumption [19]. The higher blood alcohol levels in women have historically been attributed to the lesser volume of distribution for alcohol [12].

1.1.4. Genetic and Epigenetic Factors

It is still unknown why just 10% of patients who consume high amounts of alcohol develop cirrhosis. There have been hypothesized genetic and epigenetic influences.

1.1.5. Chronic Viral Hepatitis

Alcohol and concurrent hepatitis C have a synergistic effect that increases apoptotic cell death, releases molecules linked with damage, and produces pro-inflammatory cytokines that speed up the fibrosis process [12]. Although there is conflicting evidence of both a preventive and a detrimental effect in various studies, the impact of concurrent hepatitis B infection is still unknown [24,25].

1.2. Prevention and Treatment of ALD

With national alcohol consumption trends and national liver-related mortality statistics, alcohol use is hazardous in a dose-dependent manner, not just at the individual level but also at the population level. However, the alcohol industry has a strong lobby, and developed and developing nations rely heavily on the sale of alcohol for revenue. There is enough proof to conclude that uncomplicated economic policy changes can dramatically reduce overall and alcohol-related liver mortality. These include gradual tax increases, a minimum unit price, restrictions on marketing and advertising, low-level clinical interventions, awareness campaigns, clearly labeled health warnings and measures to shield youngsters from alcohol, and advertisements that promote it [26].

There are several drugs to treat alcohol dependence. However, few drugs, such as baclofen, have been tested for safety in patients with ALD [27]. Pharmacological management to facilitate abstinence remains the primary therapeutic strategy in ALD. The pharmacological action of these medications is not known. Disulfiram and naltrexone are contraindicated in ALD due to possible hepatotoxicity risk [28,29]. Nalmefene, recently approved for treating alcohol dependence by the US FDA, has limited safety data [30].

Herbal Medicines

Ayurvedic medications are categorized into three groups based on the source material: herbal, mineral, and animal. Among these, the herbal formulation has recently grown significantly and received increasing global attention. This situation is evident as significant growth in the use of herbal formulations has been noted in the developed world over the last few years, with market expansion occurring in European countries and the United States [31]. According to the World Health Organization (WHO), 80% of the world's population still primarily relies on traditional treatments for their medical care [32]. With around 45,000 plant species, the Indian subcontinent is well known for being one of the mega centers of biodiversity [33]. This abundance of vegetation has led to its reputation as a source of medicinal plants throughout human history. About 15,000 medicinal plants have been identified in India, of which 7000–7500 were employed by the local populations to treat various illnesses. About 700 different plant species are recognized in Ayurveda's medical systems [34]. The word "herbal drug" refers to the part(s) of a plant (leaves, flowers, seeds, roots, barks, stems, and so forth) used in the preparation of medicines. Each and every component of the herbs is used to its fullest potential for the many pharmacological effects they may create and turned into various herbal preparations. Today's scientific advancements have led to the identification of an increasing number of pharmacologically active components in ayurvedic medicines, as well as their value in medication therapy. A single herb may have one or more phytochemical ingredients that combine synergistically to produce pharmacological activity [35].

Over the years, herbal medicines are another class of medications that have gained popularity and are considered a potential therapy for ALD treatment. Natural treatment is readily available, has lesser side effects, and provides long-lasting effects compared to conventional medicines [36]. Herbal medicines and formulations widely used worldwide originated from Africa, China, India, Japan, Africa, and South America. Most of these

traditional medicines benefit by reducing serum/plasma enzymes such as alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Other hepatoprotective benefits include lipid-lowering, antioxidant action, and anti-inflammatory and anti-fibrotic effects [37]. A significant complication of ALD is malnutrition, which occurs due to poor dietary intake from anorexia, vomiting, poor digestion, iatrogenic causes, metabolic disturbance, hypermetabolic state, impaired protein synthesis, or improper absorption [38,39]. Natural therapy and herbal products may play a role in addressing this malnutrition and ALD treatment [40].

2. Liv.52

First introduced in 1955 by The Himalaya Drug Company, Liv.52 is a hepatotonic used in India to treat various chronic liver diseases such as ALD [41,42]. Liv.52 consists of natural ingredients with potent hepatoprotective action against chemically induced hepatotoxicity [43]. Liv.52 is currently indicated for the prevention and treatment of various liver disorders such as viral hepatitis, ALD, pre-cirrhotic conditions and early cirrhosis of the liver, anorexia, loss of appetite and liver damage due to radiation therapy, and liver disorders (including fatty liver associated with protein-energy malnutrition). Liv.52 is also used as an adjuvant during prolonged illness and convalescence and as an adjuvant to hepatotoxic drugs (anti-tubercular drugs, statins, chemotherapeutic agents, and antiretrovirals) [44,45]. The recommended dosage of Liv.52 syrup is 2–3 teaspoons two to three times per day, while the tablet dosage is 2–3 tablets twice daily [43–45].

3. Liv.52 Constituents and Their Efficacy

Based on Indian Ayurvedic principles, Liv.52 contains several hepatoprotective ingredients known to protect the liver from damage produced by toxic substances, including alcohol [46–48]. Unlike herbal drugs such as silymarin, ursodeoxycholic acid, diphenyl dimethyl dicarboxylate, and glycyrrhizin, all of which originate from a single medicinal plant, Liv.52 consists of several ingredients including *Capparis spinosa* (Himsara), *Cichorium intybus* (Kasani), *Mandur bhasma*, *Solanum nigrum* (Kakamachi), *Terminalia arjuna* (Arjuna), *Cassia occidentalis* (Kasamarda), *Achillea millefolium* (Biranjasipha), and *Tamarix gallica* (Jhavaka). The components of Liv.52 are reported to have a broad spectrum of hepatoprotective properties: *Capparis spinosa* and *Cichorium intybus* containing esculetin and p-methoxybenzoic acid which has antioxidative and hepatoprotective effects in animal models [49–51]. Arjunolic acid and flavonoids, isolated from *Arjuna*, increased the glutathione levels, while *Solanum* markedly protected hepatocytes from the DNA damage caused by free radicals [52,53]. Antioxidative and hepatoprotective effects were also found in *Cassia occidentalis* and *Achillea millefolium* [54,55].

The current review describes the preclinical and clinical studies supporting the efficacy of Liv.52 in treating ALD.

4. Liv.52 in ALD—Preclinical Studies

Several preclinical studies of Liv.52 have shown promising results for ALD. In rats, Liv.52 treatment prevented the ethanol-induced increase in gamma-glutamyl transpeptidase (GGT) [56]. A decrease in ethanol accentuated lipid peroxidation in the liver following Liv.52 treatment. The activity of superoxide dismutase, glutathione peroxidase enzyme, and glutathione levels are known to reduce following ethanol ingestion. The preclinical data indicated that Liv.52 had a protective effect on the activity of superoxide dismutase and glutathione levels [56]. Consistent with these findings, another study showed that Liv.52 induced the expression of peroxisome proliferator activator receptor gamma (PPAR γ) and concomitantly suppressed the ethanol-induced elevation of tumor necrosis factor-alpha (TNF α) in HepG2 cells, thereby suggesting the hepatoprotective activity of Liv.52 [57] (Figure 1).

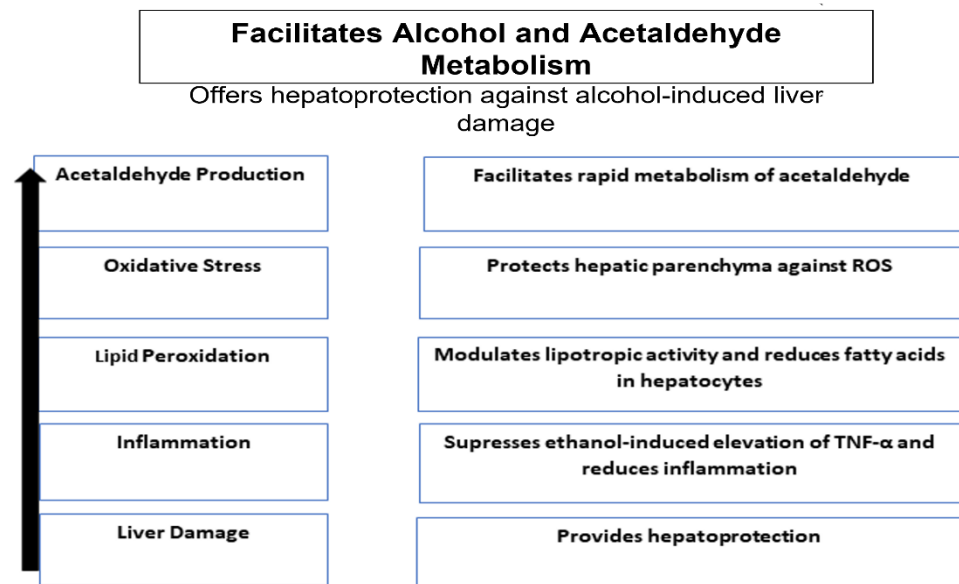


Figure 1. Mechanism of action of Liv.52 in alcoholic liver disease—results from preclinical studies.

A preclinical study was conducted to understand the metabolism of ethanol in rat liver following Liv.52 treatment using radiolabeled ethanol (^{14}C ethanol) and acetaldehyde (^{14}C -acetaldehyde). Liv.52 reduced the hepatic damage by rapidly converting ethanol to acetaldehyde and significantly inhibiting the accumulation of acetaldehyde in the hepatic organelles [58] (Figure 1). These results are further corroborated by another study conducted to assess the effect of Liv.52 on blood ethanol and acetaldehyde levels after chronic alcohol administration; results demonstrated that Liv.52 normalized the elevated blood ethanol levels and acetaldehyde levels in a dose-related manner [59] (Figure 1).

The adverse effects of maternal alcohol consumption on fetal development are well known. Liv.52 administration to pregnant rats fed with 20% (v/v) ethanol in drinking water showed that while ethanol ingestion caused a decrease in gestational weight gain, total fetal weight, and increased resorptions of live fetuses, Liv.52 administration reduced the deleterious effects of ethanol. The concentration of acetaldehyde in the amniotic fluid of ethanol-consuming animals was 0.727 mcg/mL compared to 0.244 mcg/mL in the Liv.52 group [60].

5. Liv.52 and Alcohol Absorption

One of the major concerns in ALD is acetaldehyde protein adduct formation resulting in liver damage. A study was conducted on eight social drinkers following the ingestion of 30 mL whisky in 5 min. Those who received a single dose of Liv.52 tablets demonstrated that the $t_{1/2}$ absorption with Liv.52 was significantly less than the placebo (3.62 min versus 6.29 min). Although the peak concentration of ethanol was significantly enhanced with Liv.52 (49.9 mg/100 mL) than with the placebo (40.5 mg/100 mL), participants reported significantly reduced acetaldehyde levels at 3 and 4 h after Liv.52 treatment. This was corroborated by the increased urinary excretion of aldehyde (four-fold) in participants treated with Liv.52. Thus, the Liv.52 probably destabilizes acetaldehyde protein adducts in the liver, reducing blood acetaldehyde levels in moderate alcohol users. This action may explain the hepatoprotective effect of Liv.52 on ethanol-induced liver damage [61,62].

6. Liv.52 in ALD: Clinical Efficacy

Liv.52 continues to be one of the most widely prescribed over-the-counter drugs by physicians in India. In a retrospective observational study using prescriptions of in-patients with ALD at a tertiary care teaching hospital in India, Liv.52 was the highest prescribed hepatoprotective drug (40% of prescriptions) [63]. This data is evident from several clin-

ical studies demonstrating the hepatoprotective effect of Liv.52 (Table 1). An open-label, prospective clinical study conducted on 50 adult patients suffering from early alcoholic cirrhosis showed a significant reduction ($p < 0.005$ to $p < 0.0001$) in clinical symptom scores of asthenia, easy fatigability, tiredness, nausea, anorexia, abdominal discomfort, abdominal pain, stool frequency, and muscle cramps following six months of treatment with Liv.52 DS tablets (1 tablet twice daily). The improvements were observed as early as the first month of the treatment. Physical sign scores significantly reduced ($p < 0.023$ to $p < 0.001$) that including muscle wasting, jaundice, anemia, edema, ascites, and hepatomegaly, observed at the end of the six months [64]. Patients also reported significant improvements in liver function test parameters (ALT, AST, total bilirubin, ALP, albumin, and prothrombin time) at the end of the six months [64]. Hematological and other biochemical safety parameters remained unchanged. The study thus demonstrated that Liv.52 plays a favorable and protective role in maintaining liver integrity and restoring its function in alcoholic cirrhosis [64]. Similar observations were also seen following the Liv.52 tablet formulation treatment for one year. The subjective condition and clinical parameters improved in patients with liver damage without undesirable side effects after one year of treatment [41,44]. In another phase 3 randomized, prospective study conducted on 25 patients with ultrasound-confirmed alcoholic hepatitis, marked sonographic improvements were observed for echogenicity ($n = 7$) and a significant clearance of ascites ($n = 5$) was seen following 8-week treatment with Liv.52 tablets (two tablets twice daily). This was corroborated by significant improvements in liver function test values seen before and after the treatment [65].

Table 1. Clinical findings supporting the efficacy of Liv.52 in the treatment of alcoholic liver disease.

Study	Study Design	N	Formulation and Dose	Findings
Agal [64]	Open-label, nonrandomized, noncomparative, prospective 6-month treatment study	50	1 DS tablet (twice daily)	<p>Significant reduction in clinical symptom scores of asthenia, easy fatigability, tiredness, nausea, anorexia, abdominal discomfort, abdominal pain, stool frequency, and muscle cramps with improvements from the first month of the treatment.</p> <p>Significant reduction ($p < 0.023$ to $p < 0.001$) in physical sign scores was seen in muscle wasting, jaundice, anemia, edema, ascites, and hepatomegaly.</p> <p>Significant improvements in liver function test values: (mean (SD) pre- vs. post-treatment).</p> <p>ALT 95.88 (87.15) IU/L vs. 55.96 (38.98) IU/L; $p < 0.005$).</p> <p>AST (123.20 (64.74) IU/L vs. 79.84 (49.57) IU/L; $p < 0.0001$).</p> <p>Total bilirubin (3.11 (2.15) mg/dL vs. 1.92 (1.21) mg/dL; $p < 0.0009$).</p> <p>ALK (232.30 (102.30) IU/L vs. 200.70 (84.43) IU/L; $p < 0.03$).</p> <p>Albumin (3.33 (0.69) gm/dL vs. 3.62 (0.54) gm/dL; $p < 0.01$).</p> <p>Prothrombin time (1.43 (0.32) INR vs. 1.18 (0.19) INR; $p < 0.0001$).</p>
Mahto et al. [65]	Phase 3 randomized, prospective 8-week study	25	2 DS tablets (twice daily)	<p>Marked sonographic improvements with respect to echogenicity ($n = 7$) and significant clearance of ascites ($n = 5$).</p> <p>Significant improvements in liver function test values.</p>

Table 1. Cont.

Study	Study Design	N	Formulation and Dose	Findings
Kalab and Krechler [41]	Retrospective, one-year treatment study	19	2 DS tablets (twice daily)	Improved appetite, fatigue, dyspepsia symptoms, and reduced tenderness in the right subcostal region. Significant improvements in ALT and AST levels. Significant reduction of cholesterol levels. Decrease in bilirubin levels. Significant diminishing measurement of the anteroposterior size of the right lobe of the liver.
Nikam et al. [66]	Prospective, 8-week treatment study	50	NA	Improved antioxidant vitamin E (5.02 (2.51) mg/dL vs. 6.25 (2) mg/dL) and vitamin C (0.70 (0.11) mg/dL vs. 1.30 (0.09) mg/dL) levels. Reduced lipid peroxidation (5.20 (0.15) moles/mL vs. 3.10 (0.25) moles/mL). Significantly improved liver function test values (mean (SD) pre- vs. post-treatment). AST (425(126) IU/L vs. 120(74) IU/L, $p < 0.001$). ALT (385(165) IU/L vs. 83 (42) IU/L, $p < 0.001$). ALK (240 (3.5) IU/L vs. 140 (4.0) IU/L, $p < 0.001$). GGT 195.55 (5.15) IU/L vs. 60 (7.00) IU/L, $p < 0.001$. Total bilirubin 6.11(3.15) mg% vs. 1.28(0.20) mg%, $p < 0.001$.

7. Liv-52 in Alcoholic Hepatitis

A study conducted on 50 patients with alcoholic hepatitis treated with Liv.52 for eight weeks demonstrated that the 8-week therapy with Liv.52 increased the antioxidant levels and reduced lipid peroxidation of hepatic cellular and intracellular membranes, thus protecting the liver from damage due to free radicals. The study demonstrated a significant increase in nonenzymatic antioxidant vitamin E and vitamin C levels following 8-week Liv.52 therapy, indicating that liver cells may be regenerating after Liv.52 treatment, which helps cure hepatitis [66].

8. Discussions

Even though ALD is the most critical health harm caused by alcohol abuse, the spectrum of current pharmaceuticals acting as hepatoprotectives is relatively small. Preclinical and clinical studies have demonstrated that Liv.52 prevents hepatic damage by promoting protein biosynthesis. It reduces intrahepatic edema and prevents further necrosis; this relieves intrahepatic cholestasis and aids in regenerating hepatic cells. Clinical studies further support that there is improvement in the subjective state of the patient and many laboratory parameters. Liv.52 is well tolerated, non-toxic, and has no side effects reported.

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