Liver SAP

Science-based nutraceuticals and botanical extracts for liver detoxification

The liver is the largest glandular organ in the body, with numerous vital functions including glucose, fat, and protein metabolism; regulation of blood sugar levels; storage of vitamins; and digestion. It is also one of the major organs of detoxification, playing a key role in the neutralization of external substances such as drugs and alcohol, processing metabolic waste, and breaking down insulin and other hormones. The liver also has the unique property of being the only internal organ capable of regeneration. **Liver SAP** contains a blend of high-quality botanical extracts and nutraceuticals that support liver function, protect against hepatotoxicity, and encourage regrowth of damaged hepatocytes.

ACTIVE INGREDIENTS

Each vegetable capsule contains:

Milk thistle (*Silybum marianum*), 80% silymarin	250 mg
Curcuminoids, (from 125 mg of Turmeric (*Curcuma longa*) root extract, 95% curcuminoids, providing curcumin I, demethoxycurcumin, and bisdemethoxycurcumin)	118.75 mg
α-Lipoic acid	100 mg
Calcium D-glucarate	50 mg
Schizandra (*Schizandra chinensis*), 9% schizandrin	50 mg
Artichoke (*Cynara scolymus*), 5% cynarin	50 mg
Dandelion (*Taraxacum officinale*), 3% flavonoids	50 mg
L-Methionine	50 mg
N-Acetylcysteine	25 mg

This product is non-GMO.

Contains no: Gluten, soy, wheat, eggs, dairy, yeast, citrus, preservatives, artificial flavour or colour, starch, sugar.

Liver SAP contains 90 or 180 capsules per bottle.

DIRECTION FOR USE

Adults: Take 1 capsule twice daily with food or as directed by your healthcare practitioner. Hepatoprotectant/liver protectant agent function: Use for a minimum of 3 weeks to see beneficial effects. Consult a healthcare practitioner for use beyond 6 weeks.

INDICATIONS

Liver SAP is effective in:

- The management of various liver pathologies including hepatitis B and C, inflammation, cirrhosis, fatty accumulation, and hepatocellular carcinoma, and protects against the toxic effects of alcohol and certain pharmaceutical agents.
- Stimulating liver function and regeneration in detoxification protocols.
- Restoration of optimal liver function through the use of **Liver SAP** may positively affect digestion, skin quality, regulation of blood glucose and lipid levels, and hormone balance.

EXTRACTION TO ENHANCE CONTENT

- The botanicals in **Liver SAP** are ethanol-extracted for standardized isolation of active constituents.
- **Liver SAP** is supplied in a vegetable capsule for easy digestion.

PURITY, CLEANLINESS, AND STABILITY

All ingredients listed for all **Liver SAP** lot numbers have been tested by a third-party laboratory for identity, potency, and purity.

Scientific Advisory Panel (SAP): adding nutraceutical research to achieve optimum health

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Milk Thistle (*Silybum marianum*)

Milk thistle is one of the best-studied medicinal plants for the treatment of liver disease and is approved by German Commission E Monographs in the management of inflammatory liver conditions such as hepatitis, cirrhosis, and fatty infiltration.[1] This herb and its extracts prevent liver destruction and stimulate the growth of new hepatocytes,[1] and are known to be safe and well-tolerated, even in long-term trials.[2] The main seed extract from this herb is silymarin, of which 60% is silybin (aka silybinin), a water-soluble flavonoid with antioxidant and antiproliferative properties,[3] and both silymarin and silybin inhibit lipid peroxidation in hepatocytes and microsomal membranes.[4]

Turmeric (*Curcuma longa*)

This bright yellow spice has a long history of use in Asian medicine for digestive, inflammatory, and hepatobiliary conditions.[5] An extensive body of research has established its anti-inflammatory, antioxidant, and anticancer properties, much of which is due to the activity of curcuminoids, its main active constituents.[5] This herb has also been shown to prevent and reverse hepatic cirrhosis caused by bile duct obstruction.[6]

α-Lipoic Acid (ALA)

ALA is a naturally occurring substance that acts as a cofactor in mitochondrial metabolism, and is most recognized for its potent antioxidant activity.[7] It has demonstrated therapeutic efficacy in various liver diseases including alcohol-induced damage, mushroom poisoning, metal intoxication, and biliary cirrhosis.[7]

Globe Artichoke (*Cynara scolymus*)

Globe artichoke has been used in folk medicine for liver conditions and more recently has received attention as an antioxidant due to it high polyphenolic content.[8]

Dandelion (*Taraxacum officinale*)

Therapeutic use of dandelion was first recorded in the 10th and 11th centuries by Arabian physicians in the treatment of liver and spleen ailments,[9] and the plant is valued today for its cholorectic, diuretic, antirheumatic, and anti-inflammatory properties.[9]

Schizandra (*Schisandra chinensis*)

Schizandra (aka *bei wu wei zi*) is an important traditional Chinese medicinal herb that has been used in Asia for thousands of years in the treatment of respiratory, urinary, and reproductive conditions, and more recently for hepatitis.[10]

N-Acetylcysteine (NAC)

Supplementation with *N*-acetylcysteine (NAC) has been shown to increase levels of glutathione, an endogenous antioxidant that has a ubiquitous role in many of the body's defenses, and is effective in the treatment of many conditions characterized by oxidative stress.[12]

CLINICAL APPLICATIONS IN LIVER HEALTH

Hepatotoxicity

Alcohol is highly toxic to the liver, and abuse of this substance can lead to fatty accumulation, hepatitis, and cirrhosis. In a randomized double-blind study, liver cirrhosis patients supplemented with a silymarin extract of milk thistle had increased survival rate.[2] In addition, silybin protects against severe liver damage following poisoning by the mushroom *Amanita phalloides* (death cap) when administered within 48 h.[1] Oxidative stress is another major cause of hepatic damage; pretreatment of rats with an extract of *Cynara scolymus* was shown to be protective against carbon tetrachloride (CCl_4)-mediated liver damage.[12]

Pharmaceutical-Induced Hepatoxicity

The risk-benefit assessment of pharmaceutical agents often includes consideration of toxic effects to the liver. Liver damage is a known side effect of cyclophosphamide (CP), a drug used in chemotherapy and as an immunosuppressant in the treatment of autoimmune diseases.[13] Rats undergoing CP therapy for 10 weeks exhibited depressed antioxidant enzyme activity as well as depleted antioxidant status; these changes were not seen in animals that were pretreated intraperitoneally with α-lipoic acid (ALA).[13] This nutrient, as well as *N*-acetylcysteine (NAC), have also been shown to protect against an acute oral dose of acetaminophen in animal models.[14, 15]

Tuberculosis (TB) is a deadly infectious disease that warrants the use of intensive treatment. The current first-line antituberculosis drugs rifampin, isoniazid, and pyrazinamide are associated with liver toxicity and hepatitis.[16] Supplementation with silymarin in a rat model,[16] and curcumin in a human trial,[17] significantly decreased TB drug-induced liver damage.

Hepatic Ischemia/Reperfusion Injury

Ischemia/reperfusion injury (IRI) of the liver occurs primarily in extended surgical resection procedures in which large amounts of reactive oxygen species (ROS) are generated following ischemia, leading to subsequent inflammation, tissue damage, and cell death upon reperfusion.[18] Rats injected with α-lipoic acid (ALA) prior to the induction of ischemia suffered less liver necrosis, and apoptosis-related cell death, and had higher levels of ATP in liver tissue and enhanced hepatic regeneration.[18] A similar study using *N*-acetylcysteine (NAC) yielded comparable results, with supplementation being associated with lower plasma-AST and ALT activities and mild elevations in liver glutathione status.[19]

An important application of this research is in organ transplantation, where IRI can lead to loss of even the healthiest of donor organs. In a prospective, randomized, double-blind clinical trial of 50 liver transplant recipients, 100 mg/kg NAC was administered to the intervention group at 5 min before reperfusion, at 10, 20, and 60 min after reperfusion, and at 1 h after completion of liver transplantation. Intraoperative levels of interleukin-4 and 10, two cytokines that dampen the inflammatory response, were measured. Significant increases in recipient IL4 plasma levels before and after reperfusion, and IL10 plasma values before reperfusion were seen, both of which correlated with protection against IRI.[20]

Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver diseases characterized by macrovesicular steatosis in the absence of significant alcohol ingestion.[21] This condition is strongly linked to obesity, insulin resistance, and metabolic syndrome,[22-24] affecting an estimated 20% of adults in industrialized countries,[25] and accounting for the majority of liver pathologies in these regions.[22]

In a study of 85 NAFLD patients, silybin, a component of *Silybum marianum*, was conjugated with vitamin E and phospholipids to enhance its antioxidant activity. The formula was well-tolerated, and supplementation over 12 months resulted in significant reductions in liver steatosis scores as well as favorable shifts in liver enzymes, serum insulin levels, and liver fibrosis.[25]

Sterol regulatory binding protein-1c (SREBP-1c) is one of the major regulators of the expression of genes involved in hepatic triglyceride synthesis, and its activity is dictated by nutritional status; under fasting conditions, activation of adenosine monophosphate-activated protein kinase (AMPK) reduces lipogenesis in the liver by suppressing SREBP-1c activity. Conversely, activation of liver X receptor (LXR) and specificity protein 1 (Sp1) increases SREBP-1c expression under insulin-stimulated conditions, and leads to hepatic lipogenesis.[24] α-Lipoic acid (ALA) suppresses SREBP-1c activity through the activation of AMPK, inhibition of LXR and Sp1, and elicits an overall reduction in hepatic lipogenesis in insulin-resistant rats fed a high-fat diet.[24] Additionally, schisandrin B (Sch B), a constituent of *Schisandra chinensis*, has been shown to decrease hepatic total cholesterol and triglyceride levels and increase liver weight in hypercholesterolemic mice.[21]

Mild forms of NAFLD can be reversible, but in 10–20% of patients, initial steatosis is followed by inflammation, necrosis, apoptosis, and fibrosis,[23] a condition called non-alcoholic steatohepatitis (NASH) that can lead to liver failure, cirrhosis, and hepatocellular carcinoma.[21, 24] Oxidative stress has been proposed as the triggering factor for the progression of NAFLD to NASH, and antioxidant therapies have been investigated in the treatment of this disease. *N*-Acetylcysteine (NAC), a precursor to the antioxidant glutathione, was examined in a study of 20 patients also receiving metformin therapy. At a dose of 1.2 g/d NAC, significant decreases in liver steatosis and fibrosis were observed over a 12-month period.[22]

HEPATITIS

Hepatitis B

Approximately 300 million people worldwide are afflicted with chronic hepatitis B virus (HBV), with the highest incidence in African and Asian countries.[13] The virus resides in hepatocytes, inflicting hepatic injury and inflammation, and is a major cause of cirrhosis and hepatocellular carcinoma.[26] Oral administration of KY88, a herbal blend containing *Schisandra chinensis,* to HBV-infected rats lead to reductions in the secretion and gene expression of HBsAg and HBeAg.[26]

Hepatitis C

Hepatitis C virus (HCV) infects an estimated 170 million people around the world, resulting in roughly 500,000 deaths per year due to complications of end-stage liver disease including hepatocellular carcinoma,[3] and is the most frequent indication for liver transplants worldwide.[27] Current treatments are based on antiviral and anti-inflammatory drugs that have high rates of nonresponders, relapse following termination of treatment, and severe and frequent adverse.[27] Daily oral supplementation of 50 chronic HCV patients over a period of 20 weeks with a combination of seven antioxidants, including silymarin, schisandra, and α-lipoic acid, was associated with improvements in liver enzymes, HCV RNA levels, histology, viral load, and quality of life.[27]

Inflammation in HCV is mediated by nuclear factor kappa B (NF-κB), which induces the release of inflammatory cytokines and chemokines.[3] A standardized silymarin extract administered to HCV patients resulted in inhibition of T-cell inflammatory cytokines, hepatocyte NF-κB signalling, and HCV infection in vivo.[3]

A number of studies have reported a positive relationship between serum iron markers — including serum ferritin — and HCV mortality, and this correlation is thought to be a reflection of the release of iron and ferritin from damaged hepatocytes.[4] Furthermore, excess iron is detrimental to the liver through the formation of reactive oxygen species (ROS), leading to fibrogenesis and inflammation of the liver tissue.[4] Studies in which iron depletion has been induced in HCV patients via phlebotomy have resulted in improvements in parameters of disease status, including liver histology and AST levels.[4] 37 subjects with chronic HCV were randomized to oral doses of 314, 628, and 942 mg t.i.d. milk thistle (standardized to 38.2% silybin) for 12 weeks. Significant reductions in serum ferritin were observed, with the greatest decreases occurring in patients with more advanced liver fibrosis and higher baseline values. Researchers also documented the formation of stable silybin-iron complexes, suggesting the chelation of iron in vivo as a possible mechanism of action.[4]

Hepatocellular Carcinoma (Hepatoma)

Hepatocellular carcinoma (HCC) is highly malignant[28] and a major cause of cancer-related deaths.[7] α-Lipoic acid (ALA) improves outcomes for cancer patients by increasing the activity of glutathione peroxidase and relieving oxidant stress, which has been implicated as a key perpetrator in the development and progression of cancer.[7] ALA has also been shown to have differential effects on tumour v. nontransformed cells; it is protective towards normal cells, such as neurons and hepatocytes, yet it triggers apoptosis in human cancer-cell lines.[7] Exposure of human HCC cells to ALA in vitro leads to an initial increase in ROS generation and DNA damage, activation of the p53 tumour suppressor protein and cell cycle arrest, and eventually, cancer-cell death.[7] *Cynara scolymus* has similar differential activity: it is hepatoprotective via its antioxidant activity, but has also been shown to induce apoptosis in human HCC line HepG2.[8]

Neovascularization, which enhances blood supply to support tumour growth, is a common characteristic of HCC.[6] Curcumin has received much attention for its anticarcinogenic activity, which is suggested to be due in part to its antiangiogenic effects.[28] This hypothesis was studied in vivo using a mouse model in which human HCC cells were implanted into the dorsal skin-fold chambers, and the animals were then fed daily oral doses of curcumin at 300 mg/kg. This study confirmed the antiangiogenic and antiproliferative effects of curcumin; along with previous research documenting its ability to suppress nuclear factor kappa B (NF-κB)-mediated inflammation, this research provides a basis for both the direct and indirect anticarcinogenic activity of curcumin.[28]

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