# Liver GB+™

**Author**: Joseph Katzinger, ND

Active Ingredients: Artichoke (Cynara cardunculus L. or Cynara scolymus L.) leaves extract, 250 mg per serving; Siliphos® complex (Milk thistle fruit extract, phosphatidylcholine from sunflower lecithin) (AKA Siliphos® Milk thistle fruit extract), standardized to ~30% Silybin, 240 mg per serving; Turmeric (Curcuma longa) extract (root, 95% curcumin), 150 mg per serving; TUDCA (Tauroursodeoxycholic acid), 100 mg per serving; Tangerine extract (Chen Pi (Citrus reticulata)) (peel, 10:1), 100 mg per serving; Ginger (Zingiber officinale) extract (root, 5% gingerols), 50 mg per serving; Bupleurum (Bupleurum chinense) extract (root, 10:1), 25 mg per serving.

# Overview

Liver GB+™ is a unique combination of six botanicals and the bile acid tauroursodeoxycholic acid, formulated to support healthy liver and gallbladder function, promote optimal digestion and detoxification, and protect the liver from multiple endogenous and exogenous toxins. The liver performs vital functions that influence activities and systems throughout the body, including the modulation of insulin sensitivity, lipid and energy metabolism, microbiome composition, intestinal barrier function, and the immune and cardiovascular systems. Despite an increase in the prevalence of environmental toxins and metabolic liver disease, very few therapies support liver function and protect it from injury.[1,2]

Many of the botanicals in Liver GB+™ have proven efficacy as hepatoprotective agents, reducing markers of liver injury, inflammation, and oxidative stress. Many have been used traditionally to improve stagnant Qi. In addition, they have a robust evidence base for their ability to reduce cholestasis by supporting bile secretion and flow, to directly improve antioxidant status and upregulate antioxidant enzyme expression, and to protect the liver from various types of injury ranging from pollutants such as bisphenol A to the endogenous injury associated with metabolic disease and diabetes. Rich in bioactive compounds, the components in Liver GB+™ have complementary effects, including protection of the intestinal barrier and restoration of tight junctions; improving symptoms of dyspepsia by supporting digestive function, bile secretion, and gallbladder activity; and promoting liver protection, detoxification, repair, and regeneration.

[1] Mardinoglu A, Boren J, Smith U, et al. Systems biology in hepatology: approaches and applications. Nat Rev Gastroenterol Hepatol. 2018 Jun;15(6):365-377.

[2] Wahlang B, Appana S, Falkner KC, et al. Insecticide and metal exposures are associated with a surrogate biomarker for non-alcoholic fatty liver disease in the National Health and Nutrition Examination Survey 2003-2004. Environ Sci Pollut Res Int. 2020 Feb;27(6):6476-6487.

# Active Ingredients

## Artichoke (*Cynara cardunculus L.* or *Cynara scolymus L.*) leaves extract

**Scientific Evidence:**

Artichoke leaves contain many bioactive compounds that contribute to their antioxidant, anti-inflammatory, hepatoprotective, and choleretic (promoting bile secretion) properties. They contain flavonoid derivatives of luteolin and apigenin, sesquiterpene lactones such as chloropicrin, and polyphenols, including chlorogenic acid (CLA) and cynarin (1,3-di-caffeoylquinic acid).[3] Many of the traditional uses of artichoke, such as regulating stagnant liver Qi, promoting bile flow, and as a hepatoprotective agent, have been validated in modern studies and attributed to the polyphenols found in artichoke leaves.[4,5] Impaired hepatobiliary production and bile excretion results in cholestasis, an inflammatory process in which an accumulation of bile acids in the liver causes cytotoxic injury to both bile ducts and hepatocytes and may interrupt a host of processes mediated by bile acids, from digestion and absorption of lipids to the catabolism of cholesterol and the regulation of glucose and energy metabolism.[6,7] In a double-blind placebo-controlled crossover trial, artichoke extracts (administered intraduodenally) were shown to significantly increase bile secretion compared to placebo, with an increase of over 150% relative to baseline.[8] An increase in choleretic activity has also been observed in animal studies, with effects similar to dehydrocholic acid (DHCA).[9]

Artichoke extracts have also exhibited hepatoprotective properties, partly attributed to the antioxidant activity of its polyphenols. An *in vitro* study indicated that artichoke extracts could prevent the formation of malondialdehyde (a marker for lipid peroxidation) in hepatocytes exposed to hydroperoxide, with a concentration-dependent effect. Artichoke extracts also prevented hepatic necrosis and the depletion of glutathione (GSH), a critical antioxidant that itself promotes bile flow and hepatic detoxification.[10,11] Another animal-based experiment indicated that artichoke extracts were able

---

[3] Porro C, Benameur T, Cianciulli A, et al. Functional and Therapeutic Potential of Cynara scolymus in Health Benefits. Nutrients. 2024 Mar 17;16(6):872.

[4] Zhao YM, Wang CD, Zhang R, et al. [Study on literature of artichoke and properties of traditional Chinese medicine]. Zhongguo Zhong Yao Za Zhi. 2020 Jul;45(14):3481-3488.

[5] Speroni E, Cervellati R, Govoni P, et al. Efficacy of different Cynara scolymus preparations on liver complaints. J Ethnopharmacol. 2003 Jun;86(2-3):203-11.

[6] Hirschfield GM, Heathcote EJ, Gershwin ME. Pathogenesis of cholestatic liver disease and therapeutic approaches. Gastroenterology. 2010 Nov;139(5):1481-96.

[7] Di Ciaula A, Garruti G, Lunardi Baccetto R, et al. Bile Acid Physiology. Ann Hepatol. 2017 Nov;16(Suppl. 1: s3-105.):s4-s14.

[8] Kirchhoff R, Beckers C, Kirchhoff GM, et al. Increase in choleresis by means of artichoke extract. Phytomedicine. 1994 Sep;1(2):107-15.

[9] Saénz Rodriguez T, García Giménez D, de la Puerta Vázquez R. Choleretic activity and biliary elimination of lipids and bile acids induced by an artichoke leaf extract in rats. Phytomedicine. 2002 Dec;9(8):687-93.

[10] Gebhardt R. Antioxidative and protective properties of extracts from leaves of the artichoke (Cynara scolymus L.) against hydroperoxide-induced oxidative stress in cultured rat hepatocytes. Toxicol Appl Pharmacol. 1997 Jun;144(2):279-86.

[11] Grattagliano I, Portincasa P, Palmieri VO, et al. Contribution of canalicular glutathione efflux to bile formation. From cholestasis associated alterations to pharmacological intervention to modify bile flow. Curr Drug Targets Immune Endocr Metabol Disord. 2005 Jun;5(2):153-61.

to increase GSH levels prior to exposure to carbon tetrachloride and significantly reduce biomarkers for hepatic injury – including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and superoxide dismutase (SOD) activity – after exposure compared to control.[12] An *ex vivo* trial demonstrated that human hepatocytes were protected against lipotoxic stress (palmitate-induced) when exposed to human serum enriched with metabolites of artichoke extract.[13]

The hepatoprotective effects of artichoke leaves have been partially attributed to their antioxidant phenolic compounds, such as CLA and luteolin, but artichoke extract may also induce an upregulation in antioxidant gene expression.[14,15] For example, an *in vitro* study found that artichoke extract prevented TNF-α-induced NF-κB inflammation in a model of acute intestinal inflammation (using Caco-2 cells), and improved antioxidant status via upregulating the Nrf2 (nuclear factor erythroid 2-related factor 2) transcription factor.[16] Nrf2 is the primary regulator of the expression of several antioxidant and phase 2 detoxifying enzymes, including glutathione-S-transferase, NAD(P)H quinone oxidoreductase 1, and heme oxygenase-1.[17] The upregulation of Nrf2 has been associated with improved intestinal immune function, barrier integrity, and reduced mucosal injury and inflammation.[18,19] Evidence for an additional protective effect of artichoke on the intestinal barrier was provided in an *in vitro* trial, also with Caco-2 cells, which found that it improved intestinal barrier function and promoted recovery of tight junctions, attributed to an activation of AMP-activated protein kinase (AMPK).[20]

Many clinical trials have been conducted with extracts from artichoke leaves, demonstrating hepatoprotective effects and improvement in related symptoms. For example, a randomized and double-blind clinical trial that enrolled nearly 250 participants with dyspepsia (often attributed to impaired bile secretion) found a significant reduction in symptoms compared to placebo, as well as an improvement in disease-specific quality of life, when receiving artichoke extract.[21] A randomized and double-blind clinical trial with 100 participants with ultrasound-diagnosed non-alcoholic fatty liver disease (NAFLD) found that artichoke extract significantly improved both liver ultrasound and serum

---

[12] Florek E, Szukalska M, Markiewicz K, et al. Evaluation of the Protective and Regenerative Properties of Commercially Available Artichoke Leaf Powder Extract on Plasma and Liver Oxidative Stress Parameters. Antioxidants (Basel). 2023 Oct 11;12(10):1846.

[13] Wauquier F, Boutin-Wittrant L, Viret A, et al. Metabolic and Anti-Inflammatory Protective Properties of Human Enriched Serum Following Artichoke Leaf Extract Absorption: Results from an Innovative Ex Vivo Clinical Trial. Nutrients. 2021 Jul 30;13(8):2653.

[14] Llorach R, Espín JC, Tomás-Barberán FA, et al. Artichoke (Cynara scolymus L.) byproducts as a potential source of health-promoting antioxidant phenolics. J Agric Food Chem. 2002 Jun 5;50(12):3458-64.

[15] Singh AK, Singla RK, Pandey AK. Chlorogenic Acid: A Dietary Phenolic Acid with Promising Pharmacotherapeutic Potential. Curr Med Chem. 2023;30(34):3905-3926.

[16] Speciale A, Muscarà C, Molonia MS, et al. In Vitro Protective Effects of a Standardized Extract From Cynara Cardunculus L. Leaves Against TNF-α-Induced Intestinal Inflammation. Front Pharmacol. 2022 Feb 11;13:809938.

[17] Xiao JL, Liu HY, Sun CC, et al. Regulation of Keap1-Nrf2 signaling in health and diseases. Mol Biol Rep. 2024 Jul 13;51(1):809.

[18] Wen Z, Liu W, Li X, et al. A Protective Role of the NRF2-Keap1 Pathway in Maintaining Intestinal Barrier Function. Oxid Med Cell Longev. 2019 Jun 26;2019:1759149.

[19] Yanaka A. Contribution of NRF2 in Gastrointestinal Protection from Oxidative Injury. Curr Pharm Des. 2018;24(18):2023-2033.

[20] Muscarà C, Speciale A, Molonia MS, et al. Intestinal epithelial differentiation and barrier function is promoted in vitro by a Cynara cardunculus L. leaf extract through AMPK pathway activation. Nat Prod Res. 2024 Jul 26:1-11.

[21] Holtmann G, Adam B, Haag S, et al. Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial. Aliment Pharmacol Ther. 2003 Dec;18(11-12):1099-105.

parameters, including increased hepatic flow, reduced ALT, AST, and lipids (total and LDL-cholesterol (LDL-C), and triglycerides).[22]

A meta-analysis of 5 randomized trials among people with NAFLD confirmed artichoke's ability to reduce markers of hepatic damage and lipids, suggesting a hepatoprotective effect, at least among this population.[23] Multiple meta-analyses of randomized clinical trials indicate that artichoke extracts reduce AST and ALT among people with and without NAFLD.[24,25] An artichoke-induced increase in bile secretion likely has a lipid-lowering effect, given that bile acid synthesis is the primary pathway for cholesterol catabolism. This is supported by a meta-analysis of 9 randomized clinical trials with over 700 participants, indicating that artichoke extracts significantly lower triglycerides and total and LDL-C without affecting HDL cholesterol (HDL-C). The degree of LDL-C reduction was positively associated with baseline levels.[26] Additionally, a pooled analysis of nine randomized and controlled trials demonstrated a significant reduction in fasting blood sugar with artichoke extract supplementation, though other glycemic indices were unchanged.[27] However, a randomized clinical trial among overweight participants with impaired fasting glucose found that artichoke extract also significantly improved the Homeostatic Metabolic Assessment (HOMA) and glycosylated hemoglobin in this population.[28]

## Siliphos® complex (Milk thistle fruit extract)

**Scientific Evidence:**

*Silybum marianum,* commonly known as milk thistle, is widely regarded for its hepatoprotective and anti-fibrotic properties, providing protection of the liver cell membrane and promoting liver repair and regeneration.[29] The biological effects of milk thistle are attributed to a group of flavonolignans found in its fruit, collectively known as silymarin, of which silybin is the chief constituent (as well as dehydrosilybin, isosilybin, silydianin, and silicristin). Silybin occurs as two trans-diastereomers, silybin A and silybin B, together known as silibinin (the terms silybin and silibinin are often used interchangeably).

Silymarin has multiple mechanisms for protecting hepatocytes and promoting their repair and regeneration, including inhibition of de novo lipogenesis, upregulation of thioredoxin, sirtuins, and the

[22] Panahi Y, Kianpour P, Mohtashami R, et al. Efficacy of artichoke leaf extract in non-alcoholic fatty liver disease: A pilot double-blind randomized controlled trial. Phytother Res. 2018 Jul;32(7):1382-1387.

[23] Kamel AM, Farag MA. Therapeutic Potential of Artichoke in the Treatment of Fatty Liver: A Systematic Review and Meta-Analysis. J Med Food. 2022 Oct;25(10):931-942.

[24] Moradi S, Shokri-Mashhadi N, Saraf-Bank S, et al. The effects of Cynara scolymus L. supplementation on liver enzymes: A systematic review and meta-analysis. Int J Clin Pract. 2021 Nov;75(11):e14726.

[25] Amini MR, Sheikhhossein F, Talebyan A, et al. Effects of Artichoke Supplementation on Liver Enzymes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Nutr Res. 2022 Jul 25;11(3):228-239.

[26] Sahebkar A, Pirro M, Banach M, et al. Lipid-lowering activity of artichoke extracts: A systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2018;58(15):2549-2556.

[27] Jalili C, Moradi S, Babaei A, et al. Effects of Cynara scolymus L. on glycemic indices: A systematic review and meta-analysis of randomized clinical trials. Complement Ther Med. 2020 Aug;52:102496.

[28] Rondanelli M, Opizzi A, Faliva M, et al. Metabolic management in overweight subjects with naive impaired fasting glycaemia by means of a highly standardized extract from Cynara scolymus: a double-blind, placebo-controlled, randomized clinical trial. Phytother Res. 2014 Jan;28(1):33-41.

[29] Zhang X, Liu M, Wang Z, et al. A review of the botany, phytochemistry, pharmacology, synthetic biology and comprehensive utilization of Silybum marianum. Front Pharmacol. 2024 Jul 11;15:1417655.

bile salt export pump, and exerting an anti-fibrotic effect on stellate cells in myofibroblasts.[30,31,32] Silymarin also protects against multiple exogenous toxins, mediated in part by activation of Nrf2.[33,34] Silibinin, specifically, has demonstrated antioxidant and anti-inflammatory properties in LPS-stimulated human monocytes through an inhibitory effect on hydrogen peroxide release and tumor necrosis factor-alpha (TNFα) production.[35] Silybin's anti-inflammatory targets may also include the NLRP3 inflammasome, with several models citing an inhibition of NF-κB and NLRP3 signaling pathways, both involved in multiple inflammatory conditions including NAFLD and diabetes.[36,37,38] Silibinin has also been shown to improve the insulin resistance associated with NAFLD in animal models through several pathways, including upregulated adiponectin expression, decreased resistin expression, inhibition of NF-κB, etc., marked by improvements in HOMA.[39] *In vitro* data also has demonstrated protection of hepatic cells against both ethanol and acetaldehyde-induced ferroptosis by silibinin, as well as recovery of mitochondrial function following exposure.[40,41] Despite its many favorable effects, the largest clinical limitation of silymarin and its constituents has been poor bioavailability.[31]

Siliphos® is a lipophilic complex (phytosome) of silybin and phosphatidylcholine in a 1:1 molar ratio, designed to enhance the absorption of silybin. Initial experimental animal data found that neither silybin nor silymarin in isolation was well absorbed, yet Siliphos® increased plasma levels of silybin, with a 10-fold greater bioavailability than isolated silymarin.[42,43] Similar trials in humans found Siliphos® to have nearly 5-fold greater bioavailability on average than silymarin, allowing for as much as several-fold

[30] Federico A, Dallio M, Loguercio C. Silymarin/Silybin and Chronic Liver Disease: A Marriage of Many Years. Molecules. 2017 Jan 24;22(2):191.

[31] Tighe SP, Akhtar D, Iqbal U, et al. Chronic Liver Disease and Silymarin: A Biochemical and Clinical Review. J Clin Transl Hepatol. 2020 Dec 28;8(4):454-458.

[32] Cui CX, Deng JN, Yan L, et al. Silibinin Capsules improves high fat diet-induced nonalcoholic fatty liver disease in hamsters through modifying hepatic de novo lipogenesis and fatty acid oxidation. J Ethnopharmacol. 2017 Aug 17;208:24-35.

[33] Jee SC, Kim M, Sung JS. Modulatory Effects of Silymarin on Benzo[a]pyrene-Induced Hepatotoxicity. Int J Mol Sci. 2020 Mar 30;21(7):2369.

[34] Kiruthiga PV, Shafreen RB, et al. Silymarin protection against major reactive oxygen species released by environmental toxins: exogenous H2O2 exposure in erythrocytes. Basic Clin Pharmacol Toxicol. 2007 Jun;100(6):414-9.

[35] Bannwart CF, Peracoli JC, Nakaira-Takahagi E, et al. Inhibitory effect of silibinin on tumour necrosis factor-alpha and hydrogen peroxide production by human monocytes. Nat Prod Res. Nov 2010;24(18):1747-1757.

[36] Tian L, Li W, Wang T. Therapeutic effects of silibinin on LPS-induced acute lung injury by inhibiting NLRP3 and NF-κB signaling pathways. Microb Pathog. 2017 Jul;108:104-108.

[37] Zhang B, Wang B, Cao S, et al. Silybin attenuates LPS-induced lung injury in mice by inhibiting NF-κB signaling and NLRP3 activation. Int J Mol Med. 2017 May;39(5):1111-1118.

[38] Matias ML, Gomes VJ, Romao-Veiga M, et al. Silibinin Downregulates the NF-κB Pathway and NLRP1/NLRP3 Inflammasomes in Monocytes from Pregnant Women with Preeclampsia. Molecules. 2019 Apr 19;24(8):1548.

[39] MacDonald-Ramos K, Michán L, Martínez-Ibarra A, et al. Silymarin is an ally against insulin resistance: A review. Ann Hepatol. 2021 Jul-Aug;23:100255.

[40] Song XY, Liu PC, Liu WW, et al. Silibinin inhibits ethanol- or acetaldehyde-induced ferroptosis in liver cell lines. Toxicol In Vitro. 2022 Aug;82:105388.

[41] Song XY, Liu PC, Liu WW, et al. Protective effects of silibinin against ethanol- or acetaldehyde-caused damage in liver cell lines involve the repression of mitochondrial fission. Toxicol In Vitro. 2022 Apr;80:105330.

[42] Morazzoni P, Magistretti MJ, Giachetti C, et al. Comparative bioavailability of Silipide, a new flavanolignan complex, in rats. Eur J Drug Metab Pharmacokinet. 1992 Jan-Mar;17(1):39-44.

[43] Morazzoni P, Montalbetti A, Malandrino S, et al. Comparative pharmacokinetics of silipide and silymarin in rats. Eur J Drug Metab Pharmacokinet. 1993 Jul-Sep;18(3):289-97.

higher peak plasma levels and higher bile concentrations (indicating significantly greater liver exposure).[44,45,46]

In clinical trials, Siliphos® has demonstrated an ability to improve markers of hepatic damage and liver function among people with chronic hepatitis. In an open-label trial, Siliphos® was shown to significantly reduce markers of liver damage (AST and ALT), markedly reduce lipid peroxidation (indicated by serum malondialdehyde), and improve the metabolic capacity of the liver (galactose elimination capacity test) among participants with chronic viral hepatitis.[47,48] A small trial that enrolled participants with chronic, active hepatitis cited significant reductions in AST, ALT, γ-GT (γ-glutamyl transpeptidase), and total bilirubin levels after only one week of supplementation with Siliphos® compared to placebo.[49] In a phase II trial, 60 participants with biopsy-proven chronic hepatitis (with a viral or alcoholic etiology) were given 1 of 3 doses of Siliphos®. After only two weeks of treatment, significant reductions in AST, ALT, and γ-GT were observed, especially at the two higher doses of 240 - 360 mg per day.[50] A longer trial enrolling people with chronic hepatitis C found that in the majority of participants, Siliphos® lowered ferritin levels (often elevated because of release from damaged hepatocytes), especially in those with advanced fibrosis.[51] Phosphatidylcholine, part of the Siliphos® phytosome, is an essential phospholipid also recognized to have hepatoprotective, antioxidative, and antifibrotic properties, and is associated with clinical and objective improvements among people with NAFLD.[52,53]

Extensive clinical data also exists for the beneficial effects of silymarin and silybin supplementation among people with NAFLD. A systematic review of eight randomized trials of participants with NAFLD found a significant reduction in transaminase levels with silymarin use, and a second meta-analysis points to a general improvement in the glycemic profile of participants with

[44] Barzaghi N, Crema F, Gatti G, et al. Pharmacokinetic studies on IdB 1016, a silybin- phosphatidylcholine complex, in healthy human subjects. Eur J Drug Metab Pharmacokinet. 1990 Oct-Dec;15(4):333-8.

[45] Schandalik R, Gatti G, Perucca E. Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. Arzneimittelforschung. 1992 Jul;42(7):964-8.

[46] Orlando R, Fragasso A, Lampertico M, et al. Silybin kinetics in patients with liver cirrhosis: a comparative study of a silybin-phosphatidylcholine complex and silymarin. Metab Sci Res. 1990;18:861–863.

[47] Munk DE, Björklund J, Lund Laursen T, et al. The galactose elimination capacity test to monitor liver disease course in patients with Wilson's disease. Scand J Gastroenterol. 2022 May;57(5):589-594.

[48] Moscarella S, Giusti A, Marra F, et al. Therapeutic and antilipoperoxidant effects of silybin-phosphatidylcholine complex in chronic liver disease: Preliminary results. Current Therapeutic Research. 1993. Vol. 53(1):98-102.

[49] Buzzelli G, Moscarella S, Giusti A, et al. A pilot study on the liver protective effect of silybin-phosphatidylcholine complex (IdB1016) in chronic active hepatitis. Int J Clin Pharmacol Ther Toxicol. 1993 Sep;31(9):456-60.

[50] Vailati A, Aristia L, Sozze E, et al. Randomized open study of the dose-effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis. Fitoterapia. 1993;64:219–231.

[51] Bares JM, Berger J, Nelson JE, et al. Silybin treatment is associated with reduction in serum ferritin in patients with chronic hepatitis C. J Clin Gastroenterol. 2008 Sep;42(8):937-44.

[52] Maev IV, Samsonov AA, Palgova LK, et al. Real-world comorbidities and treatment patterns among patients with non-alcoholic fatty liver disease receiving phosphatidylcholine as adjunctive therapy in Russia. BMJ Open Gastroenterol. 2019 Aug 18;6(1):e000307.

[53] Dajani AI, Popovic B. Essential phospholipids for nonalcoholic fatty liver disease associated with metabolic syndrome: A systematic review and network meta-analysis. World J Clin Cases. 2020 Nov 6;8(21):5235-5249.

glucose or lipid abnormalities.[54,55] Yet another systematic review of 26 randomized and controlled trials (including nearly 2400 participants) concluded that silymarin supplementation had a wide variety of benefits, including significant reductions in triglyceride, LDL-C, HOMA-IR, fasting insulin and glucose levels; improvements in markers of fatty liver and hepatic steatosis, and BMI. These findings strongly suggest that silymarin helps regulate energy metabolism, attenuate liver damage, and improve liver histology.[56]

Silymarin supplementation was also associated with an improvement in antioxidant levels and total antioxidant capacity, as well as reduced inflammation in a triple-blind trial of participants with diabetes.[57] It may also favorably modulate the gut microbiome, as indicated by a 24-week randomized, double-blind, placebo-controlled trial that enrolled participants with metabolic dysfunction-associated steatotic liver disease (MASLD). Supplementation significantly reduced liver stiffness and serum levels of γ-GT, associated with increased species diversity and abundance of *Oscillospiraceae*.[58]

## Turmeric (*Curcuma longa*) extract (95% curcumin)

**Scientific Evidence:**

The main constituents of turmeric include volatile oils (natlantone, tumerone, and zingiberone) and curcuminoids (curcumin, demethoxycurcumin, cyclocurcumin, and bisdemethoxycurcumin), as well as proteins, sugars, and resins.[59] While the bulk of published research has been focused on curcumin, there is evidence that other components found in turmeric root also have important biological actions. For example, bisdemethoxycurcumin has been shown to induce apoptosis in activated hepatic stellate cells (fibrogenic cells in the liver) more effectively than curcumin, and to help protect gastrointestinal integrity in animal studies.[60,61] Demethoxycurcumin has been found to help preserve endothelial function, inhibit COX-2 expression and NF-κB activation,

[54] Kalopitas G, Antza C, Doundoulakis I, et al. Impact of Silymarin in individuals with nonalcoholic fatty liver disease: A systematic review and meta-analysis. Nutrition. 2021 Mar;83:111092.
[55] Xiao F, Gao F, Zhou S, Wang L. The therapeutic effects of silymarin for patients with glucose/lipid metabolic dysfunction: A meta-analysis. Medicine (Baltimore). 2020 Oct 2;99(40):e22249.
[56] Li S, Duan F, Li S, et al. Administration of silymarin in NAFLD/NASH: A systematic review and meta-analysis. Ann Hepatol. 2024 Mar-Apr;29(2):101174.
[57] Ebrahimpour Koujan S, Gargari BP, Mobasseri M, et al. Effects of Silybum marianum (L.) Gaertn. (silymarin) extract supplementation on antioxidant status and hs-CRP in patients with type 2 diabetes mellitus: a randomized, triple-blind, placebo-controlled clinical trial. Phytomedicine. 2015 Feb 15;22(2):290-6.
[58] Jin Y, Wang X, Chen K, et al. Silymarin decreases liver stiffness associated with gut microbiota in patients with metabolic dysfunction-associated steatotic liver disease: a randomized, double-blind, placebo-controlled trial. Lipids Health Dis. 2024 Aug 3;23(1):239.
[59] He Y, Yue Y, Zheng X, et al. Curcumin, inflammation, and chronic diseases: how are they linked? Molecules. 2015 May 20;20(5):9183-213.
[60] Lee PJ, Woo SJ, Jee JG, Sung SH, Kim HP. Bisdemethoxycurcumin Induces apoptosis in activated hepatic stellate cells via cannabinoid receptor 2. Molecules. 2015 Jan 14;20(1):1277-92.
[61] Zhang J, Yang Y, Han H, et al. Bisdemethoxycurcumin attenuates lipopolysaccharide-induced intestinal damage through improving barrier integrity, suppressing inflammation, and modulating gut microbiota in broilers. J Anim Sci. 2021 Nov 1;99(11):skab296.

and increase the expression of antioxidant enzymes in animal models and *in vitro*.[62]

Curcumin, sometimes referred to as the golden nutrient, has clearly been shown to target many signaling pathways and possesses many biological actions, including antioxidant, anti-inflammatory, antiarthritic, anti-atherosclerotic, antimicrobial, and wound healing activities.[63] It also has demonstrated an ability to both protect the liver from injury and promote contraction of the gallbladder, even at low doses. For example, a randomized, double-blind, and crossover study that enrolled a small number of healthy adults found that a single dose of 20mg curcumin reduced gallbladder volume by nearly 30%, in contrast to an increase in volume observed following a placebo.[64] A subsequent study found that a 40mg dose was associated with a 50% reduction in gallbladder volume, indicating a significant cholekinetic effect.[65] Curcumin has also demonstrated a protective effect against a variety of liver injuries in animal studies, including aflatoxins, excessive iron, ethanol, cholestasis, and carbon tetrachloride.[66]

Curcumin targets transcription factors, inflammatory mediators, and protein kinases and enzymes, with targets including Nrf2, NF-κB, p38 MAPK, COX-2, 5-lipoxygenase, PGE2, FOXO3, inducible NOS, and TNF-α.[63] Curcumin has multiple anti-inflammatory actions, including decreasing the expression of NF-κB by acting on peroxisome proliferator-activated receptor gamma (PPARγ) and inhibiting the assembly of the NLRP3 inflammasome.[67,68] The pro-inflammatory pathway associated with activation of the NLRP3 inflammasome has been associated with multiple inflammatory disease states, including stroke, pre-eclampsia, autoimmune, and cardiometabolic diseases, and may be one mechanism by which curcumin mitigates tissue damage.[69,70,71] NLRP3 has been strongly associated with the development of NASH (non-alcoholic steatohepatitis), and a recent trial with over 200 participants strongly implicated NLRP3 inflammasomes in MAFLD (metabolic-associated fatty liver disease) pathogenesis.[72] In animal studies, curcumin has demonstrated hepatoprotective properties against aflatoxin in part by preventing NLRP3 activation, as well as by activating Nrf2 and glutathione

---

[62] Hatamipour M, Ramezani M, Tabassi SAS, et al. Demethoxycurcumin: A naturally occurring curcumin analogue for treating non-cancerous diseases. J Cell Physiol. 2019 Nov;234(11):19320-19330.

[63] Kunnumakkara AB, Bordoloi D, Padmavathi G, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. Br J Pharmacol. 2017 Jun;174(11):1325-1348.

[64] He Y, Yue Y, Zheng X, et al. Curcumin, inflammation, and chronic diseases: how are they linked? Molecules. 2015 May 20;20(5):9183-213.

[65] Rasyid A, Rahman AR, Jaalam K, et al. Effect of different curcumin dosages on human gall bladder. Asia Pac J Clin Nutr. 2002;11(4):314-8.

[66] Rivera-Espinoza Y, Muriel P. Pharmacological actions of curcumin in liver diseases or damage. Liver Int. 2009 Nov;29(10):1457-66.

[67] Zhu T, Chen Z, Chen G, et al. Curcumin Attenuates Asthmatic Airway Inflammation and Mucus Hypersecretion Involving a PPARγ-Dependent NF-κB Signaling Pathway In Vivo and In Vitro. Mediators Inflamm. 2019 Apr 3;2019:4927430.

[68] Hasanzadeh S, Read MI, Bland AR, et al. Curcumin: an inflammasome silencer. Pharmacol Res. 2020 Sep;159:104921.

[69] Nunes PR, Mattioli SV, et al. NLRP3 Activation and Its Relationship to Endothelial Dysfunction and Oxidative Stress: Implications for Preeclampsia and Pharmacological Interventions. Cells. 2021 Oct 21;10(11):2828.

[70] Zhang Y, Yang W, Li W, et al. NLRP3 Inflammasome: Checkpoint Connecting Innate and Adaptive Immunity in Autoimmune Diseases. Front Immunol. 2021 Oct 11;12:732933.

[71] Duez H, Pourcet B. Nuclear Receptors in the Control of the NLRP3 Inflammasome Pathway. Front Endocrinol (Lausanne). 2021 Feb 25;12:630536.

[72] Osman HA, Abuhamdah SMA, Hassan MH, et al. NLRP3 inflammasome pathway involved in the pathogenesis of metabolic associated fatty liver disease. Sci Rep. 2024 Aug 23;14(1):19648.

defenses.[73] Curcumin also appears to interact with the farnesoid X receptor (FXR), promoting bile acid homeostasis in an animal model of cholestasis.[74] Additionally, curcumin has been shown to mitigate the insulin resistance induced by bisphenol A, in part by preventing the induced activation of JNK and p38 pathways.[75] Animal studies indicate that curcumin protects against a variety of hepatic toxins, mediated by an increase in glutathione (GSH) levels and direct free radical scavenging.[76,77]

A broad range of clinical studies in humans has supported the use of supplemental curcumin or turmeric. Two systematic reviews of randomized controlled trials found curcumin supplementation improved several parameters in study participants with diabetes, including fasting blood glucose, HbA1c, systolic and diastolic blood pressure, and serum creatinine levels, likely through antioxidant and anti-inflammatory mechanisms.[78,79] A second systematic review of gastrointestinal disease and turmeric/curcumin supplementation found generally favorable effects on inflammatory bowel disease, irritable bowel syndrome, and peptic ulcer disease.[80] Among participants with metabolic syndrome, a range of inflammatory markers, including serum levels of TNF-α, IL-6, TGF-β, and MCP-1, were reduced with curcumin supplementation compared to placebo in a randomized and controlled trial.[81] In a second controlled trial, curcumin significantly reduced hepatic fat content compared to placebo among people with NAFLD, and results from meta-analyses generally find improved lipids and AST levels in this population.[82,83,84] Although isolated curcumin has been more heavily researched, with a recent focus on more highly absorbable forms, evidence also suggests that it is the interaction of curcumin and the gut microbiota (rather than direct curcumin absorption) that at least partly underlies its biological effects.[85]

---

[73] Wang Y, Liu F, Liu M, et al. Curcumin mitigates aflatoxin B1-induced liver injury via regulating the NLRP3 inflammasome and Nrf2 signaling pathway. Food Chem Toxicol. 2022 Jan 19;161:112823.

[74] Yang F, Tang X, Ding L, et al. Curcumin protects ANIT-induced cholestasis through signaling pathway of FXR-regulated bile acid and inflammation. Sci Rep. 2016 Sep 14;6:33052.

[75] Geng S, Wang S, Zhu W, et al. Curcumin attenuates BPA-induced insulin resistance in HepG2 cells through suppression of JNK/p38 pathways. Toxicol Lett. 2017 Apr 15;272:75-83.

[76] Varatharajalu R, Garige M, Leckey LC, et al. Protective Role of Dietary Curcumin in the Prevention of the Oxidative Stress Induced by Chronic Alcohol with respect to Hepatic Injury and Antiatherogenic Markers. Oxid Med Cell Longev. 2016;2016:5017460.

[77] Farzaei MH, Zobeiri M, Parvizi F, et al. Curcumin in Liver Diseases: A Systematic Review of the Cellular Mechanisms of Oxidative Stress and Clinical Perspective. Nutrients. 2018 Jul 1;10(7):855.

[78] Jie Z, Chao M, Jun A, et al. Effect of Curcumin on Diabetic Kidney Disease: A Systematic Review and Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Clinical Trials. Evid Based Complement Alternat Med. 2021 Dec 2;2021:6109406.

[79] Marton LT, Pescinini-E-Salzedas LM, Camargo MEC, et al. The Effects of Curcumin on Diabetes Mellitus: A Systematic Review. Front Endocrinol (Lausanne). 2021 May 3;12:669448.

[80] Atefi M, Darand M, Entezari MH, et al. A Systematic Review of the Clinical Use of Curcumin for the Management of Gastrointestinal Diseases. Adv Exp Med Biol. 2021;1291:295-326.

[81] Panahi Y, Hosseini MS, Khalili N, et al. Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. Biomed Pharmacother. 2016 Aug;82:578-82.

[82] Wei Z, Liu N, Tantai X, et al. The effects of curcumin on the metabolic parameters of non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Hepatol Int. 2019 May;13(3):302-313.

[83] Rahmani S, Asgary S, Askari G, et al. Treatment of Non-alcoholic Fatty Liver Disease with Curcumin: A Randomized Placebo-controlled Trial. Phytother Res. 2016 Sep;30(9):1540-8.

[84] Aragón-Vela J, Sánchez-Oliver AJ, Huertas JR, et al. Does curcumin improve liver enzymes levels in nonalcoholic fatty liver disease? A systematic review, meta-analysis, and meta-regression. Phytother Res. 2024 Aug;38(8):4261-4271.

[85] Scazzocchio B, Minghetti L, D'Archivio M. Interaction between Gut Microbiota and Curcumin: A New Key of Understanding for the Health Effects of Curcumin. Nutrients. 2020 Aug 19;12(9):2499.

# TUDCA (Tauroursodeoxycholic Acid)

**Scientific Evidence:**

The bile acid tauroursodeoxycholic Acid (TUDCA) is a taurine conjugate of ursodeoxycholic acid (UDCA) and is recognized to be one of the most hydrophilic and cytoprotective bile acids. UDCA is formed by microbial activity from chenodeoxycholic acid (CDCA) in the large intestine, and TUDCA is generated naturally in the liver from taurine conjugation with UDCA (upon returning via enterohepatic circulation).[86,87]

In a dose-response clinical trial, 24 participants with primary biliary cholangitis (PBC, formerly referred to as primary biliary cirrhosis, characterized by inflammation and destruction of hepatic bile ducts) received 500, 1000, or 1500 mg TUDCA daily for six months. Significant reductions in serum AST, ALT, γ-GT, and ALP (alkaline phosphatase) concentrations were observed, as well as decreases in total cholesterol and HDL-C with only the two higher doses (LDL-C was not measured, and bile acids generally increase cholesterol excretion). Bile was found to be favorably enriched with both TUDCA and UDCA. Overall, this study indicates a reduction in both cholestasis and cytolysis with TUDCA supplementation.[88]

A small cross-over study compared UDCA and TUDCA for the treatment of PBC and found no significant differences between the two treatments when given for six months each (with a 3-month washout between them).[89] A subsequent and larger, multi-center randomized trial enrolled nearly 200 participants with PBC to receive either UDCA or TUDCA. Although bile acids equally improved serum levels of ALP, AST, and total bilirubin levels, 10% of people receiving UDCA reported pruritus/scratching (increased from 1.55% at baseline); no increase was observed for TUDCA, suggesting equal efficacy with greater symptom relief. Notably, approximately 80% of people in the trial had a decline in ALP with either treatment.[90] Additionally, several randomized and controlled trials have shown a reduction in markers of hepatic damage (aminotransferases, γ-GT) among people with chronic hepatitis.[91,92]

Considerable interest in TUDCA applied to neurodegenerative diseases has also grown in recent years, in part because of its ability to protect mitochondrial membranes from damage induced by reactive oxygen species as well as other toxins (including amyloid-β) in animal and *in vitro* studies.

---

[86] Li J, Huang Z, Jin Y, et al. Neuroprotective Effect of Tauroursodeoxycholic Acid (TUDCA) on In Vitro and In Vivo Models of Retinal Disorders: A Systematic Review. Curr Neuropharmacol. 2024;22(8):1374-1390.

[87] Batta AK, Salen G, Shefer S, et al. The effect of tauroursodeoxycholic acid and taurine supplementation on biliary bile acid composition. Hepatology. 1982 Nov-Dec;2(6):811-6.

[88] Crosignani A, Battezzati PM, Setchell KD, et al. Tauroursodeoxycholic acid for treatment of primary biliary cirrhosis. A dose-response study. Dig Dis Sci. 1996 Apr;41(4):809-15.

[89] Larghi A, Crosignani A, Battezzati PM, et al. Ursodeoxycholic and tauro-ursodeoxycholic acids for the treatment of primary biliary cirrhosis: a pilot crossover study. Aliment Pharmacol Ther. 1997 Apr;11(2):409-14.

[90] Ma H, Zeng M, Han Y, et al. A multicenter, randomized, double-blind trial comparing the efficacy and safety of TUDCA and UDCA in Chinese patients with primary biliary cholangitis. Medicine (Baltimore). 2016 Nov;95(47):e5391.

[91] Crosignani A, Budillon G, Cimino L, et al. Tauroursodeoxycholic acid for the treatment of HCV-related chronic hepatitis: a multicenter placebo-controlled study. Hepatogastroenterology. 1998 Sep-Oct;45(23):1624-9.

[92] Crosignani, A Battezzati, PM, Cestari, C, et al. Tauroursodeoxycholic acid for the treatment of chronic hepatitis: a multicentre dose-response study. Hepatology research.1998 13(1),10-19.

TUDCA has also been shown to mitigate endothelial reticulum (ER) stress and prevent the unfolded protein response implicated in neurological disease as well as NAFLD-associated hepatic pathology.[93,94] In a small clinical trial, TUDCA supplementation was also shown to mitigate hyperglycemia-induced endothelial dysfunction, potentially by reducing ER stress.[95] Lastly, compared to placebo, TUDCA was shown to increase insulin sensitivity in both hepatic and muscle tissues (but not in adipose tissue) among people with obesity in a randomized and controlled clinical trial.[96]

## Tangerine extract (Chenpi (*Citrus reticulata*))

**Scientific Evidence:**

Tangerine extract is the dried, ripe fruit peel of *Citrus reticulata*, often referred to as Chenpi.[97] It has been widely used as a herbal medicine in Korea, China, and Japan to treat indigestion and inflammatory disorders, promote the circulation of qi, and soothe emotions such as anger, irritability, and frustration. It is also traditionally used for a variety of "stagnation" characteristics of qi, including food stagnation with pain and distention symptoms, indigestion, abdominal fullness and distention, as well as for drying dampness and resolving phlegm.[97,98] The main bioactive constituents of Chenpi are essential oils (D-limonene, β-myrcene, α-pinene, β-pinene α-terpineol, terpinen-4-ol, γ-terpinen, and linalool) and flavonoids (primarily hesperidin, as well as nobiletin and tangeretin).[98,99]

Unique bioflavonoids found in Chenpi termed poly-methoxy flavones (PMFs) have been shown to possess anti-inflammatory effects and to modulate lipid metabolism within adipocytes, preventing lipid accumulation.[100] Animal studies suggest that modification of the gut microbiota by PMFs may underlie this effect and that it also may protect against obesity and diabetes resulting from a high-fat

[93] Khalaf K, Tornese P, Cocco A, et al. Tauroursodeoxycholic acid: a potential therapeutic tool in neurodegenerative diseases. Transl Neurodegener. 2022 Jun 4;11(1):33.

[94] Song MJ, Malhi H. The unfolded protein response and hepatic lipid metabolism in non-alcoholic fatty liver disease. Pharmacol Ther. 2019 Nov;203:107401.

[95] Walsh LK, Restaino RM, Neuringer M, et al. Administration of tauroursodeoxycholic acid prevents endothelial dysfunction caused by an oral glucose load. Clin Sci (Lond). 2016 Nov 1;130(21):1881-8.

[96] Kars M, Yang L, Gregor MF, et al. Tauroursodeoxycholic Acid may improve liver and muscle but not adipose tissue insulin sensitivity in obese men and women. Diabetes. 2010 Aug;59(8):1899-905.

[97] Qin K, Zheng L, Cai H, et al. Characterization of Chemical Composition of Pericarpium Citri Reticulatae Volatile Oil by Comprehensive Two-Dimensional Gas Chromatography with High-Resolution Time-of-Flight Mass Spectrometry. Evid Based Complement Alternat Med. 2013;2013:237541.

[98] Yu X, Sun S, Guo Y, et al. Citri Reticulatae Pericarpium (Chenpi): Botany, ethnopharmacology, phytochemistry, and pharmacology of a frequently used traditional Chinese medicine. J Ethnopharmacol. 2018 Jun 28;220:265-282.

[99] Wang Y, Yi L, Liang Y, et al. Comparative analysis of essential oil components in Pericarpium Citri Reticulatae Viride and Pericarpium Citri Reticulatae by GC-MS combined with chemometric resolution method. J Pharm Biomed Anal. 2008 Jan 7;46(1):66-74.

[100] Vajdi M, Farhangi MA. Citrus peel-derived Poly-Methoxylated Flavones (PMF). Int J Vitam Nutr Res. 2021 May 27:1-16.

diet.[101,102] PMFs have also been shown to protect intestinal tight junctions from the damage caused by ethanol *in vitro*.[103]

The PMFs in Chenpi have also been shown to be hepatoprotective *in vitro*, with multiple biological effects, including the upregulation of Nrf2 expression.[104] Indeed, a systems pharmacology study examining the anti-liver injury mechanisms of Chenpi identified 25 active components (naringenin, hesperetin, etc.) and the pathways affected by common liver toxins. This complex analysis identified 117 genes and 25 core targets, concluding that Chenpi's primary hepatoprotection may be mediated by an influence of hesperidin and naringenin on apoptotic pathways that reduces the likelihood of liver fibrosis, in addition to inhibiting AKT1 phosphorylation by naringenin and upregulating antioxidant defenses and energy (mitochondrial) metabolism.[105] Experimental data suggests that Chenpi may protect against a variety of liver insults, including drug, alcohol, and non-alcoholic injuries.[106,107]

A second systems pharmacology-based strategy identified 39 bioactive components within Chenpi and 121 potential protein targets related to diseases of the cardiovascular system, respiratory system, and gastrointestinal system.[108] One additional target appears to be PPARγ, which is upregulated by Chenpi, an effect that has the potential to improve myocardial function, prevent atherosclerosis after diabetic cardiopathy, and reduce hepatic fat and inflammation associated with NAFLD.[109,110]

Hesperidin also appears to prevent cardiomyocyte apoptosis and mitigate oxidative damage via up-regulation of PPARγ expression.[111,112] Tangeretin has also been shown to improve adipose thermogenesis as well as the diversity of the gut microbiota in an animal model.[113] Randomized clinical trials are needed to verify many of the benefits observed *in vitro* and in animal models. However, individual components of Chenpi are gaining a stronger evidence base. For example, hesperidin

---

[101] Tung YC , Chang WT , Li S , et al. Citrus peel extracts attenuated obesity and modulated gut microbiota in mice with high-fat diet-induced obesity. Food Funct. 2018 Jun 20;9(6):3363-3373.

[102] Guo J, Tao H, Cao Y, et al. Prevention of Obesity and Type 2 Diabetes with Aged Citrus Peel (Chenpi) Extract. J Agric Food Chem. 2016 Mar 16;64(10):2053-61.

[103] Chen XM, Kitts DD. Flavonoid composition of orange peel extract ameliorates alcohol-induced tight junction dysfunction in Caco-2 monolayer. Food Chem Toxicol. 2017 Jul;105:398-406.

[104] Lin ZH, Chan YF, Pan MH, et al. Aged Citrus Peel (Chenpi) Prevents Acetaminophen-Induced Hepatotoxicity by Epigenetically Regulating Nrf2 Pathway. Am J Chin Med. 2019;47(8):1833-1851.

[105] Wu J, Ye X, Yang S, et al. Systems Pharmacology Study of the Anti-Liver Injury Mechanism of Citri Reticulatae Pericarpium. Front Pharmacol. 2021 Apr 12;12:618846.

[106] Gao S, Chen X, Yu Z, et al. Progress of research on the role of active ingredients of Citri Reticulatae Pericarpium in liver injury. Phytomedicine. 2023 Jul;115:154836.

[107] Zhang X, Jiang Y, Zeng J, et al. Phytochemistry, pharmacological properties and pharmacokinetics of Citri Reticulatae Pericarpium: A systematic review. J Ethnopharmacol. 2024 Oct 28;333:118503.

[108] Zhou W, Chen Z, Lu A, et al. Systems Pharmacology-Based Strategy to Explore the Pharmacological Mechanisms of Citrus Peel (Chenpi) for Treating Complicated Diseases. Am J Chin Med. 2021;49(2):391-411.

[109] Cheng H, Wu X, Ni G, et al. Citri Reticulatae Pericarpium protects against isoproterenol-induced chronic heart failure via activation of PPARγ. Ann Transl Med. 2020 Nov;8(21):1396.

[110] Gastaldelli A, Sabatini S, Carli F, et al. PPAR-γ-induced changes in visceral fat and adiponectin levels are associated with improvement of steatohepatitis in patients with NASH. Liver Int. 2021 Nov;41(11):2659-2670.

[111] Selvaraj P, Pugalendi KV. Hesperidin, a flavanone glycoside, on lipid peroxidation and antioxidant status in experimental myocardial ischemic rats. Redox Rep. 2010;15(5):217-23.

[112] Agrawal YO, Sharma PK, Shrivastava B, et al. Hesperidin blunts streptozotocin-isoproternol induced myocardial toxicity in rats by altering of PPAR-γ receptor. Chem Biol Interact. 2014 Aug 5;219:211-20.

[113] Chen Q, Wang D, Gu Y, et al. Tangeretin prevents obesity by modulating systemic inflammation, fat browning, and gut microbiota in high-fat diet-induced obese C57BL/6 mice. J Nutr Biochem. 2022 Jan 10;101:108943.

improved metabolism and reduced inflammation when supplemented by people with the metabolic syndrome in a randomized, double-blinded and placebo-controlled trial, marked by significant reductions in fasting glucose and triglyceride levels, systolic blood pressure, and TNF-α.[114]

## Ginger (*Zingiber officinale*) extract

**Scientific Evidence:**

Ginger has a long traditional usage for treating a variety of gastrointestinal conditions, with many bioactive compounds associated with anti-inflammatory, hepatoprotective, and digestive-stimulant effects.[115] Ginger's active constituents include volatile oils, gingerol analogues, diarylheptanoids, phenylalkanoids, and sulfonates. Over 70 compounds have been identified in the volatile oil alone, including sesquiterpenoids and monoterpenes, primarily α-zingiberene and smaller amounts of β-sesquiphellandrene, β-bisabolene, β-phellandrene, and geraniol. Ginger's spicy and warm sensations are largely attributed to gingerol analogues, including gingerols (predominantly 6-gingerol), shogaols, paradols, and zingerone.[116] Over 40 diarylheptanoid compounds have been discovered in ginger, many with antioxidant, anti-inflammatory, and hepatoprotective properties. Various components of ginger have been shown to have protective effects on the gastrointestinal, nervous, and cardiovascular systems, as well as on the liver and kidney.[116]

Many of ginger's constituents have been shown to have anti-inflammatory effects; *in vitro* and animal studies have outlined several mechanisms of action for 6-gingerol, for example, including prevention of reactive oxygen species formation, upregulation of the Nrf2 pathway, inhibition of p38 MAPK activation, down-regulation of the NF-κB pathway, and protection against LPS-induced inflammation – all of which have been associated with the protection of the intestinal mucosa and maintenance of an intact barrier.[117,118,119,120] *In vitro* studies also suggest that ginger has favorable effects on the gut microbiome, promoting the growth of beneficial bacterial populations such as *Bifidobacterium* and *Enterococcus*, as well as enhancing the production of short-chain fatty acids.[121]

---

[114] Yari Z, Movahedian M, Imani H, et al. The effect of hesperidin supplementation on metabolic profiles in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled clinical trial. Eur J Nutr. 2020 Sep;59(6):2569-2577.

[115] Crichton M, Marshall S, Marx W, et al. Therapeutic health effects of ginger (Zingiber officinale): updated narrative review exploring the mechanisms of action. Nutr Rev. 2023 Aug 10;81(9):1213-1224.

[116] Zhang M, Zhao R, Wang D, et al. Ginger (Zingiber officinale Rosc.) and its bioactive components are potential resources for health beneficial agents. Phytother Res. 2021 Feb;35(2):711-742.

[117] Li Y, Xu B, Xu M, et al. 6-Gingerol protects intestinal barrier from ischemia/reperfusion-induced damage via inhibition of p38 MAPK to NF-κB signaling. Pharmacol Res. 2017 May;119:137-148.

[118] Saha P, Katarkar A, Das B, et al. 6-Gingerol inhibits Vibrio cholerae-induced proinflammatory cytokines in intestinal epithelial cells via modulation of NF-κB. Pharm Biol. 2016 Sep;54(9):1606-15.

[119] Guo XX, Zhang YD, Wang TC, et al. Ginger and 6-gingerol prevent lipopolysaccharide-induced intestinal barrier damage and liver injury in mice. J Sci Food Agric. 2022 Feb;102(3):1066-1075.

[120] Hong MK, Hu LL, Zhang YX, et al. 6-Gingerol ameliorates sepsis-induced liver injury through the Nrf2 pathway. Int Immunopharmacol. 2020 Mar;80:106196.

[121] Wang J, Chen Y, Hu X, et al. Assessing the Effects of Ginger Extract on Polyphenol Profiles and the Subsequent Impact on the Fecal Microbiota by Simulating Digestion and Fermentation In Vitro. Nutrients. 2020 Oct 19;12(10):3194.

Animal models also indicate reductions at the genus level in *Escherichia, Shigella,* and *Bacteroides* despite overall increases in bacterial diversity, as well as restoration of the tight junction protein, zonula occludens-1 (ZO-1).[122]

Ginger is well-recognized for its ability to improve many digestive symptoms, partly attributed to an acceleration of gastric emptying and stimulation of antral contractions, helping to improve digestion within the stomach.[123] For example, several clinical trials have shown that ginger supplementation enhances gastric emptying in healthy people, those with functional dyspepsia, and patients hospitalized with acute respiratory distress syndrome.[124,125,126] In a randomized and placebo-controlled clinical trial, a combination of ginger and artichoke leaf extracts significantly improved symptoms of dyspepsia, including nausea, epigastric fullness and pain, and bloating, within a 4-week period.[127]

Ginger's effectiveness for nausea relief is well established, and several mechanisms of action likely underlie ginger's anti-emetic effects, though 5-$HT_3$ receptor antagonism is perhaps the strongest candidate.[128] Interestingly, these receptors have recently been linked to inflammatory and metabolic disorders, providing another pathway for ginger's broad effects.[129] The anti-emetic and anti-nausea activities of ginger have been demonstrated in numerous clinical trials and assessed in several systematic reviews and meta-analyses, demonstrating efficacy during pregnancy, post-operatively, and for nausea/vomiting associated with chemotherapy.[130,131,132,133]

Ginger's anti-inflammatory actions may also underlie its benefit for other body systems. Among people with migraines, a meta-analysis of three randomized clinical trials found that in addition to a reduction in nausea and vomiting, ginger was associated with a significant decrease in pain.[134] A

---

[122] Ma ZJ , Wang HJ , Ma XJ , et al. Modulation of gut microbiota and intestinal barrier function during alleviation of antibiotic-associated diarrhea with Rhizoma Zingiber officinale (Ginger) extract. Food Funct. 2020 Dec 1;11(12):10839-10851.

[123] Nikkhah Bodagh M, Maleki I, Hekmatdoost A. Ginger in gastrointestinal disorders: A systematic review of clinical trials. Food Sci Nutr. 2018 Nov 5;7(1):96-108.

[124] Wu KL, Rayner CK, Chuah SK, et al. Effects of ginger on gastric emptying and motility in healthy humans. Eur J Gastroenterol Hepatol. 2008 May;20(5):436-40.

[125] Hu ML, Rayner CK, Wu KL, et al. Effect of ginger on gastric motility and symptoms of functional dyspepsia. World J Gastroenterol. 2011 Jan 7;17(1):105-10.

[126] Shariatpanahi ZV, Taleban FA, Mokhtari M, et al. Ginger extract reduces delayed gastric emptying and nosocomial pneumonia in adult respiratory distress syndrome patients hospitalized in an intensive care unit. J Crit Care. 2010 Dec;25(4):647-50.

[127] Giacosa A, Guido D, Grassi M, et al. The Effect of Ginger (Zingiber officinalis) and Artichoke (Cynara cardunculus) Extract Supplementation on Functional Dyspepsia: A Randomised, Double-Blind, and Placebo-Controlled Clinical Trial. Evid Based Complement Alternat Med. 2015;2015:915087.

[128] Walstab J, Krüger D, Stark T, et al. Ginger and its pungent constituents non-competitively inhibit activation of human recombinant and native 5-HT3 receptors of enteric neurons. Neurogastroenterol Motil. 2013 May;25(5):439-47, e302.

[129] Irving H, Turek I, Kettle C, et al. Tapping into 5-HT3 Receptors to Modify Metabolic and Immune Responses. Int J Mol Sci. 2021 Nov 2;22(21):11910.

[130] Viljoen E, Visser J, Koen N, et al. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J. 2014 Mar 19;13:20.

[131] Thomson M, Corbin R, Leung L. Effects of ginger for nausea and vomiting in early pregnancy: a meta-analysis. J Am Board Fam Med. 2014 Jan-Feb;27(1):115-22.

[132] Zhu W, Dai Y, Huang M, et al. Efficacy of Ginger in Preventing Postoperative Nausea and Vomiting: A Systematic Review and Meta-Analysis. J Nurs Scholarsh. 2021 Nov;53(6):671-679.

[133] Chang WP, Peng YX. Does the Oral Administration of Ginger Reduce Chemotherapy-Induced Nausea and Vomiting?: A Meta-analysis of 10 Randomized Controlled Trials. Cancer Nurs. 2019 Nov/Dec;42(6):E14-E23.

[134] Chen L, Cai Z. The efficacy of ginger for the treatment of migraine: A meta-analysis of randomized controlled studies. Am J Emerg Med. 2021 Aug;46:567-571.

systematic review of 16 randomized and controlled trials found a significant reduction in several biomarkers of inflammation, including CRP, hs-CRP, and TNF-α, with ginger supplementation.[135] In addition to a hypotensive effect, an increase in nitric oxide synthesis expression, and inhibition of platelet aggregation, this anti-inflammatory effect provides a plausible explanation for enhanced cardiovascular health attributed to ginger consumption.[136,137]

Ginger has been associated with hypoglycemic effects and an improvement in the metabolic profile of people with diabetes. In a systematic review of randomized and controlled trials among people with Type 2 diabetes, ginger supplementation was associated with reductions in fasting blood glucose levels as well as HbA1c, along with reductions in both systolic and diastolic blood pressure.[138] Ginger may also improve insulin sensitivity, as indicated by a systematic review of four randomized and controlled clinical trials, which showed significant improvements in ALT and HOMA-IR among people with NAFLD.[139]

## Bupleurum (*Bupleurum chinense*) root extract

**Scientific Evidence:**

*Bupleurum chinense* and Bupleurum species are widely used as tonics in traditional Chinese medicine, cited for their ability to relieve liver stagnation and elevate Yang Qi.[140] Containing more than 250 bioactive compounds, including triterpene saponins, essential oils, flavonoids, lignans, and polysaccharides, Bupleurum has hepatoprotective, antioxidant, and anti-inflammatory properties.[141] The saikosaponins (SSs) are likely the most bioactive components in Bupleurum. For example, Saikosaponin A (SSA), the most researched of these compounds, is a triterpene saponin shown to enhance intestinal barrier function and inhibit metabolic inflammation in animal studies, at least in part by Nrf2 activation, and to protect the liver from injury through anti-inflammatory mechanisms, including inhibition of NF-κB

[135] Morvaridzadeh M, Fazelian S, Agah S, et al. Effect of ginger (Zingiber officinale) on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Cytokine. 2020 Nov;135:155224.

[136] Li C, Li J, Jiang F, et al. Vasculoprotective effects of ginger (Zingiber officinale Roscoe) and underlying molecular mechanisms. Food Funct. 2021 Mar 15;12(5):1897-1913.

[137] Fakhri S, Patra JK, Das SK, et al. Ginger and Heart Health: From Mechanisms to Therapeutics. Curr Mol Pharmacol. 2021;14(6):943-959.

[138] Ebrahimzadeh A, Ebrahimzadeh A, Mirghazanfari SM, et al. The effect of ginger supplementation on metabolic profiles in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2022 Jan 11:102802.

[139] Zhou Q, Peng Y, Chen F, et al. Ginger supplementation for the treatment of non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Afr Health Sci. 2023 Mar;23(1):614-621.

[140] Ran S, Peng R, Guo Q, et al. Bupleurum in Treatment of Depression Disorder: A Comprehensive Review. Pharmaceuticals (Basel). 2024 Apr 16;17(4):512.

[141] Teng L, Guo X, Ma Y, et al. A comprehensive review on traditional and modern research of the genus Bupleurum (Bupleurum L., Apiaceae) in recent 10 years. J Ethnopharmacol. 2023 Apr 24;306:116129.

signaling *in vitro*.[142,143,144] SSA has also been shown to inhibit other pro-inflammatory cytokines in hypertrophied adipocytes *in vitro*, including tumor necrosis factor-α, interleukin (IL)-1β, and IL-6.[145] In an animal experiment, both curcumin and SSA were shown to protect the liver from injury caused by carbon tetrachloride by improving antioxidant status (with an additive benefit for the increase in glutathione and antioxidant status).[146] In an *in vitro* model of atherosclerosis, SSA prevented foam cell formation, oxidized LDL-C uptake, and assembly of the NLRP3 inflammasome, indicating an effect on lipids as well as antioxidant and anti-inflammatory activity.[147]

In an animal model, a water-soluble polysaccharide fraction from *Bupleurum chinense* was also shown to protect the liver from injury. These findings were marked by significant reductions in AST, ALT, ALP, and LDH (lactate dehydrogenase) and increases in the activity of several antioxidant enzymes, including glutathione reductase, γ-glutamylcysteine synthetase, glutathione S-transferase, and superoxide dismutase.[148] Many other preclinical findings suggest hepatoprotective, antioxidant, and anti-inflammatory effects of Saikosaponin A, though controlled human trials would help provide support for its long history of traditional use.[149]

# Liver GB+™ Safety Summary

The botanicals in Liver GB+™ have no known warnings, precautions, or contraindications at the dose recommended. However, it is contraindicated in individuals allergic to any of the individual ingredients in Liver GB+™, including individuals with a known sensitivity to plants from the Asteraceae/Compositae family.[150,151] Caution is advised when using any combination of silybin and irinotecan, as there may be an effect of silybin on UGT-1A1.[152] Given that several of the botanicals in

---

[142] Huang D, Zheng Z, Huang Y, et al. Saikosaponin A Ameliorates Metabolic Inflammation and Intestinal Barrier Damage in DIO Mice through the Nrf2/ARE Pathway. Discov Med. 2024 Jul;36(186):1408-1419.

[143] Zhu Y, Chen X, Rao X, et al. Saikosaponin-a ameliorates lipopolysaccharide and d-galactosamine-induced liver injury via activating LXRα. Int Immunopharmacol. 2019 Jul;72:131-137.

[144] He Y, Chen H, Zhao J, et al. Transcriptome and metabolome analysis to reveal major genes of saikosaponin biosynthesis in Bupleurum chinense. BMC Genomics. 2021 Nov 19;22(1):839.

[145] Kim SO, Park JY, Jeon SY, et al. Saikosaponin a, an active compound of Radix Bupleuri, attenuates inflammation in hypertrophied 3T3-L1 adipocytes via ERK/NF-κB signaling pathways. Int J Mol Med. 2015 Apr;35(4):1126-32.

[146] Wu SJ, Lin YH, Chu CC, et al. Curcumin or saikosaponin-a improves hepatic antioxidant capacity and protects against CCl4-induced liver injury in rats. J Med Food. 2008 Jun;11(2):224-9.

[147] He D, Wang H, Xu L, et al. Saikosaponin-a Attenuates Oxidized LDL Uptake and Prompts Cholesterol Efflux in THP-1 Cells. J Cardiovasc Pharmacol. 2016 Jun;67(6):510-8.

[148] Zhao W, Li JJ, Yue SQ, et al. Antioxidant activity and hepatoprotective effect of a polysaccharide from Bei Chaihu (Bupleurum chinense DC). Carbohydr Polym. 2012 Jun 20;89(2):448-52.

[149] Yang F, Dong X, Yin X, et al. Radix Bupleuri: A Review of Traditional Uses, Botany, Phytochemistry, Pharmacology, and Toxicology. Biomed Res Int. 2017;2017:7597596.

[150] Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006–. Milk Thistle. 2024 Jul 15.

[151] Soleimani V, Sahebkar A, Hosseinzadeh H. Turmeric (Curcuma longa) and its major constituent (curcumin) as nontoxic and safe substances: Review. Phytother Res. 2018 Jun;32(6):985-995.

[152] Flaig TW, Gustafson DL, Su LJ, et al. A phase I and pharmacokinetic study of silybin-phytosome in prostate cancer patients. Invest New Drugs. 2007 Apr;25(2):139-46.

GB+ may have a favorable effect on blood glucose levels, careful monitoring of blood glucose should be done while taking anti-diabetic medications.

TUDCA and several of the botanicals in Liver GB+™, such as Bupleurum and artichoke extract, are contraindicated during pregnancy and lactation (or do not have adequate safety data during these periods) and should be avoided without supervision.[153,154]

[153] Stanisiere J, Mousset PY, Lafay S. How Safe Is Ginger Rhizome for Decreasing Nausea and Vomiting in Women during Early Pregnancy? Foods. 2018 Apr 1;7(4):50.

[154] Gotardo AT, Mattos MIDS, Hueza IM, et al. The effect of Cynara scolymus (artichoke) on maternal reproductive outcomes and fetal development in rats. Regul Toxicol Pharmacol. 2019 Mar;102:74-78.