



## Grape Seed

Updated: March 20, 2023.

## OVERVIEW

### Introduction

Grape seed extracts are purported to have antioxidant, cardioprotective, antiinflammatory, and antineoplastic effects and are promoted as being helpful for general wellness as well as for diverse metabolic, vascular, heart, urinary tract, skin, and eye conditions. Extracts of grape seeds, fruit and leaves, as well as juices made from grapes, have not been associated with serum enzyme elevations during therapy nor have they been implicated in cases of clinically apparent acute liver injury.

### Background

Extracts made from grape seeds, leaves or fruit as well as grape juice have antioxidant activity and have been purported to be beneficial for health and preventing complications of stress and aging. Grapes (*Vitis vinifera*) are probably native to southern Europe and western Asia, but now comprise multiple subspecies that are grown in temperate regions throughout the world. The major uses of grapes are as edible fruit and as liquid in juices and wines. Grape horticulture is a major agricultural industry and the products a major component of human consumption. Drinking moderate amounts of wine is purported to have health benefits including cardioprotective activity, decreasing the risk of coronary artery disease. These claims are based upon observational and correlational studies and not prospective, randomized, placebo controlled trials. Drinking more than modest amounts of wine and alcohol on a regular basis is clearly associated with many social problems, health risks and shortened survival, and recent evidence suggests that even modest amounts of alcohol consumption is associated with health risks.

The seeds and leaves of grapes have multiple components with antioxidant and other possible beneficial activities and are available as extracts in multiple forms and concentrations alone or in combination with other herbal extracts, vitamins, minerals, and nutritional supplements in concentrations of 25 to 500 mg. Grape seed extracts are rich in proanthocyanidin which has antioxidant activity in vitro and has been purported to be beneficial for many conditions, including systemic arterial hypertension, hypercholesterolemia, coronary artery disease, edema, peripheral venous insufficiency, breast induration, pancreatitis, and vision problems. None of these claims, however, has been verified in properly designed and adequately powered prospective studies, and grape seed extracts have not been approved for any medical condition in the United States by the FDA. On the other hand, grape seed, leaf and fruit extracts are well tolerated with no or minimal side effects. Adverse events reported in clinical trials have included mild degrees of itchy skin, dizziness, headache, and nausea but a similar incidence of these adverse events was often found in patients receiving placebos.

## Hepatotoxicity

In multiple, largely short term clinical studies of different preparations and concentrations of grape seed extracts, adverse side effects were usually described as uncommon and minimal with no mention of either hepatotoxicity or ALT elevations. Few prospective studies have included regular monitoring of liver tests, but those that did reported no change in serum aminotransferase levels, and if anything, a slight decrease in alkaline phosphatase values. Despite widespread use, there have been no published reports of serum enzyme elevations or clinically apparent liver injury attributable to grape extracts.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

## Mechanism of Injury

The mechanism by which grape seed extracts might cause liver injury is unknown. Extracts of grape seed generally have moderately high levels of polyphenols but low levels of the polyphenolic catechins that are found in high levels in green tea (*Camellia sinensis*).

## Outcome and Management

Hepatotoxicity from extracts of grape seed, leaves or fruit has not been reported.

Drug Class: [Herbal and Dietary Supplements](#)

Other names: Proanthocyanidin

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Grape Seed – Generic

### DRUG CLASS

Herbal and Dietary Supplements

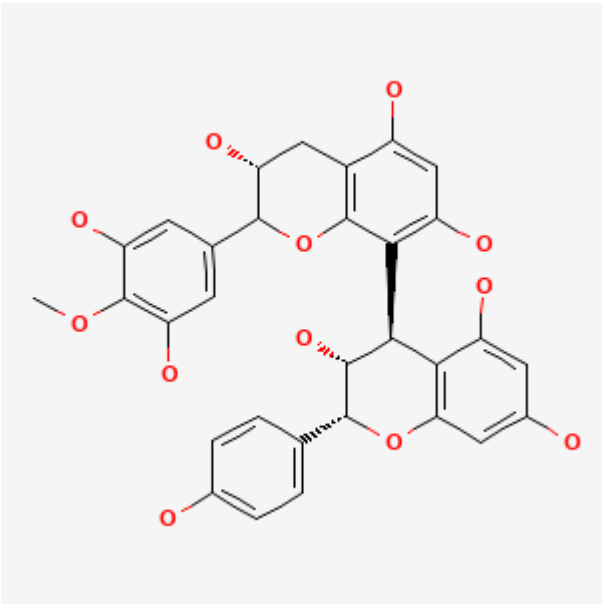
### SUMMARY INFORMATION

Fact Sheet at [National Center for Complementary and Integrative Health, NIH](#)

## CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Grape Seed	84929-27-1	Herbal	Not Applicable

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DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Proanthocyanidin	18206-61-6	C <sub>31</sub> -H <sub>28</sub> -O <sub>12</sub>	

## ANNOTATED BIBLIOGRAPHY

References updated: 20 March 2023

Abbreviations: HDS, herbal and dietary supplements.

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 731-4.

*(Expert review of hepatotoxicity published in 1999; several herbal medications are discussed, but not grape seed extract).*

Liu LU, Schiano TD. Hepatotoxicity of herbal medicines, vitamins and natural hepatotoxins. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 733-54.

*(Review of hepatotoxicity of herbal and dietary supplements [HDS] published in 2007; no mention of grape products).*

Grape. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 405-410.

*(Compilation of short monographs on herbal medications and dietary supplements).*

Banerjee B, Bagchi D. Beneficial effects of a novel IH636 grape seed proanthocyanidin extract in the treatment of chronic pancreatitis. Digestion. 2001;63:203-6. PubMed PMID: 11351148.

*(Three patients with persistent pancreatitis and pain despite conventional therapies were treated with grape seed extract [100 mg three times daily] and had marked improvement in pain within 1-2 weeks; no mention of adverse events, ALT levels or hepatotoxicity).*

Vogels N, Nijs IM, Westerterp-Plantenga MS. The effect of grape-seed extract on 24 h energy intake in humans. Eur J Clin Nutr. 2004;58:667-73. PubMed PMID: 15042136.

*(Among 51 subjects treated with grape seed extract or placebo for 3 days while undergoing extensive evaluation of energy intake and expenditure, there were no differences in energy requirements between the two groups; no mention of tolerance, adverse events, ALT levels or hepatotoxicity).*

Brooker S, Martin S, Pearson A, Bagchi D, Earl J, Gothard L, Hall E, et al. Double-blind, placebo-controlled, randomised phase II trial of IH636 grape seed proanthocyanidin extract (GSPE) in patients with radiation-induced breast induration. *Radiother Oncol.* 2006;79:45–51. PubMed PMID: 16546280.

*(Among 68 women with breast induration after radiation for breast cancer who were treated with grape seed extract [100 mg thrice daily] or placebo for 6 months, there were no differences in reduction of the area of induration or in discomfort or appearance between the grape seed extract and placebo treated groups; no mention of tolerance, adverse events, ALT levels or hepatotoxicity).*

Mellen PB, Daniel KR, Brosnihan KB, Hansen KJ, Herrington DM. Effect of muscadine grape seed supplementation on vascular function in subjects with or at risk for cardiovascular disease: a randomized crossover trial. *J Am Coll Nutr.* 2010;29:469–75. PubMed PMID: 21504973.

*(Among 50 patients with high risk for coronary artery disease treated with grape seed extract [650 mg twice daily] or placebo for 4 weeks in a crossover trial, there were no differences in changes of brachial flow mediated vasodilation, blood pressure, cholesterol [total, LDL and HDL], fasting blood glucose, hemoglobin A1c, C-reactive protein or IL-6 levels during grape seed extract vs placebo periods of therapy; no mention of adverse events, ALT levels or hepatotoxicity).*

Jacobsson I, Jönsson AK, Gerdén B, Hägg S. Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. *Pharmacoepidemiol Drug Saf.* 2009;18:1039–47. PubMed PMID: 19650152.

*(Review of 778 spontaneous reports of adverse reactions to herbals in a Swedish Registry does not list grape seed extract among products associated with 5 or more reports).*

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology.* 2010;52:2065–76. PubMed PMID: 20949552.

*(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury of which 12 [9%] were due to herbals, including several herbal mixtures, usnic acid, Ma Huang, black cohosh, and Hydroxycut, but not grape seed).*

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. *Liver Int.* 2012;32:1543–56. PubMed PMID: 22928722.

*(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs, herbal drugs and supplements, but does not mention or list grape seed extract).*

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. *Aliment Pharmacol Ther.* 2013;37:3–17. PubMed PMID: 23121117.

*(Systematic review of literature on HDS associated liver injury does not mention grape seed extract).*

Navarro VJ, Seeff LB. Liver injury induced by herbal complementary and alternative medicine. *Clin Liver Dis.* 2013;17:715–35. PubMed PMID: 24099027.

*(Review of the epidemiology, regulatory status, diagnosis, pathogenesis and causes of liver injury from herbal products with specific discussion of conjugated linoleic acid, ephedra, germander, green tea, usnic acid, flavocoxid, aloe vera, chaparral, greater celandine, black cohosh, comfrey, kava, skullcap, valerian, noni juice, pennyroyal and traditional herbal remedies).*

Sano A, Tokutake S, Seo A. Proanthocyanidin-rich grape seed extract reduces leg swelling in healthy women during prolonged sitting. *J Sci Food Agric.* 2013;93:457–62. PubMed PMID: 22752876.

*(Among 8 sedentary Japanese adults given grape seed extract or placebo in a single dose of 400 mg and another 8 subjects given 133 mg of grape seed extract for 14 days, complaints of leg swelling increased in both placebo and grape seed treated groups and there were no changes in total body water or in other symptoms, and no abnormal biochemical tests in either group).*

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. *Hepatology*. 2014;60:1399–408. PubMed PMID: 25043597.

*(Among 839 cases of liver injury from drugs collected in the US between 2004 and 2013, 130 were due to HDS products, including 45 from body building agents [probably anabolic steroids] and 85 from diverse HDS products but no case was attributed specifically to grape seed extract).*

Martinez-Zapata MJ, Vernooij RW, Uriona Tuma SM, Stein AT, Moreno RM, Vargas E, Capellà D, et al. Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev*. 2016;4:CD003229. PubMed PMID: 27048768.

*(Cochrane review of the efficacy of various herbal preparations for venous insufficiency included only one trial of grape seed extract which demonstrated a marginal effect; no mention of adverse events, ALT elevations or hepatotoxicity).*

Park E, Edirisinghe I, Choy YY, Waterhouse A, Burton-Freeman B. Effects of grape seed extract beverage on blood pressure and metabolic indices in individuals with pre-hypertension: a randomised, double-blinded, two-arm, parallel, placebo-controlled trial. *Br J Nutr*. 2016;115:226–38. PubMed PMID: 26568249.

*(Among 36 adults with “pre-hypertension” treated with grape seed extract [150 mg twice daily] or placebo for 6 weeks, there were minor changes in systolic blood pressure and “no adverse events related to treatment were reported during the study”; no mention of ALT elevations or hepatotoxicity).*

Sano A. Safety assessment of 4-week oral intake of proanthocyanidin-rich grape seed extract in healthy subjects. *Food Chem Toxicol*. 2017;108:519–523. PubMed PMID: 27889390.

*(Among 29 healthy Japanese volunteers treated with grape seed extract for 4 weeks in doses of 1000, 1500 or 2500 mg daily, mild symptoms of headache, nausea, constipation and diarrhea occurred in a few patients, but there were no changes in routine biochemical tests including ALT, AST, GGT, Alk P and bilirubin).*

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. *Food Chem Toxicol*. 2017;107:472–501. PubMed PMID: 27402097.

*(Description of an online compendium of cases of liver toxicity attributed to HDS products does not list or discuss grape seed).*

Medina-Caliz I, Garcia-Cortes M, Gonzalez-Jimenez A, Cabello MR, Robles-Diaz M, Sanabria-Cabrera J, Sanjuan-Jimenez R, et al; Spanish DILI Registry. Herbal and dietary supplement-induced liver injuries in the Spanish DILI Registry. *Clin Gastroenterol Hepatol*. 2018;16:1495–1502. PubMed PMID: 29307848.

*(Among 856 cases of hepatotoxicity enrolled in the Spanish DILI Registry between 1994 and 2016, 32 were attributed to herbal products, the most frequent cause being green tea [n=8] and Herbalife products [n=6], no mention of grape seed).*

Asbaghi O, Nazarian B, Reiner Ž, Amirani E, Kolahdooz F, Chamani M, Asemi Z. The effects of grape seed extract on glycemic control, serum lipoproteins, inflammation, and body weight: a systematic review and meta-analysis of randomized controlled trials. *Phytother Res*. 2020;34:239–253. PubMed PMID: 31880030.

*(A metaanalysis of clinical trials of grape seed extract vs placebo for effects on glycemic control, lipoproteins, inflammation and body weight identified minor average decreases in fasting blood glucose [-2 mg/dL],*

*cholesterol [-6 mg/dL], triglycerides [-6.5 mg/dL] and C reactive protein [-0.8 mg/L], but no change in hemoglobin A1c levels or body weight; no mention of tolerance or adverse events).*

Ballotin VR, Bigarella LG, Brandão ABM, Balbinot RA, Balbinot SS, Soldera J. Herb-induced liver injury: Systematic review and meta-analysis. *World J Clin Cases.* 2021;9:5490–5513. PubMed PMID: 34307603.

*(Systematic review of the literature on herb induced liver injury identified 446 references describing 936 cases due to 79 different herbal products, the most common being He Shou Wu [91], green tea [90] Herbalife products [64], kava kava [62] and greater celandine [48]; grape seed nut was not listed among the 79 implicated products).*

Bessone F, García-Cortés M, Medina-Caliz I, Hernandez N, Parana R, Mendizabal M, Schinoni MI, et al. Herbal and dietary supplements-induced liver injury in Latin America: experience from the LATINDILI Network. *Clin Gastroenterol Hepatol.* 2022;20:e548–e563. PubMed PMID: 33434654.

*(Among 367 cases of hepatotoxicity enrolled in the Latin American DILI Network between 2011 and 2019, 29 [8%] were attributed to herbal products, the most frequent being green tea [n=7], Herbalife products [n=5] and garcinia [n=3], while grape seed is not mentioned).*

Zamani M, Ashtary-Larky D, Hafizi N, Naeini F, Rezaei Kelishadi M, Clark CCT, Davoodi SH, et al. The effect of grape products on liver enzymes: a systematic review and meta-analysis of randomized controlled trials. *Phytother Res.* 2022;36:4491–4503. PubMed PMID: 36264051.

*(Systematic review identified 11 controlled trials of grape seed extract in which serum enzymes were assessed before and at the end of therapy; changes in ALT and AST did not differ between active drug and placebo [-1.9 U/L for ALT, and -1.1 U/L for AST], while alkaline phosphatase levels did decrease slightly more with grape seed extract compared to placebo [-5 U/L]).*