



Cascara

Updated: January 23, 2017.

OVERVIEW

Introduction

Cascara is a popular herbal medication and over-the-counter therapy of constipation. Cascara is generally safe and well tolerated, but can cause adverse events including clinically apparent liver injury when used in high doses for longer than recommended periods.

Background

Cascara sagrada is an herbal medication used for centuries as a laxative which is now available in the United States without prescription for short term treatment of constipation. Cascara is typically an extract from the dried, aged bark of *Rhamnus purshiana*, a species of buckthorn tree or shrub native to North America. Cascara sagrada is Spanish for “sacred bark” and was used for centuries by Native Americans as a laxative. Cascara became accepted in western medical practice in the 19th century and is still used in over-the-counter laxative preparations, often in combination with other herbals such as aloe vera. The active laxative components in cascara are anthraquinone derivatives and their glucosides, referred to as cascarosides. They appear to act locally as an irritant to the colon promoting peristalsis and stool evacuation. Anthraquinones also inhibit reabsorption of electrolytes and water from the colon. Cascara is minimally absorbed. The typical dose is 300 mg once daily, but it is recommended for short term use only (less than one week). Side effects include abdominal cramps and electrolyte imbalance. Long term use or abuse can lead to “cathartic” colon with diarrhea, cramps, weight loss and darkened pigmentation of the colonic mucosa.

Hepatotoxicity

Use of cascara in the recommended doses for a limited period of time has been associated with few side effects, most of which are mild and transient. With longer term use of high doses of cascara, however, adverse events have been described including several cases of clinically apparent liver injury. The time to onset of liver injury has varied from a few days to 2 months of use, and the pattern of serum enzyme elevations varied from hepatocellular to cholestatic. The liver injury ranged from mild to severe, but usually resolved rapidly with discontinuation. Immunoallergic features and autoimmune markers were not prominent or consistently present in the published cases.

Mechanism of Injury

The liver injury due to cascara has been attributed to the direct toxicity of anthraquinone derivatives in the herbal extract; however, the clinical characteristics of the published cases suggest an idiosyncratic rather than direct hepatotoxic etiology. Other anthraquinones used to treat constipation have been implicated in causing

liver injury with long term use, including sennosides and hydroxyanthraquinone. As with other herbal toxicities, the hepatic injury attributed to cascara may actually have been due to a undisclosed contaminant.

Outcome and Management

Liver injury from long term cascara use is rare and most cases have been self-limited and rapidly reversible upon stopping the laxative. However, severe cases with acute liver failure and development of ascites and portal hypertension have been described. There is no evidence of cross sensitivity to hepatic damage with other laxatives. Restarting cascara has been associated with recurrence of liver injury and should be avoided.

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

Other drugs in the Anthraquinone Subclass: [Senna](#)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Cascara – Generic

DRUG CLASS

Herbal and Dietary Supplements

SUMMARY INFORMATION

[Fact Sheet at MedlinePlus/Natural Medicines Comprehensive Database](#)

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Cascara	8047-27-6	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 23 January 2017

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; cascara is not discussed).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS]; cascara is listed as having been linked to cases of cholestatic hepatitis).

Cascara sagrada. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 161-4.

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

Tolman KG, Hammar S, Sannella JJ. Possible hepatotoxicity of Doxidan. *Ann Intern Med* 1976; 84: 290-2. PubMed PMID: 1259264.

(24 year old man developed fatigue 6 months after starting Doxidan [containing hydroxyanthraquinone] for chronic constipation and at 12 months developed nausea and syncope [bilirubin 0.8 mg/dL, AST 560 U/L, Alk P 339 U/L, ANA negative, slight neutropenia], liver biopsy showing chronic hepatitis, resolving within 1 month of stopping, recurring upon rechallenge).

Beuers U, Spengler U, Pape GR. Hepatitis after chronic abuse of senna. *Lancet* 1991; 337: 372-3. PubMed PMID: 1671276.

(26 year old nurse taking high doses of senna alkaloids developed jaundice and pruritus [bilirubin not given, ALT 303 U/L, Alk P 227 U/L], resolving within a few weeks of stopping and recurring upon restarting [ALT >280 U/L]).

Franz G. The senna drug and its chemistry. *Pharmacol* 1993; 47(Suppl 1): 2-6. PubMed PMID: 8234429.

(Senna is dried leaflets or fruits of Cassia senna, either acutifolia [Alexandrian] or angustifolia [Indian senna], native to Northern Africa, middle East and India, similar constituents including anthraquinone glycosides, called sennosides).

Wolf GM. Senna-induced hepatotoxicity. *Hepatology* 1999; 550A: 1560. Not in PubMed

(81 year old woman developed recurrent jaundice after taking senna for one month [bilirubin 3.2 rising to 29.6 mg/dL, peak ALT 1455 U/L, Alk P 168 U/L], recurring more rapidly and recovering more slowly after each of 3 episodes after reexposure).

Nadir A, Reddy D, Van Thiel DH. Cascara sagrada-induced intrahepatic cholestasis causing portal hypertension: case report and review of herbal hepatotoxicity. *Am J Gastroenterol* 2000; 95: 3653-7. PubMed PMID: 11151906.

(48 year old man developed jaundice 3 days after starting cascara sagrada [bilirubin 11.8 mg/dL, ALT 999 U/L, Alk P 309 U/L, ANA 1: 640], developing ascites, but recovering within 3 months of stopping).

Wurtz AS, Vial T, Isoard B, Saillard E. Possible hepatotoxicity from Copaltra, an herbal medicine. *Ann Pharmacother* 2002; 36: 941-2. PubMed PMID: 12014355.

(49 year old woman developed jaundice 3 months after starting Copaltra tea [Coutarea latiflora and Centaurium erythrae] for diabetes [bilirubin 20.8 mg/dL, ALT 3010 U/L, Alk P 132 U/L], with recovery in 3 months).

De Smet PAGM. Herbal remedies. *N Engl J Med* 2002; 347: 2046-56. PubMed PMID: 12490687.

(Review of status and difficulties of herbal medications including lack of standardization, federal regulation, contamination, safety, hepatotoxicity and drug-herb interactions; specific discussion of 4 herbs with therapeutic promise: ginkgo, hawthorn, saw palmetto and St. John's wort).

Stedman C. Herbal hepatotoxicity. *Semin Liver Dis* 2002; 22: 195-206. PubMed PMID: 12016550.

(Review and description of patterns of liver injury, including discussion of potential risk factors, and herb-drug interactions; cascara is listed as causing liver injury).

Schiano TD. Hepatotoxicity and complementary and alternative medicines. *Clin Liver Dis* 2003; 7: 453-73. PubMed PMID: 12879994.

(Comprehensive review of herbal associated hepatotoxicity; cascara is listed as a potential hepatotoxin).

Ernst E. Risks of herbal medicinal products. *Pharmacoepidemiol Drug Saf* 2004; 13: 767-71. PubMed PMID: 15386721.

(Review of the adverse effects of over-the-counter herbal medications, focusing on the hepatotoxicity of kava, drug interactions with St. John's wort, and contamination of traditional Chinese medications with heavy metals [arsenic, lead, mercury, thallium] and conventional western medications).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. *Liver Transpl* 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, including 7 [5%] for herbal medications, none attributed to cascara).

Seybold U, Landauer N, Hillebrand S, Goebel FD. Senna-induced hepatitis in a poor metabolizer. *Ann Intern Med* 2004; 141: 650-1. PubMed PMID: 15492352.

(28 year old woman developed jaundice after drinking herbal tea containing senna leaves with positive rechallenge [ALT ~1390 U/L, GGT ~190 U/L], with Rhein anthrone detectable in serum).

Vanderperren B, Rizzo M, Angenot L, Haufroid V, Jadoul M, Hantson P. Acute liver failure with renal impairment related to the abuse of senna anthraquinone glycosides. *Ann Pharmacother* 2005; 39: 1353-7. PubMed PMID: 15956233.

(52 year old woman developed jaundice, acute liver failure, lactic acidosis, and phosphate wasting nephropathy after ingesting herbal tea made from senna fruits for 3 years [bilirubin 6.2 mg/dL, ALT 9160 U/L, INR 5.3], requiring ventilator support, ultimately resolving).

Sonmez A, Yilmaz MI, Mas R, Ozcan A, Celasun B, Dogru T, Taslipinar A, Kocar IH. Subacute cholestatic hepatitis likely related to the use of senna for chronic constipation. *Acta Gastroenterol Belg* 2005; 68: 385-7. PubMed PMID: 16268429.

(77 year old male developed jaundice after taking a senna preparation for constipation for 3 months [bilirubin 4.9 rising to 16.9 mg/dL, ALT 657 U/L, Alk P 160 U/L], resolving within 1 month of stopping the herbal).

Bruguera M, Herrera S, Lazaro E, Madurga M, Navarro M, De Abajo FJ. [Acute hepatitis associated with consumption of Copalchi: a summary of 5 cases]. *Gastroenterol Hepatol* 2007; 30: 66-8. PubMed PMID: 17335712.

(Five cases of hepatotoxicity of Copalchi in 4 men and 1 woman ages 59 to 77 years, taking herb for 2 to 13 months [bilirubin 0.7-13 mg/dL, ALT 403-865 U/L, GGT 54-116 U/L], resolving in all).

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry. *Rev Esp Enferm Dig* 2008; 100: 688-95. PubMed PMID: 19159172.

(Among 521 cases of drug induced liver injury submitted to Spanish registry, 13 [2%] were due to herbals, including one due to Rhamnus purshianus [cascara], with onset after 2 months [bilirubin 7.1 mg/dL, ALT 56 times ULN, Alk P normal], resolving in 3 months).

Chalasan N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% of cases were attributed to herbal medications, but none were specifically linked to cascara).

Freeman HJ. "Melanosis" in the small and large intestine. *World J Gastroenterol* 2008; 14: 4296-9. PubMed PMID: 18666316.

(Pigment found in small and large intestine with long term anthracene laxative [cascara, senna, aloes and rhubarb], use is usually lipofuscin rather than hemosiderin or melanin and is present in macrophages in the lamina propria).

Jacobsen C, Semb S, Kromann-Andersen H. [Toxic hepatitis following consumption of the herbal medicinal product Cascara Sagrada]. *Ugeskr Laeger* 2009; 171: 3367-9. Danish. PubMed PMID: 19925744.

(49 year old woman developed jaundice 4 weeks after starting daily cascara sagrada for constipation [bilirubin 8.4 rising to 24.6 mg/dL, ALT 944 U/L, ascites], resolving within 4 months of stopping).

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 to Swedish Registry does not list or mention senna or cascara).

Mueller-Lissner SA, Wald A. Constipation in adults. *Clin Evid (Online)* 2010 Jul 5; 2010. pii: 0413. PubMed PMID: 21418672.

(Review of evidence of efficacy of conventional therapies of constipation; states that there is no published evidence from randomized controlled trials for benefit of cascara for idiopathic chronic constipation).

Vitalone A, Menniti-Ippolito F, Raschetti R, Renda F, Tartaglia L, Mazzanti G. Surveillance of suspected adverse reactions to herbal products used as laxatives. *Eur J Clin Pharmacol* 2012; 68: 231-8. PubMed PMID: 21964980.

(Among 519 adverse events attributed to herbals reported to an Italian registry between 2002 and 2011, 26 were related to herbal laxatives, including 3 cases of liver injury, 1 due to cascara and 2 to senna).

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, including 1 implicating cascara [Nadir 2000] and 3 senna [Beuers 1991, Seybold 2004, Vanderperren 2005]).

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

(Systematic review of the literature on HDS associated hepatotoxicity mentions that cascara has been implicated in causing clinically apparent acute liver injury).

Teschke R, Schulze J, Schwarzenboeck A, Eickhoff A, Frenzel C. Herbal hepatotoxicity: suspected cases assessed for alternative causes. *Eur J Gastroenterol Hepatol* 2013; 25: 1093-8. PubMed PMID: 23510966.

(Review of the literature of case series of suspected HDS related liver injury found evidence of other explanations for the liver injury in 19 of 23 publications involving 278 of 573 patients [49%], and that these other diagnoses weakened the causality assessment in most instances; cascara associated cases not mentioned).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 15 [16%] due to herbal and dietary supplements, but none were attributed to cascara containing products).

Licata A, Macaluso FS, Craxì A. Herbal hepatotoxicity: a hidden epidemic. *Intern Emerg Med* 2013; 8: 13-22. PubMed PMID: 22477279.

(Review and commentary on herb related hepatotoxicity discusses pyrrolizidine alkaloids, green tea, Echinacea, kava, usnic acid, ephedra and products made by Herbalife, Hydroxycut and LipoKinetix; no mention of cascara containing products).

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 HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment; no mention of cascara containing products).

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 85 cases of HDS associated liver injury [not due to anabolic steroids] enrolled in a US prospective study between 2004 and 2013, none were attributed specifically to cascara).

Navarro VJ, Lucena MI. Hepatotoxicity induced by herbal and dietary supplements. Semin Liver Dis 2014; 34: 172-93. PubMed PMID: 24879982.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment; lists cascara as possibly causing cholestatic hepatitis).

Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology 2015; 148: 517-532. PubMed PMID: 25500423.

(Extensive review of possible beneficial as well as harmful effects of herbal products on the liver mentions that multi-ingredient supplements have been implicated in many cases of liver injury; cascara is not discussed).

Nakasone ES, Tokeshi J. A serendipitous find: A case of cholangiocarcinoma identified incidentally after acute liver injury due to cascara sagrada ingestion. Hawaii J Med Public Health 2015; 74: 200-2. PubMed PMID: 26114074.

(77 year old woman developed jaundice shortly after a 3 day course of an over-the-counter cascara product [bilirubin 18.5 mg/dL, ALT 465 U/L, Alk P not given], while imaging showed cholangiocarcinoma; no follow up or justification of diagnosis of cascara induced liver injury given).

Stickel F, Shouval D. Hepatotoxicity of herbal and dietary supplements: an update. Arch Toxicol. 2015; 89: 851-65. PubMed PMID: 25680499.

(Extensive review of liver injury due to HDS lists cascara as possibly causing cholestatic hepatitis).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a prospective database between 2004 and 2012, HDS were implicated in 145 [16%], but none specifically implicated cascara: see Navarro [2014]).