



Tribulus

Updated: August 8, 2022.

OVERVIEW

Introduction

Tribulus is herbal product prepared from the leaves, fruit and roots of *Tribulus terrestris*, extracts of which have been used as an aphrodisiac, general tonic and mood stimulant in traditional medicine. The native plant causes serious liver injury in grazing animals, and but tribulus extracts have not been linked convincingly to instances of clinically apparent liver injury when given in typical doses in humans.

Background

Tribulus is prepared from the leaves and roots of the low-growing shrub and common weed *Tribulus terrestris* that is found in dry habitats in many parts of the world, including Asia, Africa, Australia and North and South America. Extracts of the shrub have been used in traditional medicine as an aphrodisiac, general tonic and mood stimulant for centuries. A major use of tribulus has been for sexual dysfunction such as erectile dysfunction in men and hypoactive sexual syndromes in women, but also for menopausal symptoms, premenstrual syndrome and infertility. Recently tribulus has been used commonly for increasing athletic performance. Tribulus is also purported to be beneficial for several other medical conditions, including urinary tract infections, kidney stones, hypertension, angina pectoris, hypercholesterolemia, gastrointestinal disorders, diarrhea and even liver disease. Studies in animal models suggested that tribulus increases testosterone levels in males and estrogen levels in females, but these hormonal effects have not been reproduced consistently in humans. Furthermore, in controlled trials, improvements in sexual function were no greater with *Tribulus terrestris* extracts than with placebo. The active ingredients in extracts of tribulus are believed to be saponins such as dioscin, diosgenin and protodioscin which are steroidal molecules and thought to increase levels of sex hormones. Tribulus is available in tablets and capsules of 250 and 500 mg, and the usual daily dose is 250 to 750 mg daily. *Tribulus terrestris* is also included in many multi-ingredient dietary supplements used for sexual dysfunction and body building. Tribulus is reported to be well tolerated but may be associated with mild gastrointestinal discomfort, nausea or dyspepsia. The plant, also known as puncture vine because of the sharp spines on its fruit, has been linked to outbreaks of liver injury in grazing animals known as geeldikkop or hepatogenous photosensitivity. The toxic component of the plant is believed to be the steroidal saponins which form crystals in bile ducts and renal tubules in sheep that feed upon its leaves.

Hepatotoxicity

Tribulus terrestris has been not been reported to cause serum enzyme elevations in persons taking the herbal extract, but prospective studies with regular monitoring of liver tests have not been done. Isolated case reports of renal injury with serum aminotransferase elevations have been published but may have represented instances of

ischemic or anabolic steroid induced liver and kidney injury rather than direct hepatotoxicity of the extract. Interestingly, the *Tribulus terrestris* plant is known to be toxic to grazing animals and can cause distinctive liver injury known as “geeldikkop” or hepatogenous photosensitivity. Histology of the liver from sheep dying after feeding upon the leaves of *Tribulus terrestris* demonstrates crystals in bile ducts and renal tubules. For these reasons, high doses should be considered potentially injurious, particularly in patients with preexisting liver disease or cirrhosis.

Likelihood score: E* (unproven but possible rare cause of clinically apparent liver injury when taken in high doses or in persons with pre-existing liver disease).

Other names: Puncture vine, Devil’s Thorn, Goathead, Gokhru, Nature’s Viagra, Protodioscine

Mechanism of Injury

Leaf extracts of *Tribulus* contain many components, but none has been shown to be particularly hepatotoxic in humans. In grazing animals *Tribulus terrestris* has been linked to bile duct injury and the toxic component of the plant is believed to be steroidal sapogenins which form crystals in bile ducts and renal tubules.

Outcome and Management

Clinically apparent liver injury from *Tribulus* in humans has not been convincingly shown.

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

CASE REPORT

Case 1. Severe Jaundice and Renal Dysfunction in a Patient Taking *Tribulus*.(1)

A 30 year old man developed weakness, nausea and poor appetite a few months after starting *Tribulus terrestris* extract tablets (once daily) as a part of his body building program. He began to feel poorly and over the next 6 weeks lost 50 pounds in weight, eventually developing pruritus and jaundice and seeking medical attention. He had no history of liver disease and drank alcohol only occasionally. His only other medications were naproxen for headaches and protein shakes for nutrition. Laboratory tests showed a total bilirubin of 36 mg/dL (direct 18.7 mg/dL), ALT 90 U/L, AST 49 U/L and alkaline phosphatase 219 U/L. Tests for hepatitis A, B and C and HIV infection were negative as was the ANA. Abdominal ultrasound showed a homogenous but enlarged liver but no evidence of biliary obstruction. A liver biopsy showed severe cholestasis, no inflammation and no bile duct injury or fibrosis. *Tribulus* was stopped and he was treated with ursodiol. He was discharged but then readmitted 2 weeks later with persistent jaundice (bilirubin 39 mg/dL) and an increase in serum creatinine from 1.1 to 3.1 mg/dL. One month after the second admission he was seen as an outpatient and both liver and kidney tests had improved.

Key Points

Medication:	<i>Tribulus terrestris</i> tablets once daily ~2 months
Pattern:	Bland cholestasis
Severity:	4+ (jaundice, hospitalization, renal dysfunction)
Latency:	~2 months
Recovery:	Improvement reported in 6 weeks.
Other medications:	Protein shakes, naproxen, ?anabolic steroids

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Creatinine (mg/dL)	Other
2 months	0	90	219	36.0	1.1	Admission, tribulus stopped
	1 week				1.5	Discharged, on ursodiol
	2 weeks	59	278	39.0	3.1	Readmission, kidney biopsy
4 months	6 weeks	126		4.4	1.2	Clinic follow up
Upper Limit of Normal		40	147	1.2	1.2	

Comment

While this published case was thought to represent *Tribulus terrestris* induced liver and renal injury, it was much more likely to have been due to unacknowledged use of anabolic steroids for body building. The clinical history, laboratory tests and course are typical of anabolic steroid jaundice, which usually presents with severe pruritus and jaundice in an otherwise healthy young male body builder who may or may not admit to use of anabolic steroids. The pattern of liver enzymes is usually a mild-to-moderate increase in serum aminotransferase levels and normal or only minimal increase in alkaline phosphatase despite the marked increase in serum bilirubin. Liver biopsy shows severe canalicular cholestasis with minimal cell injury or inflammation (bland cholestasis) and no fibrosis. Patients with serum bilirubin levels above 30 mg/dL can develop bilirubin nephropathy with bilirubin stained casts. The liver and renal injury can be severe, but are self-limiting and eventually resolve without evidence of chronic injury to either the liver or kidneys. Because anabolic steroids are illegal drugs, patients may refuse to admit that they were being used.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tribulus – 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
Tribulus	90131-68-3	Herbal	Not Applicable

CITED REFERENCE

- Ryan M, Lazar I, Nadasdy GM, Nadasdy T, Satoskar AA. Acute kidney injury and hyperbilirubinemia in a young male after ingestion of *Tribulus terrestris*. Clin Nephrol. 2015;83:177–83. PubMed PMID: 25295577.

ANNOTATED BIBLIOGRAPHY

References updated: 08 August 2022

- 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 tribulus).*
- 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; tribulus is not discussed).*
- Bourke CA. Hepatopathy in sheep associated with Tribulus terrestris. Aust Vet J. 1983;60:189.
- (3 sheep developed diarrhea and weight loss 15 days after starting a diet of 8 kg of Tribulus plants daily, dying within 5 weeks with jaundice and autopsy showing hepatic fibrosis, bile duct proliferation and crystals in bile ducts).*
- Glastonbury JR, Doughty FR, Whitaker SJ, Sergeant E. A syndrome of hepatogenous photosensitisation, resembling geeldikkop, in sheep grazing Tribulus terrestris. Aust Vet J. 1984;61:314-6. PubMed PMID: 6525116.
- (Two outbreaks of jaundice and photosensitization were reported in sheep both linked to grazing on Tribulus terrestris, autopsies showing needle-like clefts and crystalline material in bile ducts and kidney tubules).*
- Button C, Paynter DI, Shiel MJ, Colson AR, Paterson PJ, Lyford RL. Crystal-associated cholangiohepatopathy and photosensitisation in lambs. Aust Vet J. 1987;64:176-80. PubMed PMID: 3632500.
- (Four outbreaks of crystal associated cholangiohepatopathy and photosensitization in lambs not thought to be attributable to Tribulus terrestris [AST 82-859 U/L, Alk P 126 to 175 U/L, bilirubin 0.4 to 13.4 mg/dL] and not affecting mature sheep; possibly due to Panicum schinzii).*
- Tapia MO, Giordano MA, Gueper HG. An outbreak of hepatogenous photosensitization in sheep grazing Tribulus terrestris in Argentina. Vet Hum Toxicol. 1994;36:311-3. PubMed PMID: 7975136.
- (Description of an outbreak of liver disease in sheep grazing on Tribulus terrestris in Argentina which resembled the photosensitivity and liver injury of sheep described in Australia).*
- McDonough SP, Woodbury AH, Galey FD, Wilson DW, East N, Bracken E. Hepatogenous photosensitization of sheep in California associated with ingestion of Tribulus terrestris (puncture vine). J Vet Diagn Invest. 1994;6:392-5. PubMed PMID: 7948218.
- (A flock of 7 sheep in the US developed reddening of the skin and bright yellow mucous membranes [bilirubin 1.2 mg/dL, AST 767 U/L, Alk P 380 U/L, GGT 451 U/L], autopsy showing spotty hepatocyte necrosis, periductal concentric fibrosis and crystals in bile ducts).*
- Ukani MD, Nanavati DD, Mehta NK. A review on the ayurvedic herb tribulus terrestris L. Anc Sci Life. 1997;17:144-50. PubMed PMID: 22556836.
- (Tribulus, also known as Gokhshura, is used in several Ayurvedic herbs, largely as a diuretic).*
- Brown GA, Vukovich MD, Sharp RL, Reifenrath TA, Parsons KA, King DS. Effect of oral DHEA on serum testosterone and adaptations to resistance training in young men. J Appl Physiol. 1999;87:2274-83. PubMed PMID: 10601178.
- (In a controlled trial of DHEA vs placebo in 19 young men, DHEA increased serum androstenedione levels but testosterone, estradiol, lipids and liver enzymes were not affected and there was no improvement in strength and lean body mass in response to resistance training when compared to placebo).*

Antonio J, Uelmen J, Rodriguez R, Earnest C. The effects of Tribulus terrestris on body composition and exercise performance in resistance-trained males. *Int J Sport Nutr Exerc Metab.* 2000;10:208–15. PubMed PMID: 10861339.

(Among 15 healthy resistance trained men treated with Tribulus terrestris or placebo and undergoing an 8 week weight training period, there were no differences in changes in muscle strength or body composition between the two groups).

Brown GA, Vukovich MD, Reifenrath TA, Uhl NL, Parsons KA, Sharp RL, King DS. Effects of anabolic precursors on serum testosterone concentrations and adaptations to resistance training in young men. *Int J Sport Nutr Exerc Metab.* 2000;10:340–59. PubMed PMID: 10997957.

(Among 20 subjects treated with the combination of androstenedione, Tribulus terrestris, DHEA, Chrysin, indole-3-carbinol and saw palmetto and underwent resistance training for 8 weeks, there were no differences in changes in weight, lean body mass, strength, serum testosterone, insulin resistance and serum glucose, ALT or AST between the two groups).

Mason MA, Giza M, Clayton L, Lonning J, Wilkerson RD. Use of nutritional supplements by high school football and volleyball players. *Iowa Orthop J.* 2001;21:43–8. PubMed PMID: 11813950.

(Among 495 male high school football players, 42 [8%] reported taking dietary supplements to enhance athletic performance [usually creatine and amino acids] including 1 who was taking tribulus).

Brown GA, Vukovich MD, Martini ER, Kohut ML, Franke WD, Jackson DA, King DS. Endocrine and lipid responses to chronic androstenediol-herbal supplementation in 30 to 58 year old men. *J Am Coll Nutr.* 2001;20:520–8. PubMed PMID: 11601567.

(Controlled trial of androstenediol and herbal supplements vs placebo for 4 weeks in 56 men found and increase in free but no change in total testosterone levels and no changes in serum ALT levels).

Rowland DL, Tai W. A review of plant-derived and herbal approaches to the treatment of sexual dysfunctions. *J Sex Marital Ther.* 2003;29:185–205. PubMed PMID: 12851124.

(Review of herbal approaches to treating sexual dysfunction).

Aslani MR, Movassaghi AR, Mohri M, Pedram M, Abavisani A. Experimental Tribulus terrestris poisoning in sheep: clinical, laboratory and pathological findings. *Vet Res Commun.* 2003;27:53–62.

(Among 6 sheep fed Tribulus terrestris, all developed photosensitivity after 11 days, with jaundice and liver histology showing fibrosis and crystalloid material in bile ducts and renal tubules).

Pittler MH, Ernest E. Systematic review: hepatotoxic events associated with herbal medicinal products. *Aliment Pharmacol Ther.* 2003;18:451–71. PubMed PMID: 12950418.

(Systematic review of published cases of hepatotoxicity due to herbal medications listing 52 case reports or case series, most common agents being celandine [3], chaparral [3], germander [8], Jin Bu Huan [3], kava [1], Ma huang [3], pennyroyal [1], skullcap [2], Chinese herbs [9], valerian [1]).

Estes JD, Stolpman D, Olyaei A, Corless CL, Ham JM, Schwartz JM, Orloff SL. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. *Arch Surg.* 2003;138:852–8. PubMed PMID: 12912743.

(Among 20 patients undergoing liver transplantation for acute liver failure during 2001-2, 10 were potentially caused by herbals, but none attributed to Tribulus terrestris).

McKay D. Nutrients and botanicals for erectile dysfunction: examining the evidence. *Altern Med Rev.* 2004;9:4–16. PubMed PMID: 15005641.

- (Review of herbals used for erectile dysfunction; Tribulus has been claimed to increase dehydroepiandrosterone [DHEA] levels, but it has not been objectively studied in humans for either safety or efficacy in improving sexual function or athletic performance).*
- Neychev VK, Mitev VI. The aphrodisiac herb Tribulus terrestris does not influence the androgen production in young men. *J Ethnopharmacol.* 2005;101:319–23. PubMed PMID: 15994038.
- (Among 22 men treated with tribulus or placebo for 4 weeks, serum levels of testosterone, androstenedione and luteinizing hormone did not change).*
- Rogerson S, Riches CJ, Jennings C, Weatherby RP, Meir RA, Marshall-Gradisnik SM. The effect of five weeks of Tribulus terrestris supplementation on muscle strength and body composition during preseason training in elite rugby league players. *J Strength Cond Res.* 2007;21:348–53. PubMed PMID: 17530942.
- (A controlled trial of Tribulus terrestris vs placebo in 22 male rugby players for 5 weeks found no difference in gain in muscular strength, body composition or testosterone/epitestosterone levels).*
- García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. *Rev Esp Enferm Dig.* 2008;100:688–95. [Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry]. Spanish. PubMed PMID: 19159172.
- (Among 521 cases of drug induced liver injury submitted to Spanish registry, 13 [2%] were due to herbals, none due to aloe vera).*
- Navarro VJ. Herbal and dietary supplement hepatotoxicity. *Semin Liver Dis.* 2009;29:373–82. PubMed PMID: 19826971.
- (Overview of the regulatory environment, clinical patterns, and future directions in research with HDS; aloe vera is listed as a potential hepatotoxin but not specifically discussed).*
- 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 found no cases attributed to Tribulus terrestris).*
- 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 Tribulus).*
- Talasaz AH, Abbasi MR, Abkhiz S, Dashti-Khavidaki S. Tribulus terrestris-induced severe nephrotoxicity in a young healthy male. *Nephrol Dial Transplant.* 2010;25:3792–3. PubMed PMID: 20667992.
- (28 year old man developed seizures and fatigue 2 days after starting drinking 2 L of Tribulus terrestris water daily [creatinine 17.4 mg/dL, ALT 40 times ULN], resolving with stopping over the next 2 weeks).*
- Schmidt M, Thomsen M, Bone K. Tribulus terrestris-induced nephrotoxicity? *Nephrol Dial Transplant.* 2011;26:3065–6author reply 3066-7.
- (Letter questioning the association of tribulus ingestion with the injury reported by Talasaz [2010]).*
- Ho CC, Tan HM. Rise of herbal and traditional medicine in erectile dysfunction management. *Curr Urol Rep.* 2011;12:470–8. PubMed PMID: 21948222.
- (Review of herbals used for erectile dysfunction: Tribulus is advertised as being an aphrodisiac, but “there have been no studies yet on humans”).*

Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. *Liver Int.* 2011;31:595–605. PubMed PMID: 21457433.

(Review of current understanding of liver injury from herbals and dietary supplements focusing upon Herbalife and Hydroxycut products, green tea, usnic acid, noni juice, Chinese herbs, vitamin A and anabolic steroids; Tribulus terrestris is not discussed).

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 none contained Tribulus).

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, 15 of which [16%] were attributed to HDS products, but none were listed as containing Tribulus terrestris).

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 discuss Tribulus terrestris).

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).

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 including 1 linked with aloe vera in combination with 2 other agents).

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

(Review of the international regulatory framework for HDS products and the epidemiology, clinical presentation, diagnosis and cause of HDS associated liver injury with tables and discussion of the most commonly implicated agents, but tribulus is not mentioned).

Rossi S, Navarro VJ. Herbs and liver injury: a clinical perspective. *Clin Gastroenterol Hepatol.* 2014;12:1069–76. PubMed PMID: 23924877.

(Review of frequency, diagnosis and causes of liver injury from herbal products discusses kava, black cohosh, pyrrolizidine alkaloids, flavocoxid, glucosamine, saw palmetto, green tea, usnic acid and several proprietary herbal mixtures but not tribulus).

Santos CA Jr, Reis LO, Destro-Saade R, Luiza-Reis A, Fregonesi A. Tribulus terrestris versus placebo in the treatment of erectile dysfunction: A prospective, randomized, double blind study. *Actas Urol Esp.* 2014;38:244–8. PubMed PMID: 24630840.

(Among 30 healthy men with erectile dysfunction treated with Tribulus terrestris [800 mg] or placebo daily for 30 days, there were no differences in changes in sexual function or testosterone levels between the two groups; adverse events and serum ALT levels during therapy were not mentioned).

Akhtari E, Raisi F, Keshavarz M, Hosseini H, Sohrabvand F, Bioos S, Kamalinejad M, et al. Tribulus terrestris for treatment of sexual dysfunction in women: randomized double-blind placebo - controlled study. *Daru*. 2014;22:40. PubMed PMID: 24773615.

(Among 60 women with hypoactive sexual desire disorder treated with Tribulus terrestris [7.5 mg daily] or placebo for 4 weeks, those on Tribulus had greater improvements in desire, arousal, lubrication and satisfaction while adverse events were similar in the two treatment groups).

Ryan M, Lazar I, Nadasdy GM, Nadasdy T, Satoskar AA. Acute kidney injury and hyperbilirubinemia in a young male after ingestion of Tribulus terrestris. *Clin Nephrol*. 2015;83:177–83. PubMed PMID: 25295577.

(Healthy 30 year old man developed fatigue, weight loss, pruritus and jaundice 6 weeks after starting Tribulus terrestris as a body building supplement [bilirubin 36 mg/dL, ALT 90 U/L, Alk P 291 U/L], biopsy demonstrating bland cholestasis, with subsequent worsening and renal dysfunction [bilirubin 39 mg/dL, creatinine 3.1] but ultimate recovery; most likely due to illicit anabolic steroid use rather than Tribulus).

West E, Krychman M. Natural aphrodisiacs-A review of selected sexual enhancers. *Sex Med Rev*. 2015;3:279–288. PubMed PMID: 27784600.

(Review of the most popular aphrodisiac products marketed in the US mentions that it contains protodioscin which is converted to dehydroepiandrosterone and has been studied for effects on sexual dysfunction in women and has been well tolerating causing only minor gastrointestinal side effects; no mention of ALT levels or hepatotoxicity).

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.e3. PubMed PMID: 25500423.

(Extensive review of herbal associated liver injury does not discuss Tribulus specifically).

Cui T, Kovell RC, Brooks DC, Terlecki RP. A urologist's guide to ingredients found in top-selling nutraceuticals for men's sexual health. *J Sex Med*. 2015;12:2105–17. PubMed PMID: 26531010.

(Description and assessment of over-the-counter nutraceuticals used for male sexual dysfunction mentions that Tribulus was found in 43% of 30 products identified in doses ranging from 100 to 1000 mg and that controlled studies have found no evidence for its efficacy in improving men's sexual health and there have been two reports of renal and liver toxicity in young healthy men taking high doses).

Postigo S, Lima SM, Yamada SS, dos Reis BF, da Silva GM, Aoki T. Assessment of the effects of Tribulus terrestris on sexual function of menopausal women. *Rev Bras Ginecol Obstet*. 2016;38:140–6. PubMed PMID: 26902700.

(Among 60 postmenopausal women with sexual dysfunction treated with Tribulus terrestris [750 mg daily] or placebo for 90 day, sexual function improved to a greater extend in the Tribulus treated patients and common adverse events included diarrhea [13%], dizziness [10%] and nausea [10%], no mention of ALT levels or hepatotoxicity).

de Souza KZ, Vale FB, Geber S. Efficacy of Tribulus terrestris for the treatment of hypoactive sexual desire disorder in postmenopausal women: a randomized, double-blinded, placebo-controlled trial. *Menopause*. 2016;23:1252–1256. PubMed PMID: 27760089.

(Among 45 healthy postmenopausal women with diminished libido treated with Tribulus terrestris [750 mg daily] or placebo for 120 days, sexual desire and function improved to the same degree in both groups, although there

was a minimal increase in serum testosterone levels; 3 patients dropped out of both groups because of nausea; no mention of other adverse events, ALT levels or hepatotoxicity).

Roaiah MF, Elkhayat YI, Abd El Salam MA, Din SFG. Prospective analysis on the effect of botanical Meme (*Tribulus terrestris*) on serum testosterone level and semen parameters in males with unexplained infertility. *J Diet Suppl.* 2017;14:25–31. PubMed PMID: 27337519.

(Among 30 men with infertility treated with Tribulus terrestris [750 mg daily] or placebo for 3 months, there were no changes in testosterone and LH levels nor in semen quality; no mention of adverse events).

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, Tribulus is not listed).

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], while none were attributed to Tribulus).

Borrelli F, Colalto C, Delfino DV, Iriti M, Izzo AA. Herbal dietary supplements for erectile dysfunction: a systematic review and meta-analysis. *Drugs.* 2018;78:643–673. PubMed PMID: 29633089.

(Systematic review of the literature on herbal products used for erectile dysfunction mentions that two trials of Tribulus terrestris reported improvements in sexual function and one did not; no discussion of adverse events).

Sellami M, Slimeni O, Pokrywka A, Kuvačić G, D, Hayes L, Milic M, Padulo J. Herbal medicine for sports: a review. *J Int Soc Sports Nutr.* 2018;15:14. PubMed PMID: 29568244.

(Review of natural products used to enhance athletic performance mentions Tribulus terrestris contains saponins which may increase testosterone levels and improve physical fitness, but the medical literature demonstrates mixed results and high doses [above 1000 mg daily] may have significant side effects).

Vale FBC, Zanolli Dias de Souza K, Rezende CR, Geber S. Efficacy of Tribulus Terrestris for the treatment of premenopausal women with hypoactive sexual desire disorder: a randomized double-blinded, placebo-controlled trial. *Gynecol Endocrinol.* 2018;34:442–445. PubMed PMID: 29172782.

(Among 40 premenopausal women with diminished libido treated with Tribulus terrestris [750 mg daily] or placebo for 120 days, sexual function improved in both groups to a similar degree, and serum testosterone levels did not change; no mention of adverse events, but dropout rate was 38%).

GamalEl Din SF. Tribulus terrestris versus placebo in the treatment of erectile dysfunction and lower urinary tract symptoms in patients with late-onset hypogonadism: A placebo-controlled study. *Urologia.* 2019;86:74–78. Abdel Salam MA, Mohamed MS, Ahmed AR, Motawaa AT, Saadeldin OA, et al. PubMed PMID: 30253697.

(Among 70 “aging” men with erectile dysfunction and lower urinary tract symptoms treated with Tribulus terrestris daily for 3 months, total testosterone levels increased and sexual function was improved, while adverse events were rare and serum AST levels increased minimally [26.5 to 27.8 U/L]).

Ștefănescu R, Tero-Vescan A, Negroiu A, Aurică E, Vari CE. A Comprehensive review of the phytochemical, pharmacological, and toxicological properties of *Tribulus terrestris* L. *Biomolecules.* 2020;10:752. PubMed PMID: 32408715.

(Review of the phytochemical and toxicological features of Tribulus terrestris [spike fruit] mentions that it is a crawling herbal plant that grows in arid climates and sandy soils, extracts of which have been used in Chinese and Ayurvedic medicine and are generally well tolerated and that contamination or variation in local phytochemistry may account for occasional reports of toxicity).

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 none were attributed to Tribulus terrestris).

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]; there were no cases attributed to Tribulus terrestris).

Vale FBC, Boroni JD, Geber G, Antunes EMG, Bretas T, Lopes GP, Geber S. Effect of Tribulus terrestris in the treatment of female sexual dysfunction and clitoral vascularization. results of a randomized study comparing two different dosage regimes. *J Sex Marital Ther.* 2021;47:696–706. PubMed PMID: 34142638.

(Among 85 pre and post-menopausal women with sexual dysfunction treated with Tribulus terrestris in doses of 280 mg once daily or 94 mg three times daily for 90 days, symptoms of sexual function improved and serum levels of free testosterone levels increased while clitoral vascularization did not change).