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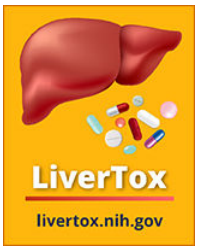

St. John's Wort

Updated: March 28, 2020.

OVERVIEW

Introduction

St. John's wort is a popular herbal medication and extract derived from the plant Hypericum perforatum which is purported to be beneficial in depression and anxiety. St. John's wort has not been implicated convincingly in cases of clinically apparent, acute liver injury, although it may increase the hepatotoxicity of other agents by herb-drug interactions that alter drug metabolism.

Background

St. John's wort (saynt jonz wort) is an extract prepared from the flowers and leaves of a flowering plant native to Europe commonly known as St. John's wort, Tipton's weed or chase-devil (Hypericum perforatum). St. John's wort is a yellow flowering perennial herb indigenous to Europe that has been introduced elsewhere. Its name refers to the Saint's day on which it is typically harvested – June 24th. The genus name Hypericum means "above the picture" in reference to its use to ward off evil by hanging the plant over a religious picture or icon. St. John's wort is an invasive weed in many countries where it has been introduced, where it can be toxic to livestock. St. John's wort has been used widely as an herbal treatment for depression. It is available as an over-the-counter herbal in the United States, but in other countries is actively prescribed for mild-to-moderate depression. Extracts of St. John's wort contain many polyphenols, including flavonoids (rutin, hyperoside, isoquercetin, quercitrin, quercetin and others), phenolic acids, naphthodianthrones (hypericin, pseudohypericin, protohypericin and others), and phloroglucinols (hyperforin, adhyperforin). The active principle responsible for the antidepressant effects of St. John's wort is not known, the most likely candidates being hypericin, pseudohypericin and hyperforin. In controlled trials, St. John's wort has shown evidence of an antidepressant effect in patients with mild to moderate depression. Side effects can occur with St. John's wort including gastrointestinal upset, dizziness, confusion, fatigue, anxiety and photosensitivity. Importantly, St. John's wort has effects on the cytochrome P450 system (induction of CYP 3A4 and 2C9) as well as the major drug transport protein – P-glycoprotein. As a result, St. John's wort has major drug interactions, particularly with birth control pills, transplant rejection agents, antiretroviral agents, digoxin, platelet inhibitors, anticoagulants and psychotropic agents. Caution should be taken and specific interactions sought when using St. John's wort with other medications.

Hepatotoxicity

Despite wide spread use, there have been no convincing case reports linking use of St. John's wort and hepatotoxicity. In controlled trials, St. John's wort has not been linked to serum enzyme elevations or to clinically apparent liver injury. Because of its many herb-drug interactions and effects on the P450 system and drug

transport and excretion, St. John's wort may increase or decrease the likelihood of drug induced liver injury from other medications.

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

Other Names: Goatweed, Hypericum

Drug Class: Herbal and Dietary Supplements

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

St. John's Wort – 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
St. John's Wort	68917-49-7	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 28 March 2020

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; St. John's wort 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]; St. John's wort is listed as nonhepatotoxic).

St. John's Wort. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 797-820.

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

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 herb-drug 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; St. John's wort is not discussed).

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

(Comprehensive review of herbal associated hepatotoxicity; St. John's wort is not listed as causing hepatotoxicity).

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 St. John's wort).

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 but none were attributed to St. John's wort).

Chalasani 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; St. John's wort is not listed).

Etogo-Asse F, Boemer F, Sempoux C, Geubel A. Acute hepatitis with prolonged cholestasis and disappearance of interlobular bile ducts following tibolone and Hypericum perforatum(St. John's wort). Case of drug interaction? Acta Gastroenterol Belg. 2008;71:36–8. PubMed PMID: 18396749.

(57 year old woman developed jaundice 2 years after starting tibolone for menopausal symptoms and 10 weeks after starting St. John's wort [bilirubin 6.3 rising to 37 mg/dL, ALT 424 U/L, Alk P 162 U/L, ANA 1:320], with prolonged jaundice and persistent Alk P elevations, biopsy showing paucity of bile ducts; authors suggest that St. John's wort may have potentiated the hepatotoxicity of tibolone).

Wang N, Li P, Wang Y, Peng W, Wu Z, Tan S, Liang S, et al. Hepatoprotective effect of Hypericum japonicum extract and its fractions. J Ethnopharmacol. 2008;116:1–6. PubMed PMID: 18178045.

(Extracts of St. John's wort provided partial protection against carbon tetrachloride injury in a rat model; fractionation of the extract suggested some of the effect was attributable to flavonoids).

Knüppel L, Linde K. Adverse effects of St. John's Wort: a systematic review. J Clin Psychiatry. 2004;65:1470–9. PubMed PMID: 15554758.

(Systematic review of side effects of St. John's wort, including 35 controlled trials found side effects were similar to those reported for placebo recipients and no serious adverse events were attributed to the herbal; case reports of adverse events included serotonin syndrome [18, with SSRIs], decrease in cyclosporine or tacrolimus levels after transplantation [16], increased INR on anticoagulants [13], phototoxicity [9] and allergic reactions [8]; among 722 reports to drug monitoring agencies, 24 [3%] were listed as hepatobiliary but no details were provided).

Gaster B, Holroyd J. St John's wort for depression: a systematic review. Arch Intern Med. 2000;160:152–6. PubMed PMID: 10647752.

(Systematic review of the literature concluded that St. John's wort is more effective than placebo in treatment of mild-to-moderate depression and has a low rate of side effects, occurring in only 2.4% of 3250 patients in open label studies and at rates only mildly higher than with placebo [and in lower rates that with conventional antidepressants] in controlled trials; no mention of ALT elevations or hepatotoxicity).

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).

Jacobson JM, Feinman L, Liebes L, Ostrow N, Koslowski V, Tobia A, Cabana BE, et al. Pharmacokinetics, safety, and antiviral effects of hypericin, a derivative of St. John's wort plant, in patients with chronic hepatitis C virus infection. Antimicrob Agents Chemother. 2001;45:517–24. PubMed PMID: 11158749.

(19 patients with chronic hepatitis C were treated with purified hypericin orally for 8 weeks; there were no changes in HCV RNA or ALT levels, but skin photosensitivity reactions were common).

Domínguez Jiménez JL, Pleguezuelo Navarro M, Guiote Malpartida S, Fraga Rivas E, Montero Alvarez JL, Poyato González A. Gastroenterol Hepatol. 2007;30:54–5. [Hepatotoxicity associated with Hypericum(St. John's wort)]. Spanish. PubMed PMID: 17266882.

(23 year old woman found to have chronic elevations in serum enzymes [ALT 48 to 265 U/L, GGT 28, Alk P 173 U/L] while taking St. John's wort; results on stopping herbal were not provided).

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; St. John's wort is not 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 mentions 44 reactions to St. John's wort, but none were categorized as hepatic).

Choi YH, Chin YW, Kim YG. Herb-drug interactions: focus on metabolic enzymes and transporters. Arch Pharm Res. 2011;34:1843–63. PubMed PMID: 22139685.

(Review of herb-drug interactions and their mechanistic basis; while in vitro studies suggest that St. John's wort might inhibit various P450 enzymes, in vivo studies show that it induces CYP 3A4, 1A and 2C9 as well as P-glycoprotein, leading to a lowering of serum levels of many drugs such as amitriptyline, cyclosporine, digoxin, fexofenadine, indinavir, methadone, midazolam, simvastatin, tacrolimus, theophylline and warfarin).

Chen XW, Sneed KB, Pan SY, Cao C, Kanwar JR, Chew H, Zhou SF. Herb-drug interactions and mechanistic and clinical considerations. Curr Drug Metab. 2012;13:640–51. PubMed PMID: 22292789.

(Review of literature on herb-drug interactions mentions that St. John's wort can lower concentrations of cyclosporine, tacrolimus, midazolam, digoxin, amitriptyline, indinavir, warfarin and theophylline).

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: St. John's wort is not discussed).

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 mentions that St. John's wort is a potent inducer of CYP 3A4 and can cause clinically significant herb-drug interactions with warfarin, aspirin, cyclosporine, methotrexate, HIV protease inhibitors, and can potentiate the intrinsic hepatotoxicity of other agents such as acetaminophen).

Posadzki P, Watson L, Ernst E. Herb-drug interactions: an overview of systematic reviews. Br J Clin Pharmacol. 2013;75:603–18. PubMed PMID: 22670731.

(Review of systematic reviews of herb-drug interactions, mentions that St. John's wort can cause induction of CYP 3A and affect levels of several drugs; no mention of adverse hepatic effects).

Posadzki P, Watson LK, Ernst E. Adverse effects of herbal medicines: an overview of systematic reviews. Clin Med (Lond). 2013;13:7–12. PubMed PMID: 23472485.

(Systematic review of systematic reviews of adverse effects of herbals mentions that Hypericum perforatum has been associated only with minor adverse events).

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, none of which were attributed to St. John's wort).

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, St. John's wort was not implicated in any case).

Agollo MC, Miszputen SJ, Diament J. Hypericum perforatum-induced hepatotoxicity with possible association with copaiba (Copaifera langsdorffii Desf): case report. Einstein (Sao Paulo). 2014;12:355–7. PubMed PMID: 25167337.

(79 year old woman developed jaundice while taking St. John's wort in addition to copaiba, glucosamine and chondroitin [bilirubin 9.0 mg/dL, ALT 1667 U/L], resolving rapidly once all medications were stopped).

Douros A, Bronder E, Andersohn F, Klimpel A, Kreutz R, Garbe E, Bolbrinker J. Herb-induced liver injury in the Berlin Case-Control Surveillance Study. Int J Mol Sci. 2016;17:E114. pii. PubMed PMID: 26784183.

(Among 198 patients with suspected drug induced liver injury seen at Berlin Hospitals and enrolled in a prospective database, 10 were attributed to herbal supplements including one case attributed to St. John's wort, in a 65 year old woman who developed symptoms of liver injury without jaundice an unspecified time after starting St. John's wort [bilirubin 2 times, ALT 19.2 times, Alk P 5.2 times ULN], resolving on stopping the supplement).

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 (Pt A): 472-501.

(Description of an online compendium of cases of liver toxicity attributed to HDS products, does not list St. John's wort as implicated in any cases of liver injury).