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Germander

Updated: March 12, 2018.

OVERVIEW

Introduction

Germander refers to about 250 species of plants in the mint family (genus: Teucrium) used for centuries in herbal teas and more recently marketed as a germander extract as an aid for weight control and management of diabetes and hyperlipidemia. Germander extracts have been linked to multiple instances of clinically apparent liver injury which can be severe and lead to fatality.

Background

Germander is derived from aerial parts of a perennial aromatic plant of the mint family (Teucrium Lamiaceae) which has been used in Europe for centuries to treat inflammatory and digestive disorders. Germander is also widely used in gardening for its attractive flowers and uniform shape. Only some species have been used as herbal medications. Germander (Teucrium chamaedrys) was purported to be beneficial in inflammatory conditions including fever, arthritis, gout and digestive complaints. Extracts of germander were developed and marketed in capsules of 600 mg in Europe as a weight loss and cholesterol lowering agent in the late 1980s. However, multiple reports of hepatotoxicity from germander (including from both pill form as well as in tea) led to its ban as an herbal medication in many countries. Nevertheless, raw germander remains available in some countries and other Teucrium L. species have been used as herbal medications and teas and have been linked to cases of liver injury.

Hepatotoxicity

Liver injury attributable to germander was first reported in a series of publications from France in 1992, a few years after a weight loss supplement containing germander ("Tealine") was commercially marketed in that country. The onset of acute injury varied from 2 to 18 weeks (averaging 9 weeks) after starting germander capsules or tea. The typical presentation was with fatigue, nausea and jaundice in an acute viral hepatitis-like syndrome with a hepatocellular pattern of serum enzyme elevations. Immunoallergic features were uncommon or minimal as were autoantibodies. Liver biopsies showed a prominence of centrilobular necrosis and inflammation with minimal fibrosis. Most patients recovered rapidly upon withdrawal of germander, but a few fatalities were reported. Rapid recurrence with reexposure was reported on multiple occasions. A second pattern of injury was identified with longer term therapy, generally after 6 to 9 months of treatment, characterized by a chronic hepatitis-like syndrome often with arthralgias and fever and low levels of autoantibodies and hyperglobulinemia, with liver biopsy showing chronic hepatitis and fibrosis. Germander was banned in several European countries and was never marketed to a major extent in the United States. Other species of Teucrium (polium, capitatum, viscidum) have been implicated in causing similar hepatocellular injury clinically and

histologically. Germander has been reported to be an adulterant of other herbal preparations including skullcap. Finally, germander has been implicated in liver injury, even when used to brew herbal teas. Because germander has been banned as a commercial extract, most recent cases have been due to brewing tea from leaves of locally collected germander plants.

Likelihood score: A (well established cause of clinically apparent liver injury).

Mechanism of Injury

Germander and other Teucrium extracts have many components including glycosides, flavonoids, saponins, volatile oils and furan containing neoclerodane diterpenoids, the last of which (Teucrin A and Teuchmaedryn A) are considered the hepatotoxins responsible for its liver injury. The furano neoclerodane diterpenoids are oxidized by the cytochrome P450 system to reactive metabolites that covalently bind to proteins, deplete glutathione and cause cell disruption (in hepatocyte cell culture). Thus, germander may be a direct hepatotoxin causing injury in a manner similar to acetaminophen overdose and attributable to use of the purified extract in higher doses for longer periods than with traditional use of the herb. On the other hand, the frequent rapid recurrence on restarting germander (even a different preparation) argues in favor of an immunologically mediated injury. Ironically, extracts of Teucrium have antioxidant effects and decrease liver injury in several animal models.

Outcome and Management

Hepatotoxicity from germander and other Teucrium extracts or tea preparations is usually self-limiting once the herbal is discontinued. Nevertheless, several cases of acute liver failure and death or liver transplantation after germander use have been reported as well as several instances of chronic hepatitis and cirrhosis. Germander has not been linked to vanishing bile duct syndrome. Because germander toxicity is associated with glutathione depletion in animal models, administration of N-acetylcysteine may be appropriate for acute, clinically apparent cases of hepatotoxicity. Recurrence upon rechallenge is common and should be avoided.

Drug Class: Herbal and Dietary Supplements

CASE REPORTS

Case 1. Acute self-limited hepatitis due to germander.

[Modified from Case 1: Pauwels A, Thierman-Duffaud D, Azanowsky JM, Loiseau D, Biour M, Levy VG. [Acute hepatitis caused by wild germander. Hepatotoxicity of herbal remedies. Two cases]. Gastroenterol Clin Biol 1992; 16: 92-5. French. PubMed Citation]

A 28 year old woman developed fatigue followed by jaundice 12 weeks after starting germander (620 mg daily) for weight loss. She had no previous history of liver disease and did not drink alcohol. She denied taking prescription medications and did not tell her physicians about the herbal use. Laboratory tests showed serum bilirubin of 9.6 mg/dL with marked elevations in ALT [35 times ULN], but minimal increase in alkaline phosphatase [1.4 times ULN]. Other causes of acute hepatitis were not found and abdominal ultrasound showed no abnormalities. Her symptoms resolved rapidly and all liver tests were normal one month after she stopped the herbal preparation (Table). Several years later, she restarted germander in combination with ephedra (500 mg/day) for weight loss, but developed nausea and fatigue within 2 to 3 weeks. Examination showed jaundice but no rash, fever or signs of chronic liver disease. Laboratory tests again showed elevations in serum bilirubin (6.1 mg/dL) and ALT (10 times ULN), with minimal increases in alkaline phosphatase (1.5 times ULN). There was no eosinophilia and the prothrombin time was normal. Tests for hepatitis A and B, cytomegalovirus, herpes simplex and human immunodeficiency virus infection were negative as were routine autoantibodies. Abdominal

ultrasound was again normal. She was advised to stop the herbals. Over the next month, her symptoms and laboratory tests abnormalities resolved completely.

Key Points

Medication:	Germander (620 mg daily)
Pattern:	Hepatocellular (R=25 initially, 6.7 on reexposure)
Severity:	3+ (jaundice, hospitalization)
Latency:	Initially 12 weeks, on restarting 2-3 weeks
Recovery:	1 month
Other medications:	On second occasion, ephedra

Laboratory Values

Weeks After Starting	Weeks After Stopping	ALT (Times ULN)	Alk P (Times ULN)	Bilirubin (mg/dL)	Other
0	Germander (620 mg daily) started for weight loss				
12 weeks	0	35	1.4	9.6	Admission
14 weeks	2 weeks	10		2.9	
20 weeks	8 weeks	5		1.6	
6 months	3 months	1	1		
Weeks After Restarting	2 years later, Germander and Ephedra started for weight loss				
3 weeks	0	10	1.5	6.1	Readmission
6 weeks	3 weeks	3.7		3.6	
12 weeks	9 weeks	0.9	0.7	0.6	
Normal Values		**<1.0**	**<1.0**	**<1.2**	

Comment

This was the initial report of germander hepatotoxicity and was typical of the average case, with onset after 12 weeks with an acute viral hepatitis-like presentation of fatigue and jaundice, markedly hepatocellular pattern of serum enzyme elevations, and rapid resolution with stopping therapy. Also typical was the more rapid recurrence and similar pattern of injury on restarting the herbal preparation. Finally, the patient did not reveal the herbal use during the initial episode, and despite its obvious link to the liver injury chose to restart the product in an attempt to induce weight loss. There is little evidence that germander causes weight loss, but there is clear evidence that it is hepatotoxic.

Case 2. Chronic hepatitis due to germander.

[Modified from Case 1: Ben Yahia M, Mavier P, Métreau JM, Zafrani ES, Fabre M, Gatineau-Saillant G, Dhumeaux D, Mallat A. [Chronic active hepatitis and cirrhosis induced by wild germander. 3 cases]. Gastroenterol Clin Biol 1993; 17: 959-62. French. PubMed Citation]

A 47 year old man developed fever, arthralgias and jaundice approximately 5 months after starting an herbal regimen for his diabetes consisting of daily tea with germander and other herbs. He had no history of liver disease, alcohol abuse or risk factors for viral hepatitis. Laboratory tests on initial presentation showed a total bilirubin of 6.3 mg/dL with marked elevations in serum ALT (50 times ULN), mild elevation in GGT (3 times ULN), but normal alkaline phosphatase and prothrombin time. White blood cell counts showed a mild

eosinophilia (770/μL). Tests for hepatitis A, B and C were negative as were autoantibodies. Jaundice resolved rapidly and serum enzymes improved, but remained elevated (2-5 times ULN) for over a year. A liver biopsy showed chronic hepatitis with portal and periportal fibrosis with centrilobular and bridging necrosis. On referral for further evaluation, his chronic ingestion of herbal tea was discovered. Within 3 weeks of stopping the preparation, serum ALT levels fell into the normal range.

Key Points

Medication:	Germander (650 mg daily) tea
Pattern:	Hepatocellular (R=50)
Severity:	3+ (jaundice, hospitalization)
Latency:	5 months
Recovery:	Enzymes normal 3 weeks after stopping
Other medications:	Other botanicals in the tea preparation included geranium, myrrh, blueberry, eucalyptus, bog bean, walnut, nettle, piquant nettle, and willow

Laboratory Values

Time After Starting	Time After Stopping	ALT (Times ULN)	GGT (Times ULN)	Bilirubin (mg/dL)	Other
5 months	0	50	3	6.3	Fever, arthralgias, jaundice
10 months	0	42	10	Normal	
20 monhts	0	5	2	Normal	Liver biopsy
2 years	0	4	1	Normal	
2.5 years	0	4	3	Normal	History of herbal use obtained
		Herbal tea with germander stopped			
31 months	3 weeks	1	1	Normal	
Normal Values		**<1.0**	**<1.0**	**<1.2**	

Comment

Drugs that can cause an acute viral hepatitis-like syndrome are often also capable of causing a chronic hepatitis pattern when given in low doses chronically (examples being methyldopa, nitrofurantoin and minocycline). The chronic hepatitis may resemble autoimmune hepatitis, but generally resolves once the agent is discontinued. Germander appears to share this characteristic, the chronic hepatitis developing in situations in which the herbal is continued despite evidence of hepatic injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Germander – Generic

DRUG CLASS

Herbal and Dietary Supplements

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Germander	ID: 0977081085	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 12 March 2018

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; mentions that germander has been implicated in at least 35 cases of hepatotoxicity, 2 of which were fatal and 4 causing chronic hepatitis).

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]*

mentions that germander was marketed in France starting in 1986 and widely used for weight control, but was then banned after reports of hepatotoxicity including acute and chronic hepatitis and liver failure were reported; mechanism of injury appears to be metabolic activation to a toxic intermediate [furan-containing neoclerodane diterpenoids]).

Germander. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007, pp 363-4.

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

Pauwels A, Thierman-Duffaud D, Azanowsky JM, Loiseau D, Biour M, Levy VG. [Acute hepatitis caused by wild germander. Hepatotoxicity of herbal remedies. Two cases]. Gastroenterol Clin Biol 1992; 16: 92-5. French. PubMed PMID: 1537487.

(Initial report of 2 cases of acute hepatitis caused by germander; 28 and 56 year old women who developed jaundice 6-12 weeks after starting germander [bilirubin 3.0-9.6 mg/dL, ALT 35-45 times ULN, Alk P 0.6-1.4 times ULN], resolving in 4-10 weeks, recurrence in one patient 3 weeks after restarting: Case 1).

Larrey D, Vial T, Pauwels A, Castot A, Biour M, David M, Michel H. Hepatitis after germander(Teucrium chamaedrys) administration: another instance of herbal medicine hepatotoxicity. Ann Intern Med 1992; 117: 129-32. PubMed PMID: 1605427.

(Concise summary of 7 cases of germander hepatotoxicity from France; 6 women and 1 man, ages 15 to 56 years, developing jaundice after taking germander capsules or tea for 3 to 18 weeks [bilirubin 4.0-27.7 mg/dL, ALT 9-61 times ULN, Alk P 0.5-3 times ULN], resolving in 1.5 to 6 months; 3 were reexposed and all had recurrence with jaundice, all ultimately recovered).

Castot A, Larrey D. [Hepatitis observed during a treatment with a drug or tea containing Wild Germander. Evaluation of 26 cases reported to the Regional Centers of Pharmacovigilance]. Gastroenterol Clin Biol 1992; 16: 916-22. French. PubMed PMID: 1493896.

(Summary of 26 patients who developed acute hepatitis while taking germander reported to French registry system; 25 women, 1 man, ages 14 to 59 years, taking germander for weight loss or digestive complaints, mostly using Tealine or Arkogelule, for 2-18 weeks, all with a hepatocellular pattern of liver enzymes [ALT 9 to 150 times ULN], almost all with jaundice and fatigue, one with pruritus, 5 with prolonged protime, 4 of 17 with low titers of autoantibodies, biopsies showing centro- or pan-lobular necrosis, all resolving within 6 to 24 weeks, 12 with positive rechallenge).

Diaz D, Ferroudji S, Heran B, Barneon G, Larrey D, Michel H. [Fulminant hepatitis caused by wild germander]. Gastroenterol Clin Biol 1992; 16: 1006-7. French. PubMed PMID: 1493887.

(35 year old woman developed nausea and abdominal pain 5 to 6 weeks after starting germander tea 4 times daily [bilirubin 17.8 rising to 29.2 mg/dL, ALT 48 times ULN, prothrombin 18%], resolving within 3 months of stopping).

Legoux JL, Maitre F, Labarrière D, Gargot D, Festin D, Causse X. [Cytolytic hepatitis and wild Germander: a new case with reintroduction]. Gastroenterol Clin Biol 1992; 16: 813-5. French. PubMed PMID: 1478415.

(A 36 year old woman developed fever, nausea and arthralgias 8 months after starting Tealine [900 mg of germander daily] and green tea [1500 mg daily], without jaundice [bilirubin 1.8 mg/dL, ALT 22 times ULN, Alk P normal], resolving in 3 months and recurring within 8 days of restarting another brand of germander [bilirubin 4 mg/dL, ALT 6 times ULN, Alk P normal], resolving in 6 months).

Mattei A, Bizollon T, Charles JD, Debat P, Fontanges T, Chevallier M, Trepo C. [Liver damage induced by the ingestion of a product of phytotherapy containing wild germander. Four cases]. Gastroenterol Clin Biol 1992; 16: 798-800. French. PubMed PMID: 1478408.

(Four cases of hepatitis due to germander; 3 women, 1 man, ages 15 to 53 with onset after 2 to 4 months, 3 with jaundice [bilirubin 2.0-19.6 mg/dL, ALT 10-80 times ULN, Alk P 1-2 times ULN], resolving in 2-3 months, 1 with recurrence on rechallenge).

Mostefa-Kara N, Pauwels A, Pines E, Biour M, Levy VG. Fatal hepatitis after herbal tea. Lancet 1992; 340 (8820): 674. PubMed PMID: 1355234.

(68 year old woman developed jaundice while taking a second course of "Tealine" which contains wilder germander [bilirubin 18.2 mg/dL, ALT 225 U/L, Alk P 80 U/L, prothrombin index 18%], with progressive hepatic failure and death 2 weeks later).

Dao T, Peytier A, Galateau F, Valla A. [Chronic cirrhogenic hepatitis induced by germander]. Gastroenterol Clin Biol 1993; 17: 609-10. French. PubMed PMID: 8253327.

(54 year old woman developed jaundice 4 months after starting daily use of germander tea [bilirubin 7.9 rising to 23.9 mg/dL, ALT 55 times ULN, Alk P 2.1 times ULN], with persistence of lesser abnormalities during long term, infrequent use [bilirubin 1.6-2.7 mg/dL, ALT 2.5-10.4 times ULN, Alk P 1-2.2 times ULN], with ascites and biopsy showing cirrhosis, enzymes improving on stopping).

Ben Yahia M, Mavier P, Métreau JM, Zafrani ES, Fabre M, Gatineau-Saillant G, Dhumeaux D, Mallat A. [Chronic active hepatitis and cirrhosis induced by wild germander. 3 cases]. Gastroenterol Clin Biol 1993; 17: 959-62. French. PubMed PMID: 8125230.

(3 cases of chronic liver injury attributed to germander; 2 women and 1 man, ages 37-47 years, developed fever, arthralgias and jaundice ~6 months after starting germander [bilirubin 6.3, 2.3 and 15.6 mg/dL, ALT 20-50 times ULN, Alk P 1-3 times ULN], biopsies showing chronic hepatitis with fibrosis or cirrhosis, enzymes improving rapidly on stopping herbal).

Loeper J, Descatoire V, Letteron P, Moulis C, Degott C, Dansette P, Fau D, Pessayre D. Hepatotoxicity of germander in mice. Gastroenterology 1994; 106: 464-72. PubMed PMID: 8299912.

(Concentrated furano neo-clerodane diterpenoids isolated from germander tea induced midzonal liver cell necrosis in mice, which was prevented by inhibition of CYP 3A activity and worsened by glutathionine depletion).

Mattei A, Rucay P, Samuel D, Feray C, Reynes M, Bismuth H. Liver transplantation for severe acute liver failure after herbal medicine(Teucrium polium) administration. J Hepatol 1995; 22: 597. PubMed PMID: 7650341.

(37 year old Greek woman developed jaundice 5 days after a second 10 day use of Teucrium polium tea [bilirubin rising to 30.9 mg/dL, ALT 150 times ULN, Alk P 198, prothrombin 21%], undergoing liver transplantation, explant showing massive necrosis).

Lekehal M, Pessayre D, Lereau JM, Moulis C, Fouraste I, Fau D. Hepatotoxicity of the herbal medicine germander: metabolic activation of its furano diterpenoids by cytochrome P450 3A depletes cytoskeleton-associated protein thiols and forms plasma membrane blebs in rat hepatocytes. Hepatology 1996; 24: 212-8. PubMed PMID: 8707265.

(The furano diterpenoids of germander was toxic to isolated hepatocytes, the injury being blocked by inhibition of CYP3A and enhanced by glutathione depletion).

Laliberté L, Villeneuve JP. Hepatitis after the use of germander, a herbal remedy. CMAJ. 1996; 154: 1689-92. PubMed PMID: 8646656.

(Two cases of germander hepatotoxicity from Canada; 55 and 45 year old women taking extract for 6 months developed jaundice [bilirubin 13.9 and 3.5 mg/dL, ALT 1500 and 451 U/L, Alk P 164 and 79 U/L], resolving in 2 months; one had severe recurrence one week after restarting).

Cartagenes PRB, Moreira CC, Teixeira AC, Silveira FAA, Dias-Junior IB, Bichara CDA. [Hepatitis from sacaca(Croton Cajucara Benth): epidemiological and clinical features of 25 cases.] Gastroenterologia Endoscopia Digestiva 18(Supl 1): 24: 1999. Not in PubMed.

Stickel F, Egerer G, Seitz HK. Hepatotoxicity of botanicals. Public Health Nutr 2000; 3: 113-24. PubMed PMID: 10948380.

(Review of hepatotoxicity of herbal medications; germander is a member of the Labiatae family used for 2000 years as a remedy and considered safe, although components were unknown; large scale use resulted in large number of acute, chronic and even fulminant hepatitis cases in France; presumed cause are the furano neoclerodane diterpenoids).

Pérez Alvarez J, Sáez-Royuela F, Gento Peña E, López Morante A, Velasco Osés A, Martín Lorente J. [Acute hepatitis due to ingestion of Teucrium chamaedrys infusions]. Gastroenterol Hepatol 2001; 24:240-3. Spanish. PubMed PMID: 11412592.

(Two cases of hepatotoxicity due to germander: 70 year old man developed jaundice 6 months after starting herbal tea containing T. chamaedrys [bilirubin 8.5 mg/dL, ALT 1846 U/L, Alk P ~2 times ULN], resolving in 3 months; 49 year old woman developed jaundice 7 months after starting herbal tea with T. chamaedrys [bilirubin 18.7 mg/dL, ALT 1444 U/L, Alk P ~1.6 times ULN] resolving within 4 months).

Dourakis SP, Papanikolaou IS, Tzemanakis EN, Hadziyannis SJ. Acute hepatitis associated with herb(Teucrium capitatum L.) administration. Eur J Gastroenterol Hepatol 2002; 14: 693-5. PubMed PMID: 12072605.

(62 year old man developed jaundice 4 months after starting Teucrium capitatum containing herbal tea [bilirubin 21.4 mg/dL, ALT 1400 U/L, Alk P 177 U/L, ANA 1:640], resolving within 9 weeks with disappearance of ANA positivity).

Polymeros D, Kamberoglou D, Tzias V. Acute cholestatic hepatitis caused by Teucrium polium (golden germander) with transient appearance of antimitochondrial antibody. J Clin Gastroenterol 2002; 34: 100-1. PubMed PMID: 11743258.

(70 year old woman developed jaundice after 3 months of taking a Teucrium polium extract [bilirubin 38 mg/dL, ALT 1321 U/L, Alk P 318 U/L, AMA 1:160], resolving in 3 weeks and AMA becoming negative).

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).

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).

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

(Comprehensive review of herbal associated hepatotoxicity, including common patterns of presentation).

Mazokopakis E, Lazaridou S, Tzardi M, Mixaki J, Diamantis I, Ganotakis E. Acute cholestatic hepatitis caused by Teucrium polium L. Phytomedicine 2004; 11: 83-4. PubMed PMID: 14971726.

(67 year old man developed jaundice 6 months after starting Teucrium polium tea [bilirubin 11.4 mg/dL, ALT 1272 U/L, Alk P 190 U/L, eosinophils 7%], resolving within 1 month of stopping).

Soares M do CP. Would Sacaca, Croton cajucara Benth(Euphorbiaceae) be an hepatotoxic plant like Germander, Teucrium chamaedrys L.(Labiatae)? Rev Soc Bras Med Trop 2004; 37 Suppl 2: 96-7. PubMed PMID: 15586905.

(Sacara [Croton cajucara Benth] is a common Brazilian shrub, the bark and leaves of which are used in herbal medicine to treat diarrhea and diabetes and have been marketed for weight loss; sacara like Teucrium chamaedrys contains a furano diterpenoid [Crotonin] similar to that found in germander [Teucrin A], which may account for the recent large number of cases of hepatotoxicity attributed to Sacara).

Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of Centella asiatica. Rev Esp Enferm Dig 2005; 97: 115-24. PubMed PMID: 15801887.

(Initial report of clinically apparent hepatotoxicity due to Centella asiatica which contains triterpenic saponsoides similar to Teucrim; 3 cases, all women, ages 49 to 61 years who developed jaundice 3-8 weeks after starting Centella for weight loss [bilirubin 2.5-15.1 mg/dL, ALT 324-1694 U/L, Alk P 472-503 U/L], one with autoantibodies, resolving in 1-2 months of stopping; recurrence within 2 weeks in one patient who restarted it).

Starakis I, Siagris D, Leonidou L, Mazokopakis E, Tsamandas A, Karatza C. Hepatitis caused by the herbal remedy Teucrium polium L. Eur J Gastroenterol Hepatol 2006; 18: 681-3. PubMed PMID: 16702859.

(70 year old man developed jaundice 1 month after starting daily ingestion of an herbal tea containing Teucrium polium [bilirubin 2.7 mg/dL, ALT 649 U/L, Alk P 121 U/L, ANA 1:80], resolving in 8 weeks [ANA negative]).

Savvidou S, Goulis J, Giavazis I, Patsiaoura K, Hytiroglou P, Arvanitakis C. Herb-induced hepatitis by Teucrium polium L.: report of two cases and review of the literature. Eur J Gastroenterol Hepatol 2007; 19: 507-11. PubMed PMID: 17489062.

(47 year old woman found to have high ALT levels having consumed Teucrium polium tea for 3 months [bilirubin 1.8 mg/dL, ALT 677 U/L, Alk P 132 U/L], worsening for a month and then resolving a month later; 64 year old woman developed jaundice after taking Teucrium polium tablets for 2 months [bilirubin 11.2 mg/dL, ALT 1260 U/L, Alk P 386 U/L, 5.7% eosinophils], worsening for 20 days and resolving a month later).

Seeff LB. Herbal hepatotoxicity. Clin Liver Dis 2007; 11: 577-96. PubMed PMID: 17723921.

(Review of herbal induced hepatotoxicity, with detail of specific herbal compounds including review of literature of germander hepatotoxicity).

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, but no case was attributed to germander).

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. Spanish. PubMed PMID: 19159172.

(Among 521 cases of drug induced liver injury submitted to a Spanish registry, 13 [2%] were due to herbals, none due to germander).

Poon WT, Chau TL, Lai CK, Tse KY, Chan YC, Leung KS, Chan YW. Hepatitis induced by Teucrium viscidum. Clin Toxicol(Phila) 2008; 46: 819-22. PubMed PMID: 18608288.

(51 year old woman developed jaundice 3 days after using herbal tea containing Teucrium viscidum [which has a similar diterpenoid: Teucvin] [bilirubin 11.4 mg/dL, ALT 2620 U/L, Alk P 186 U/L], resolving in 2 months).

Herrera S, Bruguera M. [Hepatotoxicity induced by herbs and medicines used to induce weight loss]. Gastroenterol Hepatol 2008; 31: 447-53. PubMed PMID: 18783691.

(Review of the hepatotoxicity of weight loss agents, both prescriptions and herbals; discussion of the epidemic of hepatitis caused by wild germander in France).

Chitturi S, Farrell GC. Hepatotoxic slimming aids and other herbal hepatotoxins. J Gastroenterol Hepatol 2008; 23: 366-73. PubMed PMID: 18318821.

(Review of the hepatotoxicity of botanicals used for weight loss including green tea extracts [Exolise, Hydroxycut, The Right Approach], Ma Huang, usnic acid [LipoKinetix] and Teucrium chamaedrys [germander], capitatum and polium and other terpenoid containing compounds such as skullcap and Centella asiatica).

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; germander is listed as a potential hepatotoxin, but is not specifically discussed).

Mimidis KP, Papadopoulos VP, Baltatzidis G, Giatromanolaki A, Sivridis E, Kartalis G. Severe acute cholestasis caused by Teucrium polium. J Gastrointestin Liver Dis 2009; 18: 387-8. PubMed PMID: 19795041.

(51 year old man developed jaundice two months after starting aqueous extract of Tecurium polium [bilirubin 9.8 rising to 37.4 mg/dL, ALT 863 U/L, Alk P 147 U/L], worsening for 11 days and then resolving within the next few months).

Lin LZ, Harnly JM, Upton R. Comparison of the phenolic component profiles of skullcap (Scutellaria lateriflora) and germander (Teucrium canadense and T. chamaedrys), a potentially hepatotoxic adulterant. Phytochem Anal 2009; 20: 298-306. PubMed PMID: 19402188.

(Herbal extracts of skullcap [S. lateriflora] have occasionally been contaminated with germander [T chamaedrys], but mass spectrometry can separate the two by demonstration of phenylethanoid components of germander).

Sáenz De Miera Olivera I, Fernández Marcos C, Sáez-Royuela Gonzalo F. [Ingestion of Teucrium chamaedrys infusions: evidence of acute hepatitis after its reintroduction]. Gastroenterol Hepatol. 2009; 32: 70-1. Spanish. PubMed PMID: 19174107.

(41 year old man developed mild abdominal discomfort and ALT elevations during use of Teucrium chamaedrys herbal teas on two occasions [bilirubin normal, ALT 459 U/L, GGT 84 U/L, ANA negative], resolving in 3 months of stopping).

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 usnic acid [2], thermoslim [1], Ma Huang [1], horny goat weed [1], black cohosh [1], Hydroxycut [1] and unspecified herbals [4]; germander not listed).

Goksu E, Kilic T, Yilmaz D. Hepatitis: a herbal remedy Germander. Clin Toxicol (Phila) 2012; 50: 158. PubMed PMID: 22304375.

(69 year old Turkish man developed jaundice 1 month after completing a 2 month course of daily ingestion of germander plant tea [bilirubin 3.8 mg/dL, ALT 1380 U/L, Alk P 152 U/L], resolving within 1 month).

Gori L, Galluzzi P, Mascherini V, Gallo E, Lapi F, Menniti-Ippolito F, Raschetti R, et al. Two contemporary cases of hepatitis associated with Teucrium chamaedrys L. decoction use: case reports and review of literature. Basic Clin Pharmacol Toxicol 2011; 09: 521-6. PubMed PMID: 21848806.

(A husband and wife, ages 66 and 65 years, developed fatigue and nausea after regular use of an herbal tea [bilirubin normal, ALT 340 and 155 U/L, GGT 50 and 180 U/L], which resolved within 3 months but recurred in both when they restarted the decoction; testing of the herb showed T. chamaedrys).

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 6 publications on germander [T. chamaedrys and polium]).

Sezer RG, Bozaykut A. Pediatric hepatotoxicity associated with polygermander (teucrium polium). Clin Toxicol (Phila) 2012; 50: 153. PubMed PMID: 22295888.

(2 twins who given tea made from Teurcrium polium in their infant formula daily presented with vomiting and abnormal liver tests [bilirubin 0.5 and 1.0 mg/dL, ALT 139 and 431 U/L], resolving within 4-5 weeks of stopping).

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 discusses the hepatotoxicity of germander).

Teschke R, Genthner A, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: Analysis of cases with initially reported positive re-exposure tests. Dig Liver Dis 2014; 46: 264-9. PubMed PMID: 24315480.

(Reanalysis of 34 published cases of liver injury due to herbal medications in which there was a reported positive rechallenge, finding only 21 [62%] fulfilled the criteria of a positive rechallenge using RUCAM, the others having inconsistent [18%] or incomplete data [21%]; among 4 cases attributed to germander, all 4 rechallenges were scored as positive).

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; does not include cases linked to germander).

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 germander).

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 herbal hepatotoxicity discusses Teucrium chamaedrys as an ingredient in popular slimming aids with more than 50 cases of toxic hepatitis linked to its use, largely from France and usually presenting after 2-3 months of use with an acute hepatocellular pattern of injury).

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; mentions that germander has been used as an antiinflammatory agent but also for weight loss and has been linked to many cases of hepatitis, some fatal).

Dağ MS, Aydınlı M, Oztürk ZA, Türkbeyler IH, Koruk I, Savaş MC, Koruk M, et al. Drug- and herb-induced liver injury: a case series from a single center. Turk J Gastroenterol 2014; 25: 41-5. PubMed PMID: 24918129.

(Between 2008 and 2012, 82 patients with drug or herbal supplement induced liver injury were seen at a single referral center in Turkey, 10 [12%] of which were due to HDS products, including 7 due to Teucrium polium [mountain germander] and 3 to green tea extract).

Dag M, Özturk Z, Aydnl M, Koruk I, Kadayfç A. Postpartum hepatotoxicity due to herbal medicine Teucrium polium. Ann Saudi Med 2014; 34: 541-3. PubMed PMID: 25971830.

(3 women, ages 31 to 37 years, developed liver injury while taking Teucrium polium for dyspeptic symptoms during the last trimester or immediate postpartum period [bilirubin 14-23 mg/dL, ALT 1212-2397 U/L, Alk P 200-586 U/L]).

Nencini C, Galluzzi P, Pippi F, Menchiari A, Micheli L. Hepatotoxicity of Teucrium chamaedrys L. decoction: role of difference in the harvesting area and preparation method. Indian J Pharmacol 2014; 46: 181-4. PubMed PMID: 24741190.

(A man and woman, ages 64 and 65 years, developed severe hepatitis [bilirubin and Alk P not given, ALT above 5 times ULN] which resolved within 2 months, but recurred a month after restarting a decoction of Teucrium chamaedrys, made by boiling the flowering parts of the herb that they had collected locally).

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 to a known germander containing product).

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

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and assessing causality; does not discuss germander).

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, mentions that germander has been linked to many cases of hepatotoxicity presenting as acute or chronic hepatitis, cirrhosis and acute liver failure with massive necrosis).

Korth C. Drug-induced hepatotoxicity of select herbal therapies. J Pharm Pract 2014; 27: 567-72. PubMed PMID: 25546878.

(Review of liver injury due to selected HDS discusses the literature implicating kava, green tea, germander, pyrrolizidine alkaloids and Herbalife products).

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 there have been numerous reports of liver injury from germander).

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 mentions that germander is a well established cause of liver injury, and similar cases have been linked to other members of the Teucrium family such as T. polium and T. viscidum).

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%], none of which were primarily attributed to germander: see Navarro [2014]).

Zheng EX, Navarro VJ. Liver injury from herbal, dietary, and weight loss supplements: a review. J Clin Transl Hepatol 2015; 3: 93-8. PubMed PMID: 26357638.

(Review of literature on liver injury due to HDS products used for weight loss, focusing upon the case series of liver injury attributed to Herbalife, Hydroxycut and OxyELITE Pro products which was predominantly hepatocellular (acute hepatitis-like) and had a significant mortality rate; does not discuss germander).

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by Dietary Supplements: A tabular listing and clinical characteristics. Int J Mol Sci 2016; 17. pii: E537. PubMed PMID: 27070596.

(Listing of published cases of liver injury from HDS products does not discuss germander]).

Avigan MI, Mozersky RP, Seeff LB. Scientific and regulatory perspectives in herbal and dietary supplement associated hepatotoxicity in the United States. Int J Mol Sci 2016; 17: 331. PubMed Citation (Overview of the US regulations regarding herbal and dietary supplements and role of FDA, Department of Agriculture, Federal Trade Commission and Office of Dietary Supplements of the NIH in assessment of safety of HDS products including actions taken against Hydroxycut, Lipokinetix and OxyELITE Pro when reports of liver injury appeared in postmarketing phase).

Marcus DM. Dietary supplements: What's in a name? What's in the bottle? Drug Test Anal 2016; 8 (3-4): 410-2. PubMed Citation (Commentary on regulation of HDS products concludes: "the marketing of botanical supplements is based on unfounded claims that they are safe and effective", and "there is no reason to take herbal medicines whose composition and benefits are unknown and whose risks are evident").

Brown AC. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series. Food Chem Toxicol 2017; 107(Pt A): 449-71. PubMed PMID: 27818322.

(Summary of the US regulations on safety and efficacy of herbal and dietary supplements).

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. PubMed PMID: 27402097.

(Description of an online compendium of cases of liver toxicity attributed to HDS products, mentions that germander was the most frequently implicated herb in causing liver injury, listing 23 references of single case reports and case series).

Wong LL, Lacar L, Roytman M, Orloff SL. Urgent liver transplantation for dietary supplements: an under-recognized problem. Transplant Proc 2017; 49: 322-5. PubMed PMID: 28219592.

(Among 2048 adult liver transplants recipients enrolled in the Scientific Registry of Transplant Recipients [SRTR] between 2003 and 2015, 625 were done for acute hepatic nerosis due to drug induced liver injury, half being due to acetaminophen and the 4th most frequent cause [n=21] being HDS products).

de Boer YS, Sherker AH. Herbal and dietary supplement-induced liver injury. Clin Liver Dis 2017; 21: 135-49. PubMed PMID: 27842768.

(Review of the frequency, clinical features, patterns of injury and outcomes of HDS hepatotoxicity with specific mention of anabolic steroids, black cohosh, germander, green tea, pyrrolizidine alkaloids and proprietary multi-ingredint nutrition supplements [MINS]).

Vega M, Verma M, Beswick D, Bey S, Hossack J, Merriman N, Shah A, et al.; Drug Induced Liver Injury Network (DILIN). The incidence of drug- and herbal and dietary supplement-induced liver injury: preliminary findings from gastroenterologist-based surveillance in the population of the State of Delaware. Drug Saf 2017; 40: 783-7. PubMed PMID: 28555362.

(A prospective, population based registry of cases of drug induced liver injury occurring in Delaware during 2014, identified 20 cases [2.7 per 100,000] overall, including 6 due to HDS products, all of which were proprietary multiingredient products, none specifically mentioning germander).