Liver toxicity of products containing Ashwagandha

Introduction

Withania somnifera, commonly known as “Ashwagandha” or “Indian ginseng” is a therapeutic plant, widely cultivated in India and throughout the Middle East and is found in eastern Africa. Ashwagandha belongs to the genus *Withania* and family *Solanaceae*[1, 2]. The principal bioactive compounds of *Withania somnifera* are withanolides, which are triterpene lactones. More than 40 withanolides, approximately 12 alkaloids and several sitoindosides have been isolated and identified from *Withania somnifera*. The withanolides are structurally related to the ginsenosides of Panax ginseng, hence the common name "Indian ginseng"[1]. *Withania somnifera* is supposed to have various biological actions such as anti-cancer, anti-inflammatory, anti-diabetic, anti-microbial, anti-arthritic, anti-stress/adaptogenic, neuro-protective, cardio-protective, hepato-protective and immunomodulatory properties. It is regularly used, alone or in combination with other plants for the treatment of various illnesses[2]. Ashwagandha has been used as an adaptogen, diuretic and sedative in traditional medicine[1]. Its efficacy has not been consistently shown in rigorously controlled prospective studies, but it has been used in Ayurvedic medicine for centuries and is currently becoming a popular herbal product in Western countries[3].

Information about adverse reactions is scarce, since limited clinical trials are available. Somnolence, diarrhoea and abdominal pain have been more commonly reported with ashwagandha compared to placebo[1]. In clinical trials, there have been no reports of serum liver enzyme elevations occurring during therapy and no mention of serious adverse events or hepatotoxicity[3]. Recently, however, several cases of clinically apparent liver injury have been reported in patients taking commercial herbal products that are labelled as containing Ashwagandha[3].

Products containing Ashwagandha are available in the Netherlands as dietary supplements.

Reports

In the period from November 2018 until August 2023 Lareb received four reports on liver toxicity associated with products containing Ashwagandha (Table 1). Listed ingredients of the suspected products are shown in Table 2.

Table 1. Reports on liver toxicity associated with products containing Ashwagandha

No	ID, sex, age, primary source	Drug	Dosage	Indication	Concomitant medication	Reported ADRs	Latency after start	Action taken	Outcome
1	NL-LRB-00861365, female, 20-30 years, Consumer or other non health professional	Stress-Less Viteezy	1 tablet / 1 Days	Stress	Prenatal Viteezy, Energy Assistant Viteezy	Hepatitis	5 Months	Drug Withdrawn	Recovering
2	NL-LRB-00306040, male, 30-40 years, Physician	Kudzu Optimum Exendo, NMDA Relief Exendo,	1 capsule / 1 Days	Stress		Hepatitis	3 weeks 3 months	Unknown	Recovering

		Mentalis Stress Trenker					3 months		
3	NL-LRB-00903093, female, 60-70 years, Physician	Ashwaganda organic poeder bio Hanoju	0.5 teaspoon / 1 Days	Cognitive disorder	Vitamin C, Vitamin B complex	Liver function test abnormal, Icterus, Transaminitis, Cholestasis	10 Months 10 Months 10 Months 10 Months	Drug Withdrawn	Recovering
4	NL-LRB-00899249, female, 30-40 Years, Physician	Ashwagandha Ksm 66 Holland & Barrett	1 capsule / 1 Days	Panic reaction Stress	Lorazepam, Macrogol Drink	Hepatic function abnormal	5 Months	Drug Withdrawn	Recovering

NL-LRB-00861365: Five months after start of Stress-Less Viteezy the patient experienced a hepatitis with jaundice, abdominal pain, nausea, vomiting, inflammation of the skin, myalgia, earache, fatigue and fever. She was admitted to the Emergency department where a liver biopsy, echo and blood test were performed (results are unknown). She was treated with pain medication, medication to treat her nausea and corticosteroid cream. At the moment of reporting she is recovering. The suspected product contains multiple herbs and other ingredients, however, only the ingredient Ashwagandha is mentioned as a probable cause of clinically apparent liver injury in LiverTox[3]. Her comedication also contains multiple herbs and vitamins, but these herbs and vitamins are not mentioned in LiverTox as a cause of liver injury[3]. Development of liver function test over time were not reported. Serological tests for hepatitis A,B,C, CMV, HSV, EBV were not reported. The RUCAM (Roussel Uclaf Causality Assessment Method) was used to asses causality of drug induced liver injury[4]. For this case a RUCAM causality assessment is unreliable because of missing detailed information for several key elements (no specification of liver enzyme levels, course of liver enzymes and exclusion of other causes of liver injury).

NL-LRB-00306040: The patient was hospitalised and received conservative treatment. Liver function tests showed ASAT 2600 U/L, ALAT 4100 U/L , AP 288 U/L and total bilirubin 150 umol/L. The patient has a mixed hepatic injury. Of the three suspect products only NMDA Relief Exendo and Mentalis Stress Trenker contain ingredients mentioned to cause liver injury in LiverTox. NMDA Relief Exendo contains *Scutellaria baicalensis* (very likely but rare cause of clinically apparent liver injury according to LiverTox)[3]. Mentalis Stress Trenker contains Ashwagandha (probable cause of clinically apparent liver injury according to LiverTox)[3]. It is not reported if the patient suffered from abdominal pain, fever, jaundice or itching. Development of liver function test over time were not reported. Serological tests for hepatitis A,B,C, CMV, HSV or EBV were not reported. For this case a RUCAM causality assessment is unreliable because of missing detailed information for several key elements (course of liver enzymes and exclusion of other causes of liver injury).

NL-LRB-00903093: Liver function tests one year after start of using Ashwagandha powder showed ASAT 1138 U/L, ALAT 1278 U/L, AP 157 U/L and total bilirubin 176 umol/L. Other symptoms reported were fatigue. Five weeks earlier the patient had an increased INR. The patient also used vitamin C and vitamin B complex, no other comedication was used. The patient has no history of liver function disorder and does not use alcohol. Tests excluded hepatitis A, B, C and E. HSV was not tested. Auto-immune hepatitis was excluded. Patient had had an EBV infection in the past. The initial step in the RUCAM assessment is to define whether the hepatic injury is “hepatocellular”, “mixed”, or “cholestatic.” These terms refer to the pattern of serum enzyme elevations at disease onset and are defined by calculation of the “R ratio”. This case had an R value of 23, which results in a

"hepatocellular" hepatic injury. The RUCAM score was 6 ('probable' that the drug is a cause of the liver injury).

NL-LRB-00899249: The patient was hospitalised for observation of her liver function. Liver function test were two weeks after start slightly raised, but increased further in the months thereafter. Five months after start liver function test showed ASAT 221 U/L, ALAT 489 U/L, AP 366 U/L and total bilirubin 4 umol/L (Reference values ASAT 31 U/L, ALAT 34 U/L, AP 98 U/L and total bilirubin 17 umol/L). The patient reported not to use any alcohol. She reported to use lorazepam as comedication. The product information of lorazepam mentions abnormal liver function tests as adverse drug reaction[5]. Tests excluded hepatitis C. Patient was vaccinated for hepatitis B and had had an infection of CMV and EBV in the past. Abdominal CT and abdominal ultrasound were without abnormalities. This case had an R value of 2.4, which results in a "mixed" hepatic injury. The RUCAM score was 2 ('unlikely' that the drug is a cause of the liver injury). However, not all information was available resulting in less points that could be added.

Table 2. Product information of the products containing Ashwagandha in the reports

Product	Ingredients per dose form	Recommended daily dose
Stress-Less Viteezy	*Melissa officinalis* (4:1 extract) 30 mg; *Ashwagandha* (2:1 extract) 75 mg; *Rhodiola rosea* (2:1 extract) 100 mg; *Maca* (4:1 extract) 10 mg; *Panax ginseng* (1:1 extract) 100 mg; Magnesium (taurate) 18 mg; Zinc (bisglycinate) 25 mcg; Vitamin B12 (adenosylcobalamin) 500 mcg; Vitamin B12 (methylcobalamin) 500 mcg; Taurine 50 mg	1 tablet per day
Mentalis stress Trenker	*Ashwagandha* extract (KSM-66 300 mg; 100% inactivated Saccharomyces Cerevisiae 100 mg; Magnesiumoxide 75 mg; vitamin B3 8 mg; superoxide dismutase (SOD 15000 IU/g) (*Cucumis melo* L.) 5 mg; vitamin B5 3 mg; vitamin B6 0.7 mg; vitamin B2 0.7 mg; vitamin B1 0.55 mg; vitamin B9 100 µg; vitamin B8 25 µg; vitamin B12 1,25 µg	1-2 capsules per day

Biologische Ashwagandha poeder Hanoju	*Ashwagandha* powder	3 grams per day
Ashwagandha KSM 66 Holland & Barrett	*Ashwagandha* extract KSM-66® (root) 500 mg, cellulose, zinc oxide	1 capsule per day

Other sources of information

Literature

Various cases of Ashwagandha-related liver injury have been reported in the literature. The liver enzyme abnormalities in most patients self-resolved within one to five months after withdrawal [6-17]. Björnsson et al. has published a series of five cases, with two from the USA and three from Iceland suspecting Ashwagandha-induced liver injury. The described patients had a mean age of 43 years, and developed cholestatic jaundice after a latency ranging from 2 to 12 weeks. Liver injury was cholestatic or mixed. Other causes for liver injury were excluded [6]. Ireland et al. reported another case of a 39-year old woman developing acute hepatitis, classified as hepatocellular, following the use of Ashwagandha [8]. In addition Weber et al. reported a case of a 40-year-old man with acute liver injury after using Ashwaganda. The type of liver injury was not further specified [17]. Toth et al. reported a case of Ashwagandha-induced acute liver injury, with jaundice two weeks after start of Ashwagandha [16]. The liver biopsy revealed prominent hepatocellular and canalicular cholestasis as well as spotty hepatocellular necrosis. Other causes for liver injury were excluded. Suryawanshi et al. reported a case of a 41-year-old female that developed a hepatocellular pattern of acute liver failure and required liver transplantation after two months use of Ashwagandha [15].

Other databases

The WHO database (Vigibase) contains 15 reports of Hepatobiliary disorders (SOC) and Hepatobiliary investigations (HLGT) of the Investigations (SOC) associated with Withania somnifera (Table 3).

Table 3. Cases of liver toxicity associated with Withania somnifera in Vigibase

Active ingredient	Reaction (PT)	Number of reports
Withania somnifera	Jaundice	7
Withania somnifera	Cholestasis	3
Withania somnifera	Blood bilirubin increased	2
Withania somnifera	Liver function test abnormal	2
Withania somnifera	Jaundice cholestatic	1
Withania somnifera	Acute hepatic failure	1
Withania somnifera	Hypertransaminasaemia	1

Withania somnifera	Hepatitis cholestatic	1
Withania somnifera	Drug-induced liver injury	1
Withania somnifera	Hyperbilirubinaemia	1
Withania somnifera	Liver injury	1
Withania somnifera	Hepatic failure	1
Withania somnifera	Hepatitis	1
Withania somnifera	Hepatic function abnormal	1
Withania somnifera	Aspartate aminotransferase increased	1
Withania somnifera	Alanine aminotransferase increased	1

Mechanism

The cause of hepatotoxicity from products containing Ashwagandha is unclear, but may be caused by increased withanolide levels that cause irreversible adduction to hepatocellular DNA [11] or Lubarska et al. state that evidence suggests that Ashwagandha used in excess stimulates a reduction in GSH levels in cells, which translates into cytotoxicity and may explain the cause of liver damage caused by its consumption [9].

Discussion and conclusion

Lareb has received four reports of liver toxicity associated with the use of products that contain Ashwagandha. In two reports only Ashwagandha was used and in the other two reports multiple herbs were used. In one of these reports *Scutellaria baicalensis* was also used, which is known to cause liver injury. Time to onset varied from three months to ten months. The latency of drug induced liver injury is typically between five days and three months of starting a medication. Measurement of time to onset, however, may be difficult. The latency is usually measured from the time of starting to the time of onset of jaundice, dark urine or detection of an elevation in serum bilirubin; but in other situations latency is measured to the time of the first symptom, which might be fatigue, weakness, nausea, poor appetite, abdominal pain, fever, rash or itching[18].

Three patients reported to have withdrawn the Ashwagandha containing product and of one patient the action taken is unknown, and all patients were recovering at the time of reporting. Typically, improvement of drug induced liver injury starts within a week or two of stopping therapy, and the injury resolves completely within 2 to 3 months[18].

For the determination of the RUCAM score, age ≥ 55 years is a risk factor for liver injury[4]. Three of the four patients in the reports received by Lareb were younger.

Several cases of clinically apparent liver injury have been reported in the literature of patients taking commercial herbal products that are labelled as containing Ashwagandha.

It is important to note that commercial herbal preparations are often mixtures of herbs and nutritional products and can be mislabelled and contain unknown herbs and medications. Therefore, it cannot be totally ruled out that reported cases are due to a contaminant.

Herbal products are generally considered safe by consumers, but can have serious adverse reactions. Although rare, it is important to raise awareness of the potential risk of liver toxicity of Ashwagandha-containing products.

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This signal has been raised on September 11, 2023. It is possible that in the meantime other information became available.