



Acute liver injury associated with the consumption of a neem-containing food supplement (*Azadirachta indica*): a case report

Akutna jetrna okvara, povezana z uživanjem prehranskega dopolnila z indijsko melijo (*Azadirachta indica*): prikaz primera

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ABSTRACT

Food supplements are classified as foods intended to supplement the normal diet. They are regulated by general food legislation, which requires all foods placed on the market, including food supplements, to be safe for consumption. As these products are generally not subject to a pre-market assessment of quality, safety and efficacy comparable to that required for medicinal products, it is important to moni-

IZVLEČEK

Prehranska dopolnila sodijo med živila, namenjena dopolnjevanju običajne prehrane. Njihovo področje ureja splošna živilska zakonodaja, ki določa, da morajo biti vsa živila, vključno s prehranskimi dopolnili, ki so dana na trg, varna za uživanje. Ker ti izdelki pred trženjem praviloma niso predmet presoje kakovosti, varnosti in učinkovitosti, primerljive s presojo, ki velja za zdravila,

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tor their safety after they have entered the market. Namely, food supplements may vary in quality and may contain substances in forms and/or quantities that could adversely affect human health. From a safety perspective, particular attention is paid to food supplements containing botanical ingredients, especially (medicinal) plants and preparations derived from them, such as extracts. Because of their natural origin, consumers may perceive these products as a safer alternative to synthetic medicinal products and may also use them for self-treatment. The main composition-related risk factors include the intrinsic toxicity of botanical ingredients, the presence of contaminants, and the presence of undeclared pharmacologically active substances and unauthorised substances. Nutrivigilance is a vigilance scheme for food aimed at improving consumer safety through the rapid identification of possible adverse effects associated with the consumption of specific foods. In Slovenia, the nutrivigilance system primarily monitors adverse effects associated with the consumption of food supplements. In this article, we present a case of acute liver injury associated with the consumption of a food supplement containing neem (*Azadirachta indica*), which the patient used to self-treat psoriasis.

je pomembno, da njihovo varnost spremljamo tudi po prihodu na trg. Lahko so namreč različne kakovosti in vsebujejo snovi v takšnih oblikah in/ali količinah, da lahko škodljivo vplivajo na zdravje ljudi. Z vidika varnosti je posebna pozornost namenjena prehranskim dopolnilom, ki vsebujejo rastlinske sestavine, zlasti (zdravilne) rastline in njihove pripravke, na primer izvlečke. Zaradi naravnega izvora jih uporabniki lahko dojemajo kot varnejšo alternativo sintetičnim zdravilom in jih uporabljajo tudi za samozdravljenje. Med glavne dejavnike tveganja, povezane s sestavo, sodijo intrinzična toksičnost rastlinskih sestavin, prisotnost onesnaževal ter vsebnost nedeklariranih farmakološko aktivnih snovi in neodobrenih snovi. Nutrivigilanca je vigilančna shema za živila, katere namen je izboljšati varnost potrošnikov s hitrim prepoznavanjem možnih neželenih učinkov, povezanih z uživanjem določenih živil. V Sloveniji v okviru sistema nutrivigilance spremljamo predvsem neželene učinke, povezane z uživanjem prehranskih dopolnil. V prispevku predstavljamo primer akutne jetrne okvare, povezane z uživanjem prehranskega dopolnila z indijsko melijo (*Azadirachta indica*), ki ga je bolnica uporabljala za samozdravljenje psoriaze.

INTRODUCTION

Food supplements (FSs) containing botanical ingredients – including plants, algae, fungi, or lichens, and preparations derived from them (1) – represent a rapidly expanding food market sector, characterised by a substantial increase in commercially available products and growing consumer acceptance (2). Owing to their natural origin and perceived safety, these products are frequently used for self-treatment, based on the assumption that they may be as effective as conventional medicines while posing a lower risk of adverse effects (3). This perception may encourage prolonged or long-term use, often without disclosure to health-care professionals. However, botanicals, particularly in extract form, can exert biologically relevant

effects that, depending on dose and quality of the ingredients, may be physiological, therapeutic, or toxic (2).

Several botanical ingredients used in FSs have been implicated in hepatotoxicity, including kava-kava (*Piper methysticum* G. Forst.), green tea extracts (*Camellia sinensis* L.) (4), ashwagandha (*Withania somnifera* (L.) Dunal), *Garcinia cambogia* (Gaertn.) Desr., and oral turmeric-containing formulations (5). This concern is supported by data from the French nutrivigilance system collected by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) between 2009 and 2016, which identified the liver as the most frequently affected organ, accounting for 67% of the 92 reported adverse effects likely to be associated

with the consumption of FSs containing selected plant species (6). The spectrum of liver injury following exposure to these products is broad, ranging from asymptomatic elevations of liver enzymes to acute or chronic hepatitis and, in severe cases, acute liver failure which can be fatal (7). Although causality is often difficult to establish in individual cases, FSs containing botanical ingredients should be considered among the potential contributors in the differential diagnosis of drug-induced liver injury (DILI). Most cases of DILI are idiosyncratic (8), making this condition one of the most challenging disorders encountered in clinical hepatology.

Azadirachta indica A. Juss. (neem) is incorporated into several polyherbal Ayurvedic preparations (9), and neem extracts are also marketed as FSs. Although neem-associated hepatotoxicity appears to be a rare cause of clinically apparent liver injury (10), the increasing consumption of FSs containing botanical ingredients highlights the importance of recognizing and reporting potential adverse hepatic effects.

We report a case of acute hepatitis occurring after the consumption of a neem-containing FS in an adult female admitted to the Department of Gastroenterology and Hepatology, University Medical Centre Ljubljana, for evaluation of unexplained liver injury.

CASE REPORT

A 53-year-old female patient was referred to our department after abnormal liver function tests were detected 4 days before admission at a community health centre: total bilirubin 1.5 mg/dL, aspartate aminotransferase (AST) 1775 U/L, alanine aminotransferase (ALT) 2507 U/L, alkaline phosphatase (ALP) 192 U/L, and gamma-glutamyl transferase (GGT) 172 U/L. On admission, the patient was asymptomatic, afebrile, and denied abdominal pain. Mild evening fatigue and intermittent dizziness were the only reported symptoms. Physical examination was unremarkable.

Over the preceding months, she had intentionally lost 3 kg of body weight. She denied known allergies, excessive alcohol consumption, smoking, and recent travel. Family history was notable for alcohol-associated liver disease in her father. The patient had been diagnosed with psoriasis at the age of 14 years. Detailed history taking revealed that she had been consuming a neem-containing FS at a dose of one teaspoon daily before meals for four months as a self-treatment for psoriasis. The product, purchased as a botanical preparation, was labelled as containing *A. indica* as the sole ingredient. The supplement was discontinued four days before admission due to lack of clinical improvement in psoriasis. Two weeks before admission, the patient developed symptoms consistent with a common cold and self-administered Daleron, an over-the-counter paracetamol-containing medication. During the three days preceding admission, the patient also took vitamin supplements, including a vitamin B-complex preparation and a vitamin preparation reported by patient as "Supradyn".

Initial blood work on admission showed a total bilirubin of 2.3 mg/dL, AST 1245 U/L, ALT 2299 U/L, ALP 195 U/L, GGT 225 U/L, and an international normalized ratio (INR) < 1.0. The pattern of liver injury was classified as hepatocellular based on the R-ratio (ALT/ALP, expressed as multiples of their respective upper limits of normal), with a value ≥ 5 (5). Serologic testing excluded acute infection with hepatitis A, B, C, and E viruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus type 1 (HSV-1), and varicella-zoster virus (VZV). Immunoglobulin levels were within normal limits. Autoimmune serology revealed weakly positive ANCA IgG (titer 1:20), considered clinically nonspecific in the absence of compatible systemic manifestations, and weakly positive antimitochondrial M2 antibodies (1+). The remainder of the autoimmune liver disease panel was negative. Iron metabolism studies, ceruloplasmin, serum copper, and thyroid hormone levels were unremarkable.

Abdominal ultrasound performed prior to admission showed no abnormalities of the hepatic parenchyma. A small intraluminal gallbladder lesion was identified without signs of cholecystitis; follow-up imaging was recommended in six months. Given the unexplained liver injury, a liver biopsy was performed on day 4 of hospitalization. Histological examination demonstrated features consistent with subacute hepatitis, including patchy portal and interface inflammatory infiltrates, lobular necroinflammatory activity, and focal centrilobular early collagen deposition. The presence of eosinophils within an otherwise predominantly mononuclear inflammatory infiltrate was suggestive of idiosyncratic DILI.

During hospitalization, liver function gradually improved (total bilirubin 1.7 mg/dL, AST 790 U/L, ALT 1182 U/L, ALP 164 U/L, GGT 203 U/L), and the patient was discharged on day 8 in a hemodynamically stable and asymptomatic condition. Follow-up liver function tests demonstrated normalization of hepatic parameters (total bilirubin 0.64 mg/dL and AST 31.8 U/L, ALT 34.8 U/L, ALP 64.8 U/L, and GGT 16.8 U/L), consistent with complete resolution of idiosyncratic DILI.

Causality was assessed using the validated method for determining causality in reports of adverse effects in nutrивigilance, developed by ANSES and applicable to FSs and other foods within the scope of nutrивigilance (11). This method provides a numerical score combining a chronological sub-score – time to onset, resolution after discontinuation, and recurrence upon re-exposure – and an aetiological sub-score assessing alternative causes, resulting in an overall intrinsic score. Based on a compatible onset time, a suggestive clinical course following discontinuation (progression), an absence of re-exposure and a complete aetiological investigation, the liver injury was deemed as very likely associated with neem consumption, corresponding to an intrinsic score of I4 (scale I0–I4, from excluded to very likely). The timing of the other FSs and medications was not compatible

with the onset of liver injury and was therefore scored as I0 (excluded).

DISCUSSION

To the best of our knowledge, this is the first documented case of acute hepatocellular liver injury in an adult very likely associated with the consumption of a neem-containing FS, with causality supported by liver histopathology and a validated nutrивigilance causality assessment method. Although idiosyncratic DILI is uncommon, it remains an important cause of acute and chronic liver disease worldwide. Diagnosis is challenging because no reliable animal models, *in vitro* systems, or specific biomarkers are currently available to predict or identify the condition before biochemical or histopathological abnormalities become apparent, making DILI primarily a diagnosis of exclusion (5).

A. indica, commonly known as neem, is an evergreen tree belonging to the *Meliaceae* family and has been widely used in Indian traditional systems of medicine for centuries (9). Virtually all parts of the tree have been processed to be used for medicinal purposes, due to their rich content of bioactive phytochemicals with reported antiviral, antimicrobial, anti-inflammatory, antiulcer, anticancer, antipyretic, antifungal, and antihyperglycemic properties (12). Consistent with its traditional use, *A. indica* has been primarily employed in the treatment of skin diseases, inflammatory conditions, rheumatic disorders, and fever (13). An aqueous extract of neem leaves has also been reported to be useful in the treatment of psoriasis vulgaris (14). However, the lack of rigorous controlled trials precludes recommendations for its clinical use.

Despite its long history of traditional use and general perception as a safe natural remedy, *A. indica* is listed by the European Food Safety Authority (EFSA) among botanicals of potential concern due to naturally occurring constituents that may pose

risks to human health when present in foods, including FSs (15). Compounds of concern in neem leaves and seeds include azadirachtin, nimbolide, and azadirone, highlighting that natural origin alone should not be equated with safety.

Most reported cases of neem-associated toxicity involve infants and young children exposed to neem oil through oral or nasal administration as part of traditional practices for the treatment of common cold and cough. Clinical manifestations include vomiting, drowsiness, metabolic acidosis, seizures, and toxic encephalopathy (16-18), with fatal outcomes reported in severe cases (16, 17). Histopathological findings in fatal cases included microvesicular steatosis (16, 17), patchy hepatic necrosis (17), mitochondrial damage, and cerebral edema, findings reminiscent of Reye's syndrome (16). Experimental animal studies exposed to samples of the implicated oil reproduced a similar clinical syndrome (19), supporting a causal relationship between neem oil exposure and toxicity. In adults, neem toxicity has been reported less frequently and has primarily occurred in the context of intentional self-harm (20, 21) or accidental exposure in elderly individuals (22), with neurological manifestations being most prominent.

In contrast, orally consumed neem leaf and bark preparations have generally been considered to have low toxicity (13). However, Brett et al. (23) described a 51-year-old male who developed distal renal tubular acidosis following prolonged consumption of large quantities of neem extract for self-treatment of diabetes. During hospitalization, abnormal liver function tests with a predominantly cholestatic pattern were also observed. However, no liver biopsy was performed, limiting definitive assessment of hepatic injury, although this finding suggests potential hepatic effects of orally administered neem preparations in adults.

Unlike previously reported adult cases, we performed a comprehensive diagnostic evaluation for DILI, including liver histopathology and a structu-

red causality assessment. This provides supportive evidence that prolonged consumption of a neem-containing FS, even when used according to product instructions, may pose a potential risk of hepatotoxicity, particularly given its unclear long-term effects (9). Experimental studies suggest that neem constituents may impair mitochondrial function through uncoupling of oxidative phosphorylation, resulting in reduced ATP production in rat liver mitochondria (24). This mechanism may be relevant to its hepatotoxic potential, although the precise pathophysiological pathway in humans remains unclear. In addition, several risk factors contributing to hepatotoxicity of herbal remedies should be considered. These include botanical misidentification, notably substitution with the more toxic *Melia azedarach* (13), use of an inappropriate plant part, inadequate storage conditions that may alter the native product, adulteration during processing, and mislabelling of the final product (4). Although the consumed product was labelled as a single-ingredient neem preparation, contamination or adulteration cannot be excluded in the absence of chemical analysis. This is particularly relevant for some traditional or Ayurvedic products, where metals and other elements may be present either intentionally or as contaminants (25).

Limitations

Several limitations in this case report should be acknowledged. First, this report describes a single patient, precluding generalisation of the findings. Second, the consumed FS was not chemically analysed; therefore, its composition remains unverified, and the possibility that the observed liver injury was associated with other potentially hepatotoxic constituents, contaminants, adulterants, or misidentified botanical material, rather than neem itself, cannot be excluded.

CONCLUSION

This case report highlights the importance of obtaining a detailed history of FSs and comple-

mentary medicine use in patients presenting with unexplained liver injury. It also suggests that FSs containing *A. indica* may represent a rare and previously underrecognized cause of idiosyncratic DILI in adults. As consumption of FSs containing botanical ingredients is expected to continue increasing worldwide, clinicians should remain vigilant and systematically report suspected clinical cases to national nutrивigilance systems to facilitate early signal detection, and improve consumer safety.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (no. 0120-312/2026-2711-8).

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