ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Acute Liver Failure Induced by Provitalize: A Menopause Supplement Concocted From Herbs & Probiotics

Rahul Patel, DO[1], Ahmed Hassan, DO[1], Hayle Scanlan, DO[2], Matthew Everwine, DO[3], Zhiyong Ren, MD[4], Charles Snyder, MD[5], and Hisham ElGenaidi, MD[6]

[1]*Department of Internal Medicine, Jefferson Health, Washington Township, NJ*
[2]*Division of Pulmonology & Critical Care, Louisiana State University Health, New Orleans, LA*
[3]*Division of Gastroenterology, Jefferson Health, Washington Township, NJ*
[4]*Department of Pathology, Virtua Health, Camden, NJ*
[5]*Division of Gastroenterology, Virtua Health, Camden, NJ*
[6]*Division of Hepatology, Virtua Health, Camden, NJ*

ABSTRACT

Drug-induced liver injury is one of the most common causes of acute liver failure in the Western world. Despite discontinuation of the offending agent, it can still tax a grim prognosis. We describe a case of a menopausal woman taking a herbal supplement called "Provitalize" to relieve hot flashes and bloating. This is the first case report of liver injury from this supplement. She initially presented with mild jaundice and elevated transaminases. Unfortunately, she rapidly progressed to encephalopathy, experienced multiorgan failure, and then died.

KEYWORDS: DILI; drug induced liver injury; acute liver failure; ALF; provitalize; turmeric; moringa; piperine; herbal and dietary supplements; menopause supplement

INTRODUCTION

Drug-induced liver injury (DILI) is one of the most common causes of acute liver failure (ALF) in the Western world.[1] ALF is the development of severe acute liver injury with encephalopathy and diminished synthetic function (international normalized ratio [INR] $\geq$1.5) in a patient without preexisting liver disease.[2] In the United States, the most common causes of ALF have been acetaminophen overdose (46%), indeterminate (14%), idiosyncratic drug reactions (12%), hepatitis B virus (7%), and hepatitis A virus (3%).[3] The use of non–Food and Drug Administration regulated supplements over the past 3 decades has increased with about 80% of people worldwide using them for a portion of primary health care.[4] The agents associated with DILI are prescription medications, illicit or recreational substances, and herbal and dietary supplements (HDS).

A herbal supplement called "Provitalize" (BB Company, Las Vegas, NV) has been gaining traction among menopausal women who hope to alleviate hot flashes, bloating, and weight gain. The supplement consists of a probiotic blend of *Bifidobacterium breve*, *Lactobacillus gasseri*, *Bifidobacterium lactis*, turmeric root extract, moringa leaf, curry leaf, lecithin, and black pepper fruit extract (Table 1).[5]

There is no published data on liver injury from the use of Provitalize as it had not been reported on LiverTox.[6] We present an unfortunate case of ALF in a middle-aged woman shortly after starting the Provitalize HDS.

CASE REPORT

A 49-year-old white woman with a history of asthma on no chronic medications except for a newly started herbal supplement called Provitalize presented to the hospital after her primary care physician sent her due to abnormal liver function tests. She experienced new-onset jaundice, nausea, and decreased appetite. She drank alcohol socially and denied tobacco or illicit drug use.

ACG Case Rep J 2024;11:e01509. doi:10.14309/crj.0000000000001509. Published online: September 20, 2024

Correspondence: Rahul Patel, DO (Rahul614P@gmail.com).

Table 1. Provitalize (menopausal supplement) information gathered from company (better body co./The BB Company) nutrition label

Provitalize	
Ingredient	**Quantity**
Probiotic blend	68.2 Billion colony-forming unit
B. breve (IDCC 4401) *L. gasseri* (SBT 2055) *B. lactis* (R101-8)	
Turmeric root extract (Std. to 95% Curcuminoids)	350 mg
Moringa leaf (*Moringa oleifera*)	350 mg
Curry leaf (*Helichrysum ilalicum*)	150 mg
Lecithin (from Sunflower)	50 mg
Black pepper fruit extract (BioPerine®)	3 mg

One month before admission, she began consuming 1 capsule of Provitalize daily. She consumed it for a total of about 30 days. She had been taking this supplement in hopes of alleviating menopausal symptoms of hot flashes, bloating, and weight gain.

Upon hospital arrival, she was hemodynamically stable. Initial blood work revealed alanine transaminase of 3,008 U/L, aspartate transaminase of 2,861 U/L, alkaline phosphatase 195 U/L, total bilirubin of 8.8 mg/dL, and direct bilirubin of 5.7 mg/dL. She had a platelet count of 201,000 μL, INR of 2. Her urine drug screen, acetaminophen levels, and salicylate levels were unremarkable. She was started on 7.7 g of *N*-acetyl cysteine (NAC) for a duration of 5 days due to her severely elevated hepatic enzymes.

Initial computed tomography scan of the abdomen and pelvis showed a contracted gallbladder with a slightly thickened wall. Magnetic resonance imaging of the abdomen showed mild heterogeneous abnormalities seen in the liver with a right lobe smaller in size compared to the left without any focal liver lesions and no evidence of biliary obstruction. The peritoneal cavity showed moderate abdominal ascites.

She underwent extensive hepatitis workup (viral hepatitis panel, Epstein–Barr virus, herpes simplex virus, cytomegalovirus, chlamydia–gonorrhea serologies, antinuclear antibody, antismooth muscle antibody, antimitochondrial antibody, ceruloplasmin, and alpha-1 antitrypsin), which was unremarkable. Despite the use of NAC, her total, direct bilirubin, and INR continued to rise while her transaminases remained elevated (Figure 1, Table 2 with complete lab values). Liver biopsy (Figure 2) showed significant hepatocyte necrosis with hepatic plate collapse around the central veins with focal bridging necrosis due to DILI.

She was listed for liver transplant with a model for end-stage liver disease score >35. She was offered a donor organ; however, before planned surgery, she decompensated with worsening shock, encephalopathy, respiratory failure, renal failure, and disseminated intravascular coagulation. She died before transplant.

DISCUSSION

This case highlighted the severity of DILI in the form of ALF from HDS, which has seldom been reported in the literature. Interestingly, our patient was not taking the supplement as recommended on the package label. She was taking one capsule daily. The manufacturing company recommends taking 2 capsules daily. Despite her underdosed regimen, the outcome was catastrophic.

While some of the ingredients of the supplement have been shown to be toxic in the literature, the severity and combination of them are novel in this case. There have been isolated case reports of liver injury without liver failure due to high bioavailability forms of turmeric in Italy.[7] Moringa leaf extract has been shown to cause moderate hepato-nephrotoxicity in mice with significant increases in aspartate transaminase, creatinine kinase, hepatic degeneration, and necrosis.[8] The danger of this supplement is also due to the high concentration of turmeric (curcumin) and black pepper. Piperine is the major active component of black pepper. When piperine is combined with curcumin in a complex, the bioavailability has been shown to increase 2,000%.[9] Curry leaf has not been studied in the literature as a contributor of DILI. The synergistic and/or additive effects of turmeric, piperine, moringa, and curry leaf need to be further studied to observe a mechanism of liver injury as there are no well-defined processes describing it. ALF secondary to turmeric toxicity with this poor outcome has not been seen in the literature.

The company claims that *Lactobacillus gasseri* is unique due to a 2013 Japanese study showing that individuals who ingested its fermented milk had a reduction in visceral fat areas.[10] The amalgamation of the herbs alongside bacteria brings forth the concept of gut-liver axis as a DILI mediator. The intestinal microbiome digests the herbal medication components or transports compounds that are not absorbed by the gastrointestinal tract. Furthermore, bacteria yield metabolites that compete with the drugs over the metabolic process, which either decreases the metabolism and accumulates the drug or there is a synergistic toxic phenomenon between the bacteria and supplement.[11] Since Provitalize contains probiotics, the patient's natural gut microbiome has been further altered.

Apart from cessation of the implicated agent, there is no standard therapy for DILI. While NAC is typically used for hepatoxic doses of acetaminophen, it has also been shown to be beneficial in nonacetaminophen liver failure. A 2021 meta-analysis demonstrated that NAC significantly improves overall survival, post-transplant survival, and transplant-free survival while decreasing the overall length of hospital stay.[12]

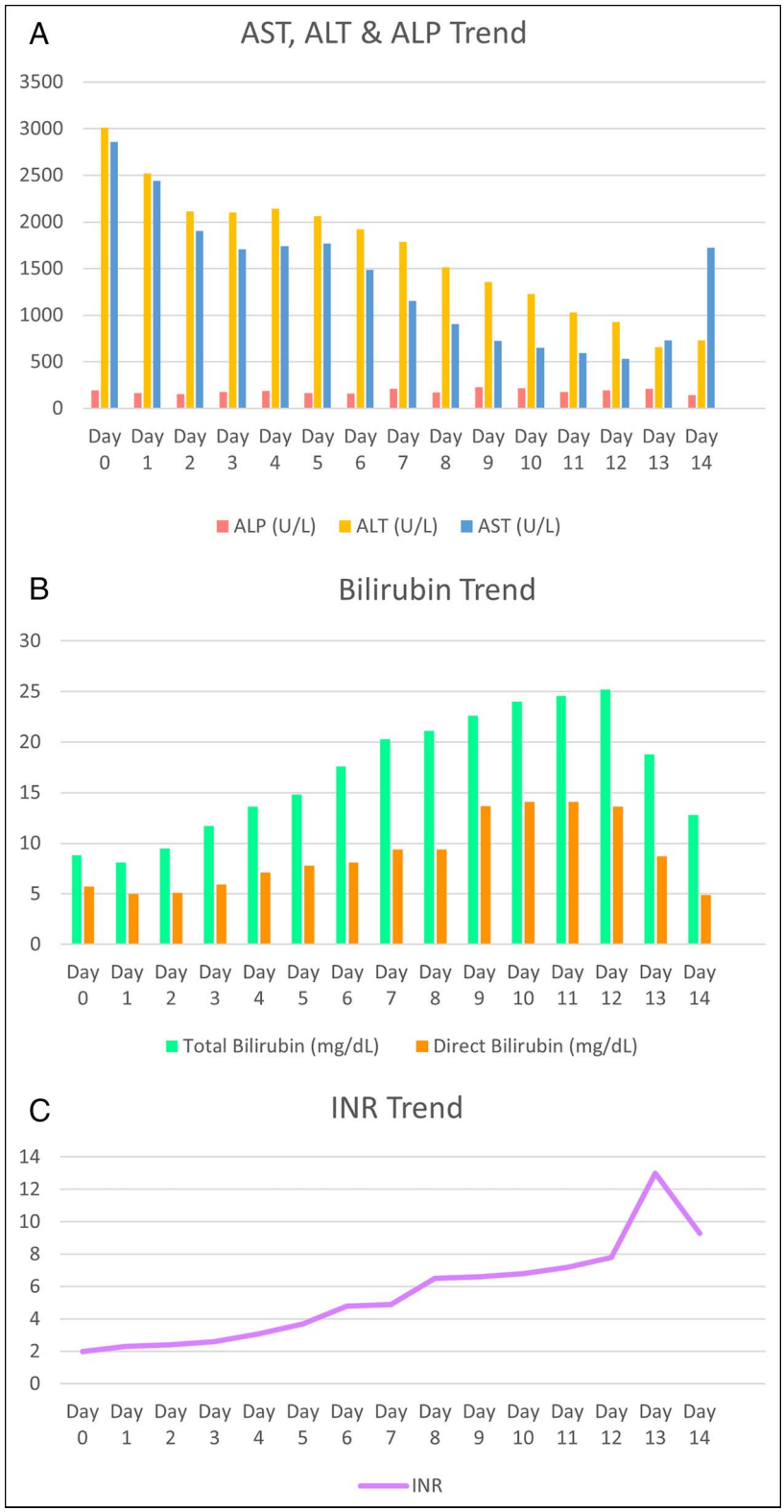

Figure 1. (A) AST/ALT/ALP, (B) bilirubin, & (C) INR trend throughout patient's entire hospitalization. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; INR, international normalized ratio.

On the other hand, corticosteroids in moderate–severe DILI and drug-induced autoimmune hepatitis have demonstrated beneficial effects, but this was not the case in drug-induced ALF.[13] Due to a lack of improvement with supportive care and increase in complications, liver transplant was indicated for our patient.

Table 2. Liver function trend throughout patient's entire hospitalization

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Total protein (g/dL)	6.7	5.4	5.1	5	5	4.6	4.6	4.7	4.4	4.2	4.1	4	4	3.8	3
Albumin (g/dL)	4.3	3.5	3.3	3.2	3.2	3.1	3.1	3.1	3	2.9	2.9	2.9	2.7	3.2	2.6
ALP (U/L)	195	166	154	177	186	165	158	210	169	225	218	174	192	211	140
ALT (U/L)	3,008	2,518	2,115	2,101	2,139	2,063	1,919	1,787	1,514	1,358	1,227	1,029	928	654	728
AST (U/L)	2,861	2,442	1,903	1,705	1,740	1,766	1,484	1,156	906	724	651	593	530	728	1,721
Total bilirubin (mg/dL)	8.8	8.1	9.5	11.7	13.6	14.8	17.6	20.3	21.1	22.6	24	24.6	25.2	18.8	12.8
Direct bilirubin (mg/dL)	5.7	5	5.1	5.9	7.1	7.8	8.1	9.4	9.4	13.7	14.1	14.1	13.6	8.7	4.9
INR	2	2.3	2.4	2.6	3.1	3.7	4.8	4.9	6.5	6.6	6.8	7.2	7.8	>10	9.3

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

Provitalize is readily available for consumers because HDS are considered to be foods and not drugs by the Food and Drug Administration. Thus, they are not required to go through rigorous testing that pharmaceutical companies go through when introducing a new drug on the market. Due to the lack of rigorous testing, the purity of the product must be questioned. A 2012 study found contamination with mercury, cadmium, arsenic, lead, and aluminum in various HDS around the world.[14]

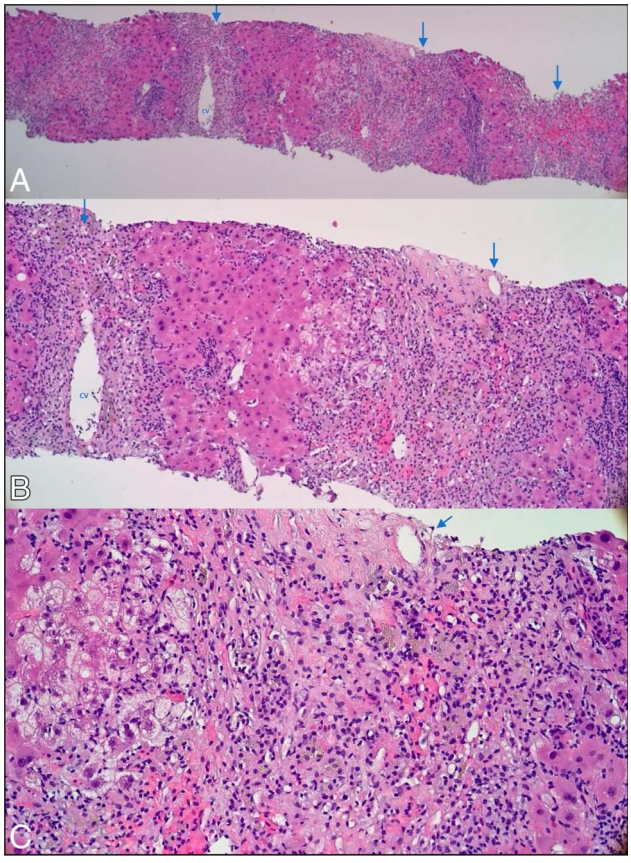

Figure 2. Liver biopsy pathology. Central vein (CV). Arrows depict necrosis. (A) 50× magnification. (B) 100× magnification. (C) 200× magnification.

This report highlights the importance of a thorough evaluation of abnormal liver function tests alongside a detailed history of home medications. This case exposed a supplement thought to be harmless against its intended demographics. Given the unfortunate outcome on our patient, this drug was submitted for review to the Food and Drug Administration. It is imperative to educate the public on risks of taking herbal supplements despite their natural albeit questionable origins and to counter companies falsely declaring their benefits.

DISCLOSURES

Author contributions: R. Patel: drafted all versions of the manuscript including the final version and is the article guarantor; A. Hassan: synthesized graphs and tables and assisted with initial draft; H. Scanlan: editor, assisted with initial draft; M. Everwine: editor, provided guidance of case; Z. Ren: provided, labeled, and analyzed liver biopsy pathology images; C. Snyder and H. ElGenaidi: provided primary guidance of case.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received March 29, 2024; Accepted August 14, 2024

REFERENCES

1. Katarey D, Verma S. Drug-induced liver injury. *Clin Med.* 2016;16(Suppl 6):s104–9.
2. Toma D, Lazar O, Bontas E. Acute liver failure. *Liver Diseases* 2020:369–80.
3. Lee WM, Squires RH, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: Summary of a workshop. *Hepatology.* 2008;47(4):1401–15.
4. Ekor M The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol.* 2014;4(177):177.
5. Company BB. *Provitalize | Best Natural Menopause Probiotic.* BB Company (https://thebbco.com/products/provitalize). Accessed June 25, 2024.
6. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases (https://www.ncbi.nlm.nih.gov/books/NBK547852/) (2012).
7. Donelli D, Antonelli M, Firenzuoli F. Considerations about turmeric-associated hepatotoxicity following a series of cases occurred in Italy: Is turmeric really a new hepatotoxic substance? *Intern Emerg Med.* 2020;15(4):725–6.
8. Aliyu A, Shaari MR, Sayuti NSA, et al. Moringa oleifera hydorethanolic leaf extract induced acute and sub-acute hepato-nephrotoxicity in female ICR-mice. *Sci Prog.* 2021;104(4):368504211004272.

9. Hewlings S, Kalman D. Curcumin: A review of its' effects on human health. *Foods.* 2017;6(10):92.
10. Kadooka Y, Sato M, Ogawa A, et al. Effect of *Lactobacillus gasseri* SBT2055 in fermented milk on abdominal adiposity in adults in a randomised controlled trial. *Br J Nutr.* 2013;110(9):1696–703.
11. Niu MW, Chen P. Gut microbiota and drug-induced liver injury: An update. *Chin Med J.* 2020;133(4):494–5.
12. Walayat S, Shoaib H, Asghar M, Kim M, Dhillon S. Role of N-acetylcysteine in non-acetaminophen-related acute liver failure: An updated meta-analysis and systematic review. *Ann Gastroenterol.* 2021;34(2):235–40.
13. Björnsson ES, Vucic V, Stirnimann G, Robles-Díaz M. Role of corticosteroids in drug-induced liver injury. A systematic review. *Front Pharmacol.* 2022;13:820724.
14. Genuis StephenJ, Schwalfenberg G, Siy AKJ, Rodushkin I. Toxic element contamination of natural health products and pharmaceutical preparations. *PLoS ONE.* 2012;7(11):e49676.