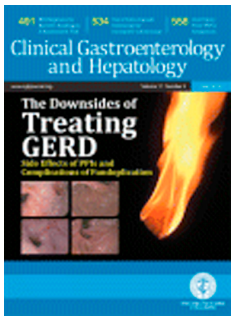

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Dario Cattaneo, PhD[,2], Andrea Giacomelli, MD, Cristina Gervasoni, MD[1,3]

[1]Gestione Ambulatoriale Politerapie (GAP) outpatient clinic, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy; [2]Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy; [3]Department of Infectious Diseases, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy

Corresponding author: Cristina Gervasoni, MD
Third Division of Infectious Diseases,
ASST Fatebenefratelli Sacco University Hospital, Milan, Italy.
Via GB Grassi 74, 20157 Milano, Italy
E mail: cristina.gervasoni@unimi.it
Tel. +39.02.39042676 Fax: +39.02.50319758

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Dear Editor,

Dietary supplements containing vitamins, antioxidants, fibers, proteins, minerals, amino acids and herbs are increasingly used with the general beliefs that they are natural, safe and helpful. By analyzing data from the Latin America-Drug Induced Liver Injury (LATINDILI) Network, Bessone et al recently reported that 8% of the 367 cases of DILI collected from 2011 to 2019 were related to herbal and dietary supplements.[1]

Evidence is available showing that herbal and dietary supplements are commonly used also by people living with HIV (PLWH) to boost immune functioning antioxidants and/or as body cleansing products to remove toxins.[2] To the best of our knowledge, only two cases have been reported in literature dealing with PLWH with hepatotoxicity related to dietary supplements.[3,4] Here, we retrospectively searched for all cases of liver damage related to dietary supplements recorded in the database of our outpatient clinic service for the management of polypharmacy in PLWH (n=700) from September 2016 to December 2020.

The four cases identified are described in Table 1. The patients, all on maintenance antiretroviral therapy with optimal immune-virologic control and with normal liver function, presented with acute elevation in liver enzymes within a few weeks (4-to-8 weeks) after starting a dietary supplement. Hepatitis A, B, C and Epstein-Barr virus, cytomegalovirus, syphilis or autoimmune diseases were excluded; in all cases ultrasound of the abdomen revealed no abnormalities. The patients denied alcohol abuse (as indirectly confirmed by the normal values of gamma-glutamyl transpeptidase) as well as medicines and/or recreational drugs known to cause liver failure. Dietary supplements, being identified as the cause of liver damage, were immediately discontinued and, in the following weeks, hepatic enzymes returned to normal values. In all cases, the association between the episode of liver injury and dietary supplement intake was scored as possible or probable (according to the Naranjo causality scale).

The proportion of patients with liver injury from dietary supplements in the Drug-Induced Liver Injury Network (DILIN) registry are increasing at a greater rate than that of injury ascribed to conventional medications.[5] The establishment of a causal association between liver injury and dietary supplements intake is mainly complicated by the issue of product composition. In fact, dietary supplements rarely contain only one ingredient; the majority of these products were complex mixtures sold under different commercial names. [5] Among the ingredients contained in the dietary supplements taken by our patients known to cause hepatotoxicity especially when taken in great amounts there are green tea, glutamine, niacin and cinnamon bark, biotin and chromium picolinate.[1,5]

Noteworthy, several dietary supplements, including those taken by our patients, contain natural extracts or synthetic compounds with presumed antioxidant properties. Very few antioxidant dietary supplements have been studied for their safety and effectiveness. The scant information published to date did not show clear benefits; conversely, in some cases, potential harmful effects have been reported (a condition referred ad the antioxidant paradox).[6] Indeed, some negative effects of antioxidants when used in dietary supplements have emerged in the last years. The primary concern regarding antioxidant supplementation is their potentially deleterious effects on reactive oxygen species (ROS) production (pro-oxidant action) especially when precise modulation of ROS levels are needed to allow normal cell function, resulting from increasing of hepatic endotoxin influx. Mechanistic investigation has revealed that dietary supplements may exhibit anti-oxidant or pro-oxidant activity depending on their dosage, the redox conditions and also the presence of free transition metals in cellular environment.[7] A recently published research in rats showed that the combination of dietary supplements ingredients, when used alone or combined with alcohol, may be responsible for the augmentation of oxidative stress and liver histopathological abnormalities.[8] Moreover, HIV can induce oxidative stress; therefore, the consumption of dietary supplements in PLWH may increase the toxicological consequences.[4]

In conclusion, our case series, thought small, may be important in informing healthcare providers about the potential risk of liver damage in PLWH taking dietary supplements. Our experience taught us that patients do not perceive dietary supplements as drugs, and therefore, they may not report their use to the HIV specialist. Therefore, we recommend physicians to include this assessment in their daily outpatients visits.

References

1. Bessone F, et al. Clin Gastroenterol Hepatol 2021 Jan 9;S1542-3565(21)00013-6.

2. Bahall M. BMC Complement Altern Med. 2017;17:422.

3. Browne R et al. Int J STD AIDS 2005;16:639–641.

4. Cattaneo D, et al.. Ann Pharmacother. 2020;54:292-293.

5. Navarro VJ, et al. Hepatology. 2017;65:363-373.

6. Aalt Bast, et al. Environ Toxicol Pharmacol. 2002;11:251-258.

7. Fikry E, et al. J Drug Deliv Ther. 2019;9:1068-1077.

8. Reis R, et al. J Food Sci. 217;82:1037-1043.