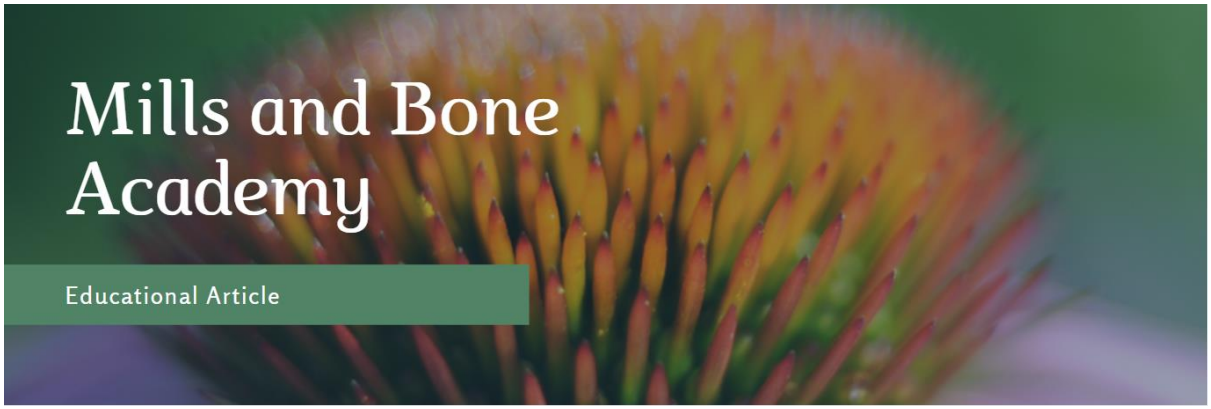

Withania and Liver Damage: Should We be Worried?–

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With the increasing use and scrutiny of medicinal plants comes the increased possibility of finding rare, unexpected adverse reactions. However, it is important that such reports are carefully analysed and backed up by other studies before definitive conclusions are formed. Recently, five cases have emerged connecting idiosyncratic drug-induced liver injury (DILI) to the use of Withania. In all cases the damage was reversible with discontinuation of the herb and resulted in no permanent liver injury. The report has been criticised for its incompleteness and a lack of plausibility.

Liver toxicity related to drugs and plants is divided into two varieties, based on the presumed mechanism of action of the intervention: intrinsic and idiosyncratic. The intrinsic (direct or predictable) type is dose-related and occurs after short exposure (hours to days) to the herb or drug, which is known to be toxic to the liver at a given threshold dose. By contrast, the idiosyncratic (indirect or unpredictable) variety of DILI is determined by the interaction of often unknown environmental and host factors with the treatment. As a consequence, idiosyncratic DILI is rare, has a longer latency period (from a few days to several months), and is not dose-related. The immune system is typically involved in driving the observed liver damage in idiosyncratic DILI.

The report from Iceland described five cases of liver injury that the authors attributed to Withania-containing supplements; three were collected during 2017-2018 from Iceland, and another two from the Drug-Induced Liver Injury Network (DILIN) in 2016 (presumably from other countries). Among the five patients, three were males and the mean age was 43 years (age range 21 to 62). All patients developed jaundice and symptoms such as nausea, lethargy, pruritus and abdominal discomfort after a latency period of 2 to 12 weeks after beginning Withania.

The liver injury was cholestatic or mixed. Pruritus and hyperbilirubinaemia were prolonged (5 to 20 weeks), but no patient developed hepatic failure. Liver tests normalised within 1 to 5 months in four

patients and one case was lost to follow-up. One biopsy was performed, showing acute cholestatic hepatitis.

Chemical analysis by the authors 'confirmed' Withania in available supplements; no other toxic compounds were identified. No patient was taking potentially hepatotoxic prescription medications, although four were consuming additional supplements, and in one case, Rhodiola was deemed to be a possible 'causative agent' along with Withania. The role of Withania in causing liver injury was judged as definite in one case, highly likely in two, probable in one and only possible in one.

Viral markers for acute hepatitis A, B and C as well as cytomegalovirus IgM were negative in all patients. However, hepatitis C virus (HCV) RNA PCR was performed in only one case (and was negative) and hepatitis E virus (HEV) testing was not undertaken. Liver injury was moderate, for example the mean peak ALT recorded in the five cases was 361 U/L, and for AST this mean was 240 U/L.

All three Iceland cases were from the same product (manufactured in the US) and one DILIN case was also linked to a different US product. I purchased and initiated analysis of the US product implicated in the three Iceland cases. According to the relevant USP (United States Pharmacopeia) method, the product was found to contain a high percentage of Withania leaf, despite the label claiming only root as the plant part. Perhaps this issue (contamination with Withania leaf) was the cause of the idiosyncratic DILI (assuming there is a link with the product, which is still uncertain). Furthermore, this US product was the only 'definite' case, as rated by the authors (see above).

At this stage it is important to be alert for a similar potential reaction in patients, but there is no cause for alarm, especially if high quality Withania products are used with a confirmed absence of leaf. Ironically, there are laboratory experiments demonstrating Withania root protects against liver damage.

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