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Spotlight Commentary: Why We Need to Pay Attention to Toxicity Associated With Herbal Medicines

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SPOTLIGHT COMMENTARY

Spotlight Commentary: Why we need to pay attention to toxicity associated with herbal medicines

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Nowadays, the popularity of medicinal herbs (MHs) and other natural products has increased dramatically worldwide. Consumers may use MHs as an alternative or complementary medicine to conventional drugs. Recently, we read two articles published in the *British Journal of Clinical Pharmacology* (BJCP) describing drug-induced liver injury (DILI) resulting in toxicity from the concomitant use of conventional drugs and MHs.[1,2]

The first article describes a patient treated with oral crizotinib who developed signs of liver distress. At that time, the patient presented with dramatically elevated levels of alanine aminotransferase (20 × ULN). Histological lesions suggested acute drug-induced hepatitis. In addition to crizotinib, the patient had consumed large quantities of hot water with honey, lemon juice and grated ginger roots (*Zingiber officinale*) for non-medical purposes. A detailed analysis of potential herb–drug interaction (HDI) revealed that ginger inhibits the activity of CYP3A4, CYP2C9 and P-gp enzymes, enzymes responsible for crizotinib metabolism. Elevated trough concentrations of crizotinib strengthen the opinion that a ginger–crizotinib drug interaction resulted in a potentiation of the crizotinib hepatotoxicity.

The second case outlining a potential HDI was reported by Laube and Liu.[2] An elderly patient presented with DILI after a long history of using atorvastatin. The patient used a dietary supplement containing Siberian ginseng (Eleuthero, *Eleutherococcus senticosus* (Rupr. & Maxim.)) and silymarin, a bioactive compound found in milk thistle (*Silybum marianum* (L.) Gaertn.), one week before elevated levels of aminotransferases were noticed (12–17 ULN). The authors proposed that 'ginseng' induced DILI via inhibition of CYP3A4, the enzyme responsible for atorvastatin metabolism. Eleuthero belongs to the same Parax genus as American ginseng (*Panax quinquefolius*) or Chinese ginseng (*Panax ginseng*) but possesses different bioactive constituents and has no effect on CYP3A4.[3] Therefore, it should not interact with atorvastatin metabolism. It is possible that concomitant use of Eleuthero and/or milk thistle with other medications taken by the patient was responsible for the observed DILI.

Another case of a potential HDI was described for a patient concomitantly using erlotinib with hibiscus (*Hibiscus sabdariffa*) tea, known for its anti-inflammatory and anti-tumour properties.[4] The patient developed cutaneous lesions shortly after drinking the hibiscus tea. Discontinuation of the tea led to the rapid improvement of the cutaneous lesions. The analysis of potential HDI demonstrated that hibiscus inhibits CYP3A4 and CYP1A2, two enzymes responsible for erlotinib metabolism.

In the case reports described above, patients self-prescribed MHs. Self-administered MHs like cassia (*Cinnamomum cassia*), chaparral (*Larrea tridentate*), gotu kola (*Centella asiatica*), comfrey (*Symphytum officinale*) and saw palmetto (*Serenoa repens*) are also capable of promoting liver toxicity.[5] Numerous reports describe MH-associated nephrotoxicity.[6] These MHs include *Taxus celebica*, *Tripterygium regelii*, *Clematis chinensis*, *Cassia obtusifolia*, *Gardenia jasminoides*, *Croton caudatus*, *Stephania tetrandra*, *Strychnos nux-vomica* and many others. Aristolochic acid and the nephrotoxic alkaloids derived from these plants are often implicated as constituents that cause kidney damage.

Chinese Traditional Medicine is often used as complementary or supportive medicine for the treatment of oncological patients.[7] It has been reported that these MHs, as well as dietary supplements, are responsible for 26.8% of DILI hospitalizations,[8] but it is not clear how many of these patients self-prescribed MHs.[7] So and colleagues reported that their preliminary data indicate that 25% of patients with solid tumours were prescribed Chinese Traditional Medicines in

[Correction added on 16 September 2020, after first online publication: Article title has been corrected in this online issue version.]

addition to conventional treatments.[7] Very few patients who were treated with traditional and conventional or conventional-only medicines presented with DILI. Additionally, there were no differences in the severity of DILI between groups. This may suggest that the majority of reported cases of DILI were associated with self-prescribed use of MHs.

Until recently, a few RCT have been reported that question safety and efficacy of MHs like ginger, Eleuthero or silymarin.[9–11] Saneei Totmaj et al. performed a systematic literature review of RCT reporting effectiveness of ginger in chemotherapy-induced nausea and vomiting and improvement[12] and concluded that ginger could reduce nausea and vomiting in breast cancer patients receiving chemotherapy. In 1986, RCT reported that Eleuthero could stimulate immunity in cancer patients receiving radiation and chemotherapy.[13] However, there is a growing interest among consumers regarding the use of MHs and dietary supplements, as well as an increase in MH-drug interactions reported by physicians. This necessitates the initiation of new RCT of MHs, especially for categories of patients like oncological patients. This RCT should determine whether or not MHs commonly used by these patients are safe when used concurrently with conventional treatment.

This brief snapshot of reported MH toxicity indicates that concomitant use of MHs with conventional drugs may result in severe adverse reactions leading to the potentiation of conventional drug toxicity. Unfortunately, many consumers consider MHs to be safe alternatives to conventional drugs and do not think that taking something that is labelled as an MH can harm them. This is becoming a growing area of concern for clinical pharmacologists as ~50% of the adult population use MHs or dietary supplements.

Many patients, including oncological patients, self-prescribe MHs, and dietary supplements to ameliorate side effects of conventional drugs or treat their diseases when conventional drugs are not effective. Providers and clinical pharmacologists should be familiar with HDIs that may occur following the concomitant use of MHs and conventional drugs, as well as the adverse reactions associated with MHs. When providers choose a treatment strategy for a patient using MHs, he/she should consider whether the expected benefits of the MH use would exceed possible risks.

COMPETING INTERESTS

C.M.T.S. is a Senior Editor for BJCP. The other authors have no competing interests to declare.

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