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Herbal medicine hepatotoxicity: A new step with development of specific biomarkers

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Hepatic impairment resulting from the use of conventional drugs is widely acknowledged, but there is less awareness of the potential hepatotoxicity of alternative medicines such as herbal preparations [1]. The increasing attraction for herbals medicines is partly explained by the return to natural products occurring along with the ecological movement in industrialized countries [1]. It is also related to the limited efficacy or the important side effects of treatments of various chronic diseases [1–5]. Several recent studies that focused on the use of herbal medicines in chronic hepatitis C are particularly demonstrative in Western countries [6,7]. A prospective inquiry carried out in France, based on outpatients seen for chronic liver diseases, has revealed that there was a herbal medicine intake for at least 1 month in 30% of included patients with hepatitis C [6]. Similarly, the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial conducted in the USA showed that 21% of enrolled patients had taken herbal medicines before and 23% at the time of inclusion [7]. In both studies, the most commonly used herbal compounds were sylimarin and valerian [6,7]. The use of herbal medicines does not require any medical prescription. Patients may find these products in various stores, some of them being specialized in herbal products but also in pharmacy stores. Furthermore, the possibility to get herbal products via the internet has markedly contributed to the increase in their sales [4]. In several areas of the world, particularly in Asia, Africa, and central and South America, the use of herbal medicines is an important part of a traditional medicine exhibiting several advantages, in particular, easy availability and low cost [1–5].

Over the last decades it has become apparent that herbal medicines may cause a very large spectrum of liver injury, affecting all cells present in the liver and biliary tree, and ranging from mild asymptomatic liver enzyme elevation to acute hepatitis, chronic hepatitis, cirrhosis, liver failure, acute and chronic cholangitis, macro- and micro-vesicular steatosis, and vascular lesions [1–5]. Furthermore, herbal medicines may produce interactions with liver drug metabolizing enzymes [2]. A representative instance is St. John's Wort (*Hypericum perforatum* L.) which can modify cytochrome P450 3A isoenzyme activity and, thereby, the metabolism of several immunosuppressive agents such as cyclosporine and tacrolimus [2].

To avoid these side effects, utilization of "natural medicine" is increasingly controlled in many countries. Marketing authorization has been given for plants considered efficient and innocuous. Indeed, in most cases, the efficiency and safety have been based more on a reputation acquired over the centuries rather than on controlled trials and toxicity studies [1–5].

Hepatotoxicity of herbal remedies is particularly difficult to demonstrate [8]. Indeed, in addition to the usual difficulties found while assessing the relationship between an adverse event and the intake of a drug largely caused by the absence of clinical specificity [8], there may be difficulties with frequent auto-medication and the reputation of safety so that the patient often forgets to mention herbal medicine ingestion to the physician [4,5,8]. In addition, there are specific risks contributing to the hepatotoxicity of herbal remedies [4]: misidentification of the plant, selection of a wrong part of the medicinal plant, inadequate storage modifying the native product, adulteration during processing, and mislabeling of the final product [4]. For instance, some Asian preparations contain more than 10 different plants [1–5]. Another instance is Herbalife® hepatotoxicity recently reported in Israel and Switzerland [9,10]. Interestingly, it seems that the complex composition of the products marketed under this brand name in these two countries was not exactly similar [9,10]. Another difficulty is that the real composition of the herbal preparation may remain unclear [1–5]. A safe herbal product may be contaminated by toxic compounds leading to hepatotoxicity. This is the case with heavy metals, pesticides, herbicides, microorganisms, and even classical pharmaceutical products [1–5]. A recent illustration is a product marketed in Scandinavian countries under the brand name Fortodol®, normally containing *Curcuma longa* (turmeric) as a gentle pain killer [11]. The occurrence of several cases of liver injury led to analyze the composition of this apparently innocuous product. It turned out that it also contained nimesulide, a non-steroidal anti-inflammatory compound, well documented to cause acute liver injury [11].

To date, around fifty medicinal preparations have been reported to be toxic to the liver [1–5]. The degree of evidence for toxicity is as variable as is for classical pharmaceutical agents. Herbal medicines with the highest level of evidence for hepatotoxicity are plants containing pyrrolizidine alkaloids,

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Editorial

germander (*Teucrium chamaedris*), *Atractylis gummifera*, plants containing pennyroyal oil (*Mentha pulegium, Hedeoma pulegioides*), great celandine (*Chelidonium majus*), kava–kava (*Piper methysticum*), and several Asian medicinal preparations [1–5]. Other compounds for which a fair level of evidence exists for hepatotoxicity are chaparral leaf (*Larrea tridentata*), senna (*Cassia angustifolia*), hydroalcoholic extracts of green tea and Herbalife® [1–5,9,10].

Pyrrolizidine alkaloids make up a remarkable illustration of the difficulties encountered with herbal medicine hepatotoxicity and the particular need to have biomarkers to overcome them. These alkaloids are found in more than 6000 plants worldwide [12]. The main implicated species are: *Heliotroprium*, *Senecio*, *Crotalaria* [17], and *Symphytum* (Comfrey) [1–5,12] but also *Gynura segetum* as illustrated in the report by Lin et al. in this issue of the Journal [13].

Pyrrolizidine poisoning is endemic in areas such as Africa and Jamaica, where toxic alkaloids are ingested as infusions, herbal teas, decoctions, or used as an enema [1–5]. Contamination of four by plants containing pyrrolizidine alkaloids has also caused epidemic intoxications in India and Afghanistan [1–5]. Pyrrolizidine alkaloids are also a concern for Chinese herbal medicines [13]. In the Journal, Lin et al. report at least 51 cases with "Tusanqi" traditional preparation [13] and stress that there are probably many more cases [13]. Hepatotoxicity occurs because of the misuse of *G. segetum* instead of non-toxic plants in the preparation.

The main liver injury induced by pyrrolizidine alkaloids is veno-occlusive disease, the so-called hepatic sinusoidal obstruction syndrome (HSOS) [2–5,14,15]. Pyrrolizidine alkaloids account for more than 8000 cases of HSOS worldwide and make up one of the major causes of this syndrome [1–5,14,15]. HSOS brings about hepatic congestion, which may lead to parenchymal necrosis. In some cases, fibrosis and even cirrhosis may develop. Different clinical subtypes have been described [4,14,15]. The acute form is characterized by markedly increased serum aminotransferase activities. When lesions are extensive, hepatic failure may occur, leading to death [4,14,15]. In contrast, the chronic form insidiously develops and may mimic cirrhosis. One fatal case of veno-occlusive disease has been described in a newborn infant whose mother had been exposed to a plant containing pyrrolizidine alkaloids during pregnancy [16].

Hepatotoxicity of pyrrolizidine alkaloids is reproducible and dose-related in laboratory animals [1–5]. It has been related to the biotransformation of unsaturated alkaloids into unstable, toxic metabolites, probably pyrrolic derivatives, by cytochrome P-450 leading mainly to lesions of endothelial cells and to a lesser extent of hepatocytes [1–5]. Up to now, however, there was no means for providing direct evidence of the direct role of pyrrolizidine alkaloids in a clinical situation.

Lin et al. have reached this new step [13]. Indeed, they have constructed a sensitive and specific assay enabling for the detection of a reactive pyrrole–protein adduct in serum [13]. This assay was used to show the presence of the reactive adduct directly in the serum of a patient with HSOS related to the Tusanqi preparation made erroneously with *G. segetum* instead of *Sedum aizoon* [13]. In addition, an animal study further showed the good correlation of liver injury with the ingestion of *G. segetum* [13].

This is the second instance in which a biomarker provides evidence for the role of a plant in a patient with liver injury. The other example of a diagnostic biomarker but with less direct evidence is germander (*T. chamaedris*) which has been responsible for numerous cases of liver injury [4,17]. Germander hepatotoxicity has been reproduced in mice and is dose-dependent [4]. The chemical composition of germander comprises furan-containing neoclerodane diterpenoids. Germander components are oxidized by cytochrome P4503A into reactive metabolites [18]. These reactive metabolites deplete glutathione and cytoskeleton-associated protein thiols, form plasma membrane blebs, and cause apoptosis contributing to liver cell death [4,19]. Finally, reactive metabolites could trigger hepatotoxicity through an immunoallergic reaction [20]. Indeed, anti-microsomal epoxide hydrolase autoantibodies have been found in the sera of patients who drank germander teas for a long period of time [20]. This serum antibody makes up a biomarker allowing for the correlation of cases of liver injury with germander ingestion.

Conclusion

Herbal medicines are increasingly recognized as causes of liver injury. Advances in the understanding of pathogenesis are needed to improve herbal medicine safety. The development of specific biomarkers is a key step to allow more accurate diagnoses and gain crucial information on complex medicinal preparation.

Conflict of interest

The authors who taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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