



Review

European medicinal and edible plants associated with subacute and chronic toxicity part II: Plants with hepato-, neuro-, nephro- and immunotoxic effects

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ABSTRACT

A tremendous surge of public interest in natural therapies has been reported in the past several decades in both developing and developed countries. Furthermore, edible wild-growing plants whose use had long been associated with poverty and famine have also gained in popularity among people in developed countries. An important fraction of herbal products evade all control measures and are generally perceived as safe. However, this may not always be true. It is important to recognize that some plants are not associated with acute toxicity but rather produce more insidious problems, which develop only with long-term exposure. In this review, we continue a systematic analysis of the subacute and chronic toxicity associated with the use of herbal preparations. The hepato-, neuro-, nephro- and immunotoxicity of plant species that either grow natively or are cultivated in Europe are discussed in some detail. The basic concepts regarding the molecular mechanisms implicated in their nonacute toxicity and their pathophysiological, clinical and epidemiological characteristics are included. Among others, we discuss the hepatotoxicity of pyrrolizidine alkaloids, the nephrotoxicity of aristolochic acid, the lathyrism associated with neurotoxin swainsonine, thiamine depletion and thyroid dysfunction of herbal cause, and finally address also the immunosuppressive effects of cannabinoids.

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1. Introduction

A high increase in public interest in natural therapies can be seen both in developing and developed countries (Bodeker et al., 2005; Braun et al., 2010; Calapai, 2008; Ekor, 2014). Herbal products such as herbal teas, spices and food supplements are widely used in European countries and are available not only in drug stores but also in food stores and supermarkets. Furthermore, edible wild-growing plants whose use had long been associated with poverty and famine and had been regarded as a last resort have gained in popularity also among people in developed countries. They have been used by increasing numbers of people, even by professional chefs, especially in high-end restaurants. Wild-growing plants generally contain more essential vitamins, minerals and antioxidants than cultivated ones, but they must be gathered by experienced individuals who are well aware of their potential toxicity and their possible contamination by pollutants.

It must be considered that an important fraction of herbal products made either for self-consumption or for sale evades all control measures. They generally have a high acceptance by consumers who often consider that “natural” equals “safe”. This is, however, an oversimplification, as numerous botanicals have been found to contain toxic compounds. Some of these are not involved in acute toxicity but rather produce more insidious problems, which develop only with long-term exposure. It is, therefore, essential to furnish the general public as well as healthcare professionals with adequate information regarding the risks associated with the use of these products, thereby promoting more rational decisions in this respect.

In this review article, we continue a systematic analysis of the subacute and chronic toxicity associated with the use of herbal preparations. The hepato-, neuro-, nephro- and immunotoxic plant species are presented, with a strong focus placed on those that either grow natively or are cultivated in Europe (sometimes we widen our selection to those non-native (introduced) species that are extensively used in Europe).

2. Hepatotoxic plants

2.1. Epidemiology and presentation of hepatotoxicity associated with herbal preparations

The data on herbal hepatotoxicity are mostly obtained from published case reports, case series, retrospective database analyses and registries of drug-induced liver injury (DILI). Nevertheless, the true incidence and prevalence of hepatotoxicity associated with herbal use are unknown (Navarro, 2009; Navarro et al., 2014; Robles-Diaz et al., 2015). Based on available data from DILI cohort studies, herbal products are estimated as a cause of hepatotoxicity in 2–16% of patients with DILI (Andrade et al., 2005; Chalasani et al., 2008; Ibanez et al., 2002; Sgro et al., 2002). This presents a substantial global health burden considering that the annual incidence rates of DILI are estimated to be from 14 to 34 per 10⁵ inhabitants

per year, as it was determined in prospective population-based studies conducted in France (Sgro et al., 2002), Iceland (Bjornsson et al., 2013), Spain (Andrade et al., 2005) and USA (Chalasani et al., 2008). These numbers reflect the magnitude of herbal hepatotoxicity in real life, however, the frequencies of DILI are likely very underestimated because hepatic adverse effects associated with the use of drugs are generally significantly underreported (Begaud et al., 2002; Sgro et al., 2002). For instance, if we extrapolate estimated DILI incidence rate in France, there should be more than 8000 cases of DILI annually, yet, only 400 to 500 such cases were actually reported (Sgro et al., 2002). As traditional herbal medications are extensively used in Africa, South and Central America and many parts of Asia (especially in Southeast Asia, Korea, China and India), it can be assumed that herbal hepatotoxicity is observed more commonly in these parts of the World than in Europe, which was also demonstrated by multiple studies (Ibanez et al., 2002; Suk et al., 2012; Wai et al., 2007).

The spectrum of liver toxicity associated with the use of traditional medicines ranges from clinically asymptomatic abnormal hepatic biochemical tests, such as elevated serum transaminases or bilirubins, to cholestasis, hepatic necrosis or fibrosis, cirrhosis, liver failure, and hepatic veno-occlusive disease, while the clinical presentation can be acute, subacute or chronic (Chalasani et al., 2008; Estes et al., 2003; Suk et al., 2012). In symptomatic individuals, the manifestation often begins with nonspecific symptoms, such as malaise, dyspepsia, inappetence and weight reduction, followed by jaundice, pruritus, oedema and blood coagulation abnormalities (Schiano, 2003; Seeff, 2007; Stickel et al., 2005). Due to the variety and complexity of herbal regimens, it is difficult to summarize the clinical manifestations of herbal hepatotoxicity in general. The toxicity of herbs can result from the interaction of several factors, including the pharmacodynamic and pharmacokinetic properties of the plant compounds used in a herbal product, the conditions of production and storage processes, the level of contaminants in the product, and the consistency and knowledge of the gatherers (Bunchorntavakul and Reddy, 2013).

2.2. Mechanisms of hepatotoxicity

Generally, two major forms of hepatotoxin-induced liver injury (HILI) can be characterized. One of these is called idiosyncratic and the other intrinsic (Uetrecht, 2007). The idiosyncratic form of injury, which is usually somehow associated with the formation of reactive metabolites and often includes the activation of the immune system, is unpredictable and independent of the dose (Uetrecht, 2007, 2008). By contrast, the intrinsic form of liver injury is predictable and dose-dependent (Uetrecht, 2007). It has been assumed that the majority of plant-associated HILI cases are probably idiosyncratic; however, the evidence for this hypothesis is not yet sufficiently convincing (Bunchorntavakul and Reddy, 2013; Teschke and Eickhoff, 2015).

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