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Editorial

Are herbals as safe as their advocates believe? ☆

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The dramatic growth of the pharmaceutical industry over the past 50–60 years has resulted in the development and marketing of an ever-increasing number of drugs. In the United States, medical drugs, both over-the-counter and those dispensed by prescription, are widely advertised on television, in the popular press, and on the worldwide web. The result is that the general public, especially in western countries, are accustomed to hearing about drugs and have come to expect their availability for all ailments, regardless of their severities. While most conventional drugs are designed to be beneficial, they can also cause undesired adverse effects that may range from trivial to death-dealing injury. Numerous epidemiologic surveys indicate that adverse reactions from conventional drugs account for between 3% and over 8% of all hospital admissions [1–4], and are responsible for a significant number of deaths [1,5,6]. Adverse reactions can affect all organ systems including the liver, the focus of this editorial.

Herbals and dietary supplements also now play an important role in the "therapeutic armamentarium." Herbals have been utilized by indigenous peoples and certain cultures for centuries, but interest in their use among western populations is a relatively recent phenomenon, although their frequency of use is growing exponentially and is beginning to parallel and even exceed that of conventional medications. In early telephone surveys conducted in the United States, the use of complementary and alternative medicines (CAM) was reported to increase among respondents from 34% in 1990 [7] to 42% in 1997 [8]. Evaluation of data from the National Health and Nutrition Evaluation Survey (NHANES) found that, between 1999 and 2000, dietary supplements were used by 52% of the surveyed population [9], and in another Health and Diet Survey conducted in the United States, as many as 73% of persons interviewed indicated they had taken dietary supplements in the preceding 12 months, 4% reporting associated adverse events [10]. Herbals use is particularly frequent by people with chronic diseases, including chronic liver disease, in the belief that they provide benefit both in treating their illnesses and in improving their sense of well-being. [11–13] The global market for CAM is said to exceed $60 billion and to have cost $17 billion in the US alone in the year 2000 [8].

There are several reasons for the increasing attention paid by the public to CAM. For some, there is waning confidence or disillusionment in conventional medical practitioners who are perceived as frequently unavailable and often lacking in empathy; others consider it important to take charge of their own lives; and for still others, there are concerns about the often unpleasant and sometimes serious adverse effects of conventional medicines, believing that since herbals are "natural" and have been used for centuries, they must be safer. This is, of course, an incorrect assumption since numerous herbals, like conventional medicines, have been identified to cause adverse reactions, including hepatotoxicity [14–16].

Allopathic (conventional) physicians are generally suspicious of herbal products, questioning both their value and their safety. Reassuring proof of efficacy is lacking because few herbal products have been evaluated

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by rigorous scientifically-designed trials [17]. Instead, the spreading focus on herbals by the public stems largely from word-of-mouth information, published individual testimonials, and wide-spread advertising. Regarding safety, the concern, certainly in the United States, is that since herbal products are categorized as dietary supplements, they cannot be labeled as a treatment for disease. They are therefore exempt from requiring approval for use by the Food and Drug Administration, as is the regulation for conventional drugs [18]. Similarly, in Europe, where herbals also are regarded as food supplements, there had previously been no safety regulations common to all countries. In 2004, a European Directive was proposed by the European Parliament and Council of Europe requiring authorization by regulatory authorities in each European country in regard to efficacy and safety issues [19]. Safety issues include the concern about the purity of herbals as well as uncertainty about whether their content is accurately displayed on the label. Although most users of herbals believe they are safe, many herbals have been clearly implicated as causes of hepatotoxicity, and indeed, several products, such as kava kava and LipoKinetix, have been restricted or removed from use in the US and Germany because of their frequency and severity of injury to the liver [20,21]. Particularly concerning are herbal mixtures that contain multiple ingredients, not all of which are identifiable. Therefore, if liver injury should occur, it may be difficult or impossible to identify which component is responsible. An additional concern is that some herbal products have been shown to contain potentially toxic contaminants such as lead, mercury or arsenic [22–24]. Indeed, many herbals and weight loss products known to have caused liver injury are purchased via the internet [25].

The relative contribution of herbal-related liver injury to the overall frequency of all cases of hepatotoxicity is not well established but probably varies by geographic region. In an ongoing multicenter study in the United States – the Drug-Induced Liver Injury Network (DILIN) study supported by the National Institute of Diabetes and Digestive and Kidney Diseases – approximately 10% of the first 300 cases of identified drug-induced liver injury were attributed to one or more herbal product [26]. In contrast, in a study reported from Singapore, 52% of 29 cases of drug-induced liver injury seen in the course of one year were caused by traditional Chinese medicines [27]. Determining the occurrence of drug-induced liver injury is, however, challenging. Without a specific diagnostic biomarker, drug-induced liver injury must be considered whenever liver dysfunction is identified for which there is no obvious etiology other than the temporal receipt of a drug. The diagnosis of hepatotoxicity, however, requires that its possibility be considered and that the affected person is carefully interrogated about all drugs used; unfortunately, interviewers not uncommonly neglect to inquire about the use of herbals and therefore their contribution to the problem of drug-induced liver injury may be underestimated. Also the diagnostic strategy most commonly used to make a diagnosis of drug-induced liver injury – the RUCAM causality assessment instrument [28] – has potential drawbacks [29].

In this issue of the *Journal of Hepatology*, Stickel and co-workers describe two cases of severe liver injury that they attribute to Herbalife® products [30]. One patient had used Herbalife® F1 Shake Strawberry and Cappuccino, and the other had consumed multiple diverse Herbalife® products. The liver disease in the first patient manifested as cholestatic and lobular/portal hepatitis with cirrhosis, and in the other as biliary fibrosis and ductopenia. Because of the difficulty in determining the precise contents of these products, the authors sought contaminants as a potential basis for the liver injury, and after careful study, identified the presence of *Bacillus subtilis* in some of the products ingested by both patients, showing also that cultures of the bacteria induced dose-dependent leakage of LDH from HepaG2 cells which they interpreted as the basis for the liver injury. Another possible mechanism advanced was the possibility of drug-induced autoimmune hepatitis because of the identification of a positive ANA of 1:1280 in the one patient and 1:160 in the other. While autoimmune hepatitis as an adverse reaction to drugs has been well described [31], it more commonly presents as hepatocellular rather than as cholestatic liver disease. It is conceivable, as suggested by the authors, that bacterial contamination was indeed responsible for the liver disease, but Gram-positive bacteria are extremely rare causes for liver injury, so that it is unclear whether the identified bacterium truly accounted for the identified liver disease despite the evidence of enzyme leakage.

Still, there are at least three reports of liver injury attributed to Herbalife® products, one from Israel [32], another from Switzerland [33], and a third from Spain [34]. Together, these 4 reports describe 28 cases of liver injury attributed to Herbalife®. Two affected patients developed fulminant hepatitis requiring liver transplantation. The manifestation of liver disease ran the gamut from a hepatocellular, to a mixed, to a cholestatic pattern. All the authors used reasonable strategies to implicate the Herbalife® products, but not all the cases received the highest grades of causality scoring; some were called probable rather than certain. However it seems quite likely that liver injury does occur among some people who receive these products, but the precise mechanism or responsible agent in the herbal products is uncertain, in part because the complete listing of the ingredients of these products are not known and the

manufacturer apparently is unwilling to provide the needed information.

Undoubtedly, definitively establishing causality in the face of existing liver disease can be difficult. This has prompted Herbalife® personnel to strongly question whether the described hepatotoxicity cases, some with other liver diseases, can really be attributed to their products [35]. This questioning is not uncommon by manufacturers of drugs – conventional and alternative – when instances of drug-induced liver injury involving their products are reported. Until a specific biomarker is identified, there will always be some uncertainty in implicating a specific product as a potential hepatotoxin. However, the causality likelihood is greatly increased when there are multiple reports, particularly if from well-regarded investigators.

Finally, both conventional drugs and herbals are well-known to cause drug-induced liver injury. The greater concern about alternative medications is that, since they are not regulated in the same way as conventional drugs, their entire contents, advertised and otherwise, may not be known. Ideally, all medicinal products consumed by the public, whether conventional or alternative, should be subjected to the same safety scrutiny. Until that occurs, manufacturers of herbals should be completely transparent about their products by openly reporting all ingredients contained in the product as well as the dose of each of them. Consumers, however, should be aware that herbals are no safer than conventional medications.

References

[1] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998;279:1200–1205.

[2] Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. BMJ 2004;329:15–19.

[3] McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Paharmacother 2002;36:1331–1336.

[4] Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA 2006;296:1858–1866.

[5] Wester K, Jonsson AK, Spigset O, Druid H, Hagg S. Incidence of fatal adverse drug reactions: a population based study. Br J Clin Pharmacol 2007;65:573–579.

[6] Leone R, Sottosanti L, Luisoa Iorio M, Santuccio C, Conforti A, Sabatini V, et al. Drug-related deaths: an analysis of the Italian spontaneous reporting database. Drug Saf 2008;31:703–713.

[7] Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States: prevalence, costs, and patterns of use. N Engl J Med 1993;328:246–252.

[8] Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. JAMA 1998;280:1569–1575.

[9] Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey: 1999–2000. Am J Epidemiol 2004;160:339–349.

[10] Timbo BB, Ross MP, McCarthy PV, Lin CT. Dietary supplements in a national survey: prevalence of use and reports of adverse events. J Am Diet Assoc 2006;106:1966–1974.

[11] Seeff LB, Lindsay KL, Bacon BR, Kresina TF, Hoofnagle JH. Complementary and alternative medicine in chronic liver disease. Hepatology 2001;34:595–603.

[12] Strader DB, Bacon BR, Lindsay KL, La Brecque DR, Morgan T, Wright EC, et al. Use of complementary and alternative medicine in patients with liver disease. Am J Gastroenterol 2002;97:2391–2397.

[13] Seeff LB, Curto TM, Szabo G, Everson GT, Bonkovsky HL, Dienstag JL, et al. Herbal product use by persons enrolled in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial. Hepatology 2008;47:605–612.

[14] Stickel F, Patsenker E, Schuppan D. Herbal hepatotoxicity. J Hepatol 2005;43:901–910.

[15] Furbee RB, Barlotta KS, Allen MK, Holstege CP. Hepatotoxicity associated with herbal products. Clin Lab Med 2006;26:227–241.

[16] Seeff LB. Herbal hepatotoxicity. Clin Liver Dis 2007;11:577–596.

[17] Modi AA, Wright EC, Seeff LB. Complementary and alternative medicine (CAM) for the treatment of chronic hepatitis B and C: a review. Antivir Ther 2007;12:285–295.

[18] US Food and Drug Administration. Overview of dietary supplements. US Food and Drug Administration, Center for Food Safety and Applied Nutrition; 2003. Available from: http://vm.cfsan.fda.gov/~dms/ds-oview.html#regulate.

[19] Calipai G. European legislation on herbal medicines: a look into the future. Drug Saf 2008;31:428–431.

[20] Favreau JT, Ryu ML, Braunstein G, Orshansky G, Park SS, Coody GL, et al. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. Ann Intern Med 2002;136:590–595.

[21] Centers for Disease Control and Prevention. Hepatic toxicity possibly associated with kava-containing products: United States, Germany, and Switzerland, 1999–2002. MMWR Morb Mortal Wkly Rep 2002;51:1065–1067.

[22] Ernst E. Heavy metals in traditional Indian remedies. Eur J Clin Pharmacol 2002;57:891–896.

[23] Centers for Disease Control and Prevention. Lead poisoning associated with use of Ayurvedic medication – five states, 2000–2003. MMWR Morb Mortal Wkly Rep 2004;53:582–584.

[24] Saper RB, Phillips RS, Sehgal A, Khouri N, Davis RB, Paquin J, et al. Lead, mercury,and arsenic in US- and Indian-manufactured Ayurvedic medicines sold over the internet. JAMA 2008;300:915–923.

[25] Joshi D, Cross TJS, Wong VS. Acute drug induced hepatitis secondary to a weight loss product purchased over the internet. Nutr J 2007;6:13–15.

[26] Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al. Causes, clinical features and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology, 2008 September 17 [Epub ahead of print].

[27] Wai CT. Presentation of drug-induced liver injury in Singapore. Singapore Med 2006;47:116–120.

[28] Benichou C, Uclaf R. Criteria of drug-induced disorders: report of an international consensus conference. J Hepatol 1990;11:272–276.

[29] Rochon J, Protiva P, Seeff LB, Fontana RJ, Liangpunsakul S, Watkins PB, et al. Reliability of the Roussel Uclaf Causality Assessment method for assessing causality in drug-induced liver disease. Hepatology 2008;48:1175–1183.

[30] Stickel F, Droz S, Patsenker E, Bögli-Stuber K, Aebi B, Leib SL. Severe hepatotoxicity following ingestion of Herbalife® nutritional supplements contaminated with *Bacillus subtilis*. J Hepatol 2009;50:111–117.

[31] Liu ZX, Kaplowitz N. Immune-mediated drug-induced liver disease. Clin Liver Dis 2002;6:755–774.
[32] Elinav E, Pinsker G, Safadi R, Pappo O, Bromberg M, Anis E, et al. Association between consumption oh Herbalife® nutritional supplements and acute hepatotoxicity. J Hepatol 2007;47: 514–520.
[33] Schoeffer AM, Engel A, Fattinger K, Marbet UA, Criblez D, Reichen J, et al. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife® products. J Hepatol 2007;47:521–526.
[34] Duque JM, Ferreiro J, Salgueiro E, Manso G. Hepatotoxicity associated with the consumption of herbal slimming products. Med Clin I (Barc.) 2007;128:238–239.
[35] Ignarro L, Heber D, Steven Henig Y, Bejar E. Herbalife nutritional products and liver injury revisited. J Hepatol 2008;49:291–293.