CHAPTER

35

Hepatotoxicity of Herbals and Dietary Supplements

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INTRODUCTION

Centuries before globalization and the ability to travel widely, indigenous peoples relied for treatment of diseases on what is now referred to as *alternative medicine*. This included among others, prayer, animal sacrifice, incantations, scarifications, massage, body manipulations, acupressure, acupuncture, and moxibustion (burning mugwort near an acupuncture site). In addition, virtually all peoples of the world utilized products derived from plants and trees for medicinal purposes, a practice dating back centuries, especially in the Far East. Herbals used for treatment were, and continue to be, extracted from the seeds, roots, stems, leaves, berries, barks, and flowers of plants and trees, which vary by region, depending on the local weather, geographic location, geographic elevation, and other conditions [1].

Westernized, pharmaceutically developed medications began to be introduced only a little more than a century ago and, indeed, some drugs, such as digitalis, ephedrine, ipecac, quinine, salicylic acid, and others, including more recently, vincristine and camptothecin, are actually derived from plants. Over the ensuing century, there has been an explosive increase in the numbers and types of commercial drugs developed through chemical and molecular biologic manipulation and synthesis that are evaluated in well-controlled trials to determine their effectiveness and safety, thus clearly revolutionizing medical care. Patients have obviously welcomed and benefitted from these new medicinal discoveries, but some have expressed concern about the often high cost and the fact that a number of drugs are associated with uncomfortable and sometimes serious side effects.

For these reasons, and because many consumers feel that general medical care has become too complex, time restricted, and seemingly less receptive, some have elected to assume greater personal care of their health by turning to the use of complementary and alternative medicine (CAM), which includes the use of herbals and dietary supplements (HDS); their belief is that herbals, having been used for centuries, must be effective and safe. Some will use only herbals for their medical care, referred to as *alternative medicine*, while others will take them together with commercial drugs, referred to as *complementary medicine*, hence the term *CAM*. A recent review of the published data aimed at determining expectations among proponents of CAM use found that the goals of users, in order of prevalence, are to influence the natural history of their disease, promote well-being, reduce side effects, take control of one's health, relieve symptoms, boost the immune system, provide emotional support, improve their quality of life, cope better with illness, support natural healing, and others [2].

EPIDEMIOLOGY OF AND EXPENDITURE ON HERBALS AND DIETARY SUPPLEMENTS

Prevalence of Complementary and Alternative Medicine Use in the United States

Numerous surveys have been undertaken in the United States and elsewhere to determine the prevalence of use of HDS in the general public and among those with various medical conditions. A telephone survey performed in the United States in 1990 revealed that 34% of the general population was currently utilizing CAM [3], with 2.5% using herbal medicines, and that 67.6% had used at least one CAM therapy during their lifetime [4]. A follow-up survey in 1997 by the same investigators found that the frequency of CAM use had increased to 42%, with 12.1% now admitting to use of herbals [5]. Information has also come from reviews of the National Health and Nutrition Examination Survey (NHANES) databases. In the NHANES I study, covering the period 1971–1974, 23% of respondents reported using vitamin supplements [6]. In the NHANES II survey of 1976–1980, the figure for users of supplements was 35% [7]. The figure in the NHANES III survey (1988–1994) rose to 30–42% for men and 42–55% for women [8], while for NHANES IV, covering 1999–2000, the overall figure was 52% [9]. Another source of information in the United States is data from the National Health Interview Survey (NHIS), which covers the noninstitutionalized US civilian population. In this survey of 1999, 28.9% of adults admitted to using at least one CAM therapy in the preceding year, with 9.6% representing herbal medicines [10]. A resurvey of this database 3 years later revealed that 19% of participants had used herbs or supplements in the previous year, from which it was estimated that 38.2 million US adults had taken herbals or supplements during 2002, with their use being significantly higher in women than men [11]. A far higher frequency of dietary supplement use in the same year (2002) was found in a Health and Dietary Survey sponsored by the US Food and Drug Administration (FDA): 73% of the noninstitutionalized US adult population admitted the use of dietary supplements in the preceding 12 months, with approximately half using herbs or botanicals [12]. Despite variations in the reported rates of HDS use, the data collectively indicate that their use has been increasing in the United States over time. This is noteworthy, since in virtually all surveys, patients are reluctant to inform their health care

providers of their use of CAM therapies unless specifically asked and, even then, somewhat grudgingly. Hence, for reasons to be discussed, it is essential for medical providers to consistently and nondisparagingly inquire whether their patients are presently or have in the past used herbal products, what the products are, and where they were acquired.

Prevalence of Complementary and Alternative Medicine Use in Other Parts of the World

CAM use is, of course, practiced worldwide, and in some countries represents the primary form of medicinal care. General surveys from Europe attest to the high frequency of herbal use in that continent [13,14], including reports from such countries as Germany [15], Italy [16], Sweden [17], and Spain [18]. High usage is also reported from the Middle East, including Jordan [19], the United Arab Emirates [20], Turkey [21], and Israel [22]. Not surprising is the high frequency of use in the Far East [23–26] and Africa [27–30]; a high frequency has also been reported in Australia [31]. Fact sheets from the World Health Organization (WHO) indicate that in some Asian and African countries, 80% of the population depend on traditional medicine for their primary health care [32].

Complementary and Alternative Medicine Use for Chronic Illnesses

A large body of published data also attests to the frequent use of CAM, including herbals, among persons with a variety of chronic diseases [33]. This includes, but is not limited to, those with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome [27,34], rheumatologic disease [35], cancers [29,36], chronic pain [37], cardiovascular disease [38], diabetes [39], and liver diseases [40–46]. Regarding liver disease, 23% of enrollees in a long-term treatment trial of persons with chronic hepatitis C admitted to their current use (an additional 21% having used them in the past), despite having previously suffered uncomfortable antiviral treatment and now committing themselves to another 3.5 years of treatment with pegylated interferon [42].

Expenditure on Complementary and Alternative Medicine Use

The financial outlay on CAM therapies in the United States, mostly out-of-pocket expenses, is vast. An analysis conducted in 1997 conservatively estimated that expenditure on CAM therapies was US$27 billion, taking into account the cost of both purchasing herbal products and vitamin and CAM professional services [5]. This amount was said to be comparable to the total out-of-pocket expenditures for all physician services. The estimated expenditure 7 years earlier had been US$14.6 billion. In 2007, the estimate had risen to US$33.9 billion in the United States, based on analyses performed at the National Center for Complementary and Alternative Medicine (NCCAM) and the National Institutes of Health (NIH), using data derived from the NHIS [47]. Placing these data in context, the researchers noted that the cost to purchase natural products was "equivalent to about 1/3 of total out-of-pocket spending on prescription drugs," and that the cost for "CAM practitioner visits was equivalent to approximately 1/4 of total out-of-pocket spending on physician visits." In their estimate, in 2007 38% of adults and 12% of children in the United States had utilized some form of CAM [47]. More recently, data published by the American Botanical Council showed that during the period 1999–2009 there had been an estimated increase in sales and monetary outlay for herbals in the United States every year in that decade, except for 2002 and 2003 (Table 35-1) [48].

ORIGIN AND PRODUCTION OF HERBALS AND BOTANICALS FOR MEDICINAL PURPOSES

The use of botanicals as medicines dates back thousands of years in many cultures, particularly in Far Eastern countries, such as China. However, herbs

TABLE 35-1 Total Estimated Herb Sales in the United States, 1999–2009

Year	US$ Total Sales (Billions)	% Change
1999	4.110	+2.7
2000	4.230	+2.9
2001	4.356	+3.0
2002	4.278	−2.7
2003	4.146	−2.2
2004	4.290	+3.5
2005	4.381	+2.1
2006	4.561	+4.1
2007	4.759	+4.3
2008	4.800	+0.9
2009	5.030	+4.8
2010	5.200	+3.3

for healing purposes have also been used in the distant past by Greeks, Egyptians, Indians, and indigenous peoples from Africa and the South Sea Islands and by Native Americans. Unlike Western medicines that are generally designed to treat a specific disease or set of symptoms, the traditional use of herbals is meant to have a broad impact on strengthening the body's ability to deal with a variety of illnesses. Thus, herbalism is an art rather than a science. Herbals in the traditional Chinese medicine (TCM) culture have consisted of single products believed, through trial and error, to induce a particular response for a given set of symptoms, but may be mixed or bundled with other specific herbs that together are considered complementary and therefore more effective. The intent is to readjust and bring into balance the *yin* and *yang*, i.e., the polar opposites, that are possibly responsible for health problems. This requires the expertise of an experienced traditional herbalist who selects the most effective herb, which may differ according to the season of harvest, soil characteristics, prevailing climate, and elevation where grown. Many such herbalists dispute the current pharmacological effort to chemically isolate and extract the presumed active ingredient because the plant is believed to contain other substances that may enhance the healing process and also protect against possible toxicity.

In addition to the traditional use of herbals, consisting either of a single ingredient or a carefully selected but restricted mixture of ingredients, there has been a dramatic increase in the use of commercially developed products that often contain multiple ingredients, as many as a dozen or more. These may be grouped together not necessarily because they are known to complement one another, but because each individual ingredient is reputed to have an independently positive effect. They are advertised as being useful for healthy living, bodybuilding, weight loss, weight gain, or an improved sense of well-being. Many are sold in health food stores, but some are advertised on the Internet, sometimes by fly-by-night companies or individuals [49].

The nature of herbal production unfortunately lends itself to contamination with potentially toxic items or to the unexpected addition of adulterants. The original herb may have been specifically cultivated, requiring spraying with pesticides, or collected from the wild. After it is grown, it is harvested, dried naturally or artificially, cleansed and sorted, and then subjected to extraction of constituents using organic solvents, maceration, percolation, countercurrent extraction, extraction with supercritical gases, irradiation, or cold compression. Extracts are then usually stored and packaged prior to distribution. At any step, there may be contamination with microbials [50,51], mycotoxins [52], and heavy metals [49,53–58], or there may be adulteration with pharmaceuticals [59], which have included chlordiazepoxide, chlormethiazole, chlorpheniramine, diclofenac, diphenhydramine, hydrochlorothiazide, promethazine, sildenafil citrate, and triamterene [60], as well as benzodiazepines, corticosteroids, and antiinflammatory drugs [61]. Specific examples are an herbal product, PC-SPES, used to treat prostate cancer, that has been found to contain pharmacological dosages of diethylstilbestrol [62], indomethacin [63], and warfarin [63,64] and herbal products marketed to treat erectile dysfunction, found to be contaminated with phosphodiesterase type 5 inhibitors [65]. A disturbing finding from the NHANES data obtained between 1999 and 2004 was that blood levels of lead were significantly higher in women who used herbal supplements than among nonusers, the relative difference being 10–24% higher [66].

REGULATION OF DIETARY SUPPLEMENTS

The United States

Preceded by a vigorous and sometimes rancorous debate among stakeholders, the US Congress promulgated the Dietary Supplement and Education Act of 1994 (DSHEA), signed into law on 15 October 1994, during the waning moments of the 103rd Congress. Prior to that time, the FDA permitted manufacturers of drugs but not conventional food and dietary supplements to label their products with claims of disease prevention, mitigation, treatment, or cure. The Act was therefore viewed by the supplement industry as a positive step, since the FDA would now regulate dietary supplements and its ingredients differently from those regulating conventional foods and drugs. The manufacturers of dietary supplements would themselves become responsible for ensuring that supplements and their ingredients were safe before its marketing. Furthermore, manufacturers would not need to register their product with the FDA or get FDA approval before producing or selling their supplements. Manufacturers did have to ensure that their product labeling information was truthful and not misleading and that it complied with current good manufacturing practices (cGMP) for quality control. The role left to the FDA was to take action against any unsafe dietary supplement product, but only once it reached the market. Accordingly, the manufacturer, packager, or distributor of dietary supplements marketed in the United States would be required to notify the FDA of all adverse events associated

with the use of the dietary supplement. Unfortunately, it is estimated that less than 1% of instances of adverse events caused by herbals and dietary supplements are in fact reported to the FDA (Inspector General, Department of Health and Human Services; Government Accountability Office Report to Congressional Requesters, January 2009, Dietary Supplements: FDA Should Take Further Actions to Improve Oversight and Consumer Understanding). In this regard, in a survey published in 2001 [67], while a large proportion of interviewed persons admitted using supplements, most did not inform their regular physicians of this use because they believed that their physicians knew little about these products or were biased against their use, and many were convinced of their value and would continue to use them even if scientifically conducted studies did not prove their effectiveness. However, the majority believed that the FDA should be permitted to review the safety of these products prior to their distribution and, if found unsafe, that they should be removed from use, and furthermore that government regulation should be increased to ensure that claims of safety were in fact true. In 2007, the FDA required a modification to the cGMPs regarding manufacturing, packaging, labeling, and holding operations for dietary supplements and a Final Rule was published on 22 June 2007. More recently, the FDA has developed draft guidance for industry regarding new dietary ingredients notification. Needless to say, there continues to be controversy about the Act, including the question of what actually constitutes a dietary supplement and what represents a new dietary ingredient [68].

Other Regions

Other regions that have had or have begun to develop regulations regarding herbals include the European Union, the United Kingdom, and Canada.

European Union

Current regulations are based on the Traditional Herbals Medicine Products Directive 2004/24/EC announced on 31 March 2004 [69]. The intent was that all traditional medicines in health food shops and pharmacies must be formally registered and the products approved before they could be sold. Acceptable products for licensure were considered to be those whose use was "plausible on the basis of long-standing use and experience" and whose quality and safety could be guaranteed. The duration required to prove their safety was at least 30 years in all, and at least 15 years in the EU. The Directive allowed the passage of 7 years from its announcement for manufacturers to gather the necessary information on their products and on 1 May 2011, the requirement that herbal medicines and their ingredients be registered with evidence of safety went into effect [69]. Based on this Directive, no herbals from China would meet the specifications and they are therefore currently banned in the EU.

United Kingdom

The Herbal Medicines Advisory Committee was established in 2005 to advise on the safety, quality, and efficacy of herbal medicinal products for human use. Although there is no requirement for proof of efficacy, pharmacological effects must be plausible and supported by long-standing use and experience. The herbal medicinal product must be eligible under the Traditional Herbals Medicine Products Directive 2004/24/EC [70]. Prior to this, regulation of the herbal industry was covered by the 1968 Medicines Act. Under the current act, suspected adverse reactions to herbal medicines are reported voluntarily, but are compulsory for manufacturers with registration of a product under the Traditional Herbal Medicines Registration Scheme that has published guidelines for retailers, wholesalers, importers, and manufacturers on its requirements [71].

Canada

Consultations with various stakeholders led to the creation of the Natural Health Products Regulation that addresses the availability and safety of natural health products. All natural health products must have a product license and manufacturers, packagers, labelers, and importers must have site licenses. Licensing requires specific labeling and packaging requirements, cGMP, and evidence of safety and efficacy.

Global Regulatory Environment for Herbal Medicinal Products

The WHO, in response to the proliferation of herbal medicine use in many countries, both developed and underdeveloped, as well as the safety concerns surrounding herbal medicines raised by its member countries, conducted a survey of the 191 member states in 2001 that explored policies, regulations, and areas for more action in the arena of traditional and complementary and alternative medications (TM/CAM). Among 141 respondents, only 45 (32%) reported having a policy on TM/CAM; these policies are loosely defined and include laws, regulations, and consideration of intellectual property issues. Regarding regulations for herbal medicines, 53 (37%) respondents reported having laws and regulations in place as of 2003, although the majority (86 of the 141 respondents;

61%) had a registration system in place for herbal medicines. Responding member states requested continued support from the WHO to address the lack of research, appropriate control mechanisms, and formalized education and training in the use of TM/CAM [72].

THE USE OF HERBAL PRODUCTS TO TREAT LIVER DISEASE

Philosophy

There are vast differences in the views of Western and Eastern practitioners regarding the philosophy of health care administration. The Western approach to treatment consists largely of the administration of drugs or the performance of surgery targeting a specific condition or disease. It requires defining the etiology and pathogenesis of the disease, developing and utilizing medications directed specifically at the illness, and conducting rigorous, scientifically defined studies to establish the efficacy and safety of medications; thus, treatment directed at the disease is evidence based. In contrast, the Eastern approaches are integrative and holistic, directed at the body and mind rather than the disease, and based on the view that in order to preserve health, the vital energy that maintains life must flow freely through the entire body [73]. Ideally, with regard to the use of herbals, treatment is administered by an experienced local healer whose knowledge derives from information passed from generation to generation.

In the West, people tend to use herbals or dietary supplements largely to maintain or improve their well-being or health, for bodybuilding purposes, or to treat chronic rather than acute illness; the focus on chronic diseases is because few conventional medications actually cure chronic diseases and many are associated with uncomfortable or even serious adverse effects. Moreover, cost issues can represent a burden for developing countries. The focus on herbals comes from the belief that, having been used for centuries, they are likely to be effective but, more importantly, that being natural they must surely be safe. Western practitioners, however, tend to decry this alternative approach, particularly the use of herbals, because of their seeming unscientific origins, the lack of well-controlled trials to prove their efficacy and safety, the concern of contamination and adulteration, and the not uncommon proclamation of a miracle cure, often delivered as a testimonial. Unsurprisingly, therefore, herbal users tend not to inform their conventional health care practitioners of this fact for fear of being disparaged or reprimanded. However, in view of the prolific use of herbals, because they are sometimes used as a substitute for potentially curative conventional medication by persons with serious disease, and because many have been associated with severe, life-threatening side effects, it is essential that conventional health care practitioners educate themselves about this form of health care and be willing to considerately question their patients about its utilization or advise them on how to use herbals safely.

While HDS are most often employed in Western countries to improve or sustain well-being and general health, for weight reduction, and for muscle-building purposes by bodybuilders, the present discussion will be confined to their recent use for the treatment of liver diseases, predominantly viral hepatitis.

Herbals to Treat Viral Hepatitis

Following the discoveries of the hepatitis A, B, and C viruses (HAV, HBV, and HCV), pharmaceutical companies attempted to identify and evaluate medications in well-designed, controlled trials aimed largely at treating patients with chronic hepatitis B and C. A number of drugs developed clearly represented vitally important advances in the management of these chronic liver diseases but were initially found to be effective in only a limited number of patients, were associated with frequent serious side effects, and their costs were extremely high and, hence, could not be afforded by many affected individuals. Accordingly, viral hepatitis became and continues to be a prime target for self-treatment with herbals.

Various herbal products have been evaluated for treating viral hepatitis, the most prominent being silymarin, glycyrrhizin, Japanese traditional medicine (Kampo medicine; TJ-9, Sho-Saiko-To), TCM, and *Phyllanthus amarus* [43,74]. Unfortunately, the adherence to generally accepted scientific methods to evaluate drug therapy has been rare; few studies have been conducted as randomized, blinded, controlled trials or have estimated sample size or defined end points ahead of time, have ensured a homogeneous population or disease characteristics, or have measured outcome using appropriate serological tests or other biomarkers, let alone establishing hard end points such as histology or sustained viral clearance. Moreover, there is uncertainty about the quality of the herbals evaluated in studies, whether or not they are appropriately absorbed, and the adequacy of doses given. Finally, reporting of results has lacked uniformity and is often biased by the reporting of only positive results. In this regard, a group of investigators collaborated in the 1990s to develop standards for reporting results of randomized controlled trials, termed the Consolidated

Standards of Reporting Trials (or CONSORT) Statement [75]. Although this effort focused on reporting conventional drug results, it did include creating a modified version for evaluating herbal medication [76,77].

Silymarin (Milk Thistle)

Silybum marianum has been used for centuries to treat liver and biliary disorders; in Europe, its use has focused on treating mushroom (*Amanita phalloides*) poisoning [78]. It is also the most common herbal product used by patients with chronic viral hepatitis [40–42]. Its main constituent is silymarin, consisting of four isomers: silibinin A and B, isosilibinin A and B, silichristin, and sildianin. Numerous studies indicate that it has antioxidant, antifibrotic, and antiinflammatory activities, that it neutralizes free radicals and stabilizes cell membranes, and that it is cytoprotective [79–81]. Until recently, there has been no evidence that it has antiviral properties.

Two important early treatment trials brought attention to silymarin as a potential therapy for chronic liver disease, focusing on alcoholic cirrhosis [82,83]. The results of the two studies were, however, contradictory and data were compromised by high dropout rates and the lack of alcohol consumption during treatment. They were followed by a number of other randomized, controlled trials involving patients with alcoholic cirrhosis, acute and chronic viral hepatitis, and primary biliary cirrhosis, almost all administering treatments for only 1–2 months' duration [43]. A Cochrane review of these trials concluded that silymarin had no significant effect on reducing fibrosis, morbidity, or mortality, but noted that the methodological qualities of the trials were low [84].

In 2007, a standardized silymarin extract (MK-001) was found for the first time to have antiviral activity against HCV [85]. In an in vitro study, standardized silymarin (MK-001) was shown to inhibit infection of human hepatoma Huh7 and Huh7.5.1 cells by the JFH (Japanese fulminant hepatitis)-1 virus, expression of tumor necrosis factor (TNF-α) in anti-CD3-stimulated peripheral blood mononuclear cells, and nuclear factor NF-kappa-B (NFκB)-dependent transcription in Huh7 cells. Thus, silymarin appeared to exert anti-inflammatory and antiviral effects. A key study, published 1 year later, reported that silibinin given intravenously dramatically reduced levels of HCV RNA in patients with chronic hepatitis C who had not responded to previous standard treatment with pegylated interferon and ribavirin [86]. This unexpected result was noted in two protocols that involved administering increasing doses of silibinin infused intravenously for 4 h for either 7 or 14 consecutive days, followed by pegylated interferon and ribavirin or by triple therapy for up to 24 or 48 weeks. The inhibitory effect disappeared, however, when the silibinin infusion was completed. Other than mild gastrointestinal symptoms, intravenous treatment with silymarin was well tolerated. A similar antiviral inhibitory effect on HCV and on inhibition of HIV replication was reported in patients coinfected with HIV plus HCV [87], and silymarin was also shown to prevent reinfection with HCV of a liver graft following liver transplantation [88]. Additional studies to determine the mechanistic effects of silymarin and silibinin on the HCV and on liver cell necrosis have continued to be performed, yielding improved knowledge of the compound and suggesting that it may have a future role in the treatment of patients with HCV infection [89–92].

On this basis, the NCCAM and the National Institute of Diabetes and Digestive and Kidney Disease, NIH, embarked on scientifically designed studies to evaluate silymarin to treat patients with chronic hepatitis C who had failed to respond to conventional pegylated interferon and ribavirin therapy, as well as for those with nonalcoholic steatohepatitis. Termed *SyNCH*, the study began as a phase I/II trial using a standardized milk thistle product (Legalon, Madaus AG, Frankfurt, Germany). The phase I study, designed to evaluate absorption characteristics and pharmacokinetics, and to determine effective doses, consisted of administering increasing oral doses of silymarin given at 8-h intervals for 7 days. Among its findings were that steady state exposures suggested nonlinear pharmacokinetics, that the product appeared to be safe, and that it did not produce a meaningful reduction in serum aminotransferase levels or reduce serum levels of HCV RNA at lower doses, but that higher doses may overcome the low bioavailability [93]. Unfortunately, recently reported results of the hepatitis C trial indicate that treatment with oral doses of silymarin, even when pushed to the limit of oral intake, did not lead to reduction of aminotransferase or HCV RNA levels [94]. Clearly, treating by intravenous infusion, although seemingly effective while the infusion continues, is not a viable treatment option. There may, however, be a role for silymarin as an adjunct to the new direct antiviral drugs that have or will become available in the future, or even as an addition to the older standard-of-care drugs, pegylated interferon and ribavirin, in parts of the world where the new drugs are unavailable or cannot be afforded. These possibilities will need to be investigated, however, in future well-controlled trials [95].

Glycyrrhizin

Derived from the root of the licorice plant, *Glycyrrhiza glabra*, glycyrrhizin contains glycyrrhetic acid, flavonoids, hydroxycoumarins, and β-sitosterol. It has been commonly used in Japan to treat chronic hepatitis, where it is referred to as Stronger

Neo-Minophagen C (SNMC); the parenteral preparation contains 2% glycyrrhizin, 0.1% cysteine, and 2% glycine [96,97]. It appears to have antioxidant, anti-inflammatory, and immunosuppressive properties [98,99]. A number of clinical trials have used this herbal to treat HCV infection, almost all consisting of open-label studies and involving short-term treatment, therefore most being of questionable quality [43]: some involved the treatment of hepatitis C, some the treatment of hepatitis B, and at least one was for the treatment of hepatocellular carcinoma (HCC) in chronic hepatitis C. The main effect seen in these short-term studies is an improvement in serum aminotransferase levels without an effect on the HCV. Glycyrrhizin has to be given intravenously (although liquid, powder, and tablet formulations have recently become available but have not yet been fully evaluated in persons with liver disease) and, because of its mineralocorticoid properties, it can cause hypertension, fluid retention, and hypokalemia. Since only a few randomized controlled trials have been performed with this product, additional high quality trials are needed.

Sho-Saiko-To (TJ-9)

Used in Japan and China to treat chronic liver diseases, this is an herbal product containing seven herbs (*Bupleurum* root, ginger rhizome, *Ginseng* root, *Glycyrrhiza* root, jujube fruit, *Pinellia tuber*, and *Scutellaria* root) [100,101]. Its name, Sho-Saiko-To, is Japanese and TJ-9 is its label within the Kampo system of medicine, which comprises certain Chinese medicinal herbal combinations adapted to Japanese preference and categorized for composition, indications for use, and presumed health effects. Within this system, another preparation, TJ-108, has an additional apparent antiviral constituent, Gomisin A [102]. Numerous experimental studies indicate that TJ-9 has antifibrotic properties through downregulating RNA expression of genes encoding procollagen alpha I and III, inhibiting TIMP (metalloproteinase inhibitor), reducing expression of α-smooth muscle actin, lipid peroxidation in hepatocytes, and proliferation and activation of hepatic stellate cells [103–106]. One randomized controlled trial and one pilot study with TJ-9 have been performed to treat patients with HBV infection [107,108] and one randomized, controlled trial was conducted to prevent HCC in patients with chronic HBV infection [109]. Each study suggested some positive effect without being convincingly well performed. A number of serious adverse effects have been reported with this product [110–113]. Clearly, additional well-designed trials are still necessary to fully determine whether this product has any meaningful effect on viral hepatitis.

Traditional Chinese Medicine

Herbals used in China date back centuries and their medicinal role differs from that required of therapy administered in the modern-day Western world. As already noted, the philosophy behind this form of treatment aims at stabilizing altered and opposing body energies, i.e., to bring the *yin* and *yang* into alignment. In TCM, several herbs are combined, one being the active *King* herb, while the others act synergistically as its protective modifiers [114]. TCM may consist of half a dozen or even more herbs, including a product containing 10 herbs, referred to as compound 861, or 19 herbs, referred to as CH100, each of which contains the individual *King* herb [115–118]. Small studies with these compounds have been performed to treat both hepatitis B and C, and were reported to lead to reductions in serum enzymes but not the respective viruses; they have also been used to treat HCC and were reported to have some efficacy, but in poorly conducted studies [118]. Once again, better-designed studies are needed to determine whether TCM has any real efficacy in treating chronic viral hepatitis.

Phyllanthus amarus

Plants of the Phyllanthus genus, found in tropical and subtropical countries, contain alkaloids, flavonoids, lignans, and terpenes. They have been used in India and China to treat diabetes, diarrhea, hepatitis B, and urinary tract conditions [119]. In vitro studies using human cell lines infected with the hepatitis B and woodchuck hepatitis viruses have found that the herbal has an inhibitory effect on HBV polymerase activity and that it decreases mRNA transcription in hepatitis B transgenic mice [120–122]. Several studies have reported contradictory results using this herbal to treat patients with HBV infection: some reported loss of HBeAg and hepatitis B surface antigen (HBsAg), while others have failed to replicate these results. The positive effect, however, appeared more likely when *Phyllanthus* was used together with interferon [123–126]. Thus, it appears that *Phyllanthus* may have antiviral activity but, as is true for other herbal products, there is a need for reliable controlled trials to prove that it is indeed an effective product.

Numerous other herbal products have been studied as treatments for liver disease, including Ayurvedic medicines used in India (picrorrhiza and Liv-52), ellagic acid and curcumin, oxymatrine, and a wide array of Chinese herbal concoctions (Bing Gan Ling, Bing Gan Tang, Gansu, Qinggaan and Bushen granules, Yi Er Gan Tang, and Yi Zhu decoction) [43,127,128]. Valid evidence of efficacy for all these products will remain uncertain until they are studied using appropriate scientific methods.

LIVER INJURY CAUSED BY HERBALS AND DIETARY SUPPLEMENTS

Although there is modestly encouraging but clearly unproven or uncertain evidence for the efficacy of HDS for the treatment of liver diseases—as has been hoped for by the public who use them—there is unquestioned evidence that they are sometimes responsible for causing liver injury, contrary to the belief of users. The real frequency of hepatotoxicity from HDS is unknown. Furthermore, the types of products that cause hepatotoxicity in the United States and their relative frequencies have been described only recently by the NIH-supported Drug-Induced Liver Injury Network (DILIN) study. In a preliminary review of data collected from 93 patients with hepatotoxicity attributable to HDSs prospectively enrolled into the DILIN over an 8-year period, the most commonly implicated products were supplements used for bodybuilding and for weight loss, representing 31% and 18%, respectively, of the 93 collected cases (unpublished). Regarding the bodybuilding supplements, all were men who experienced characteristically protracted periods of jaundice, with modest elevations in aminotransferase levels. In contrast, weight loss supplement injury occurred predominantly among females and was characterized by more prominent elevations in aminotransferase levels.

It seems prudent to distinguish between true herbal drugs and dietary supplements, of which the latter may or may not contain plant extracts, since the reasons for using each are different. Herbal drugs are used mostly to specifically treat or prevent certain diseases, while dietary supplements are usually consumed to compensate for existing or presumed nutrient deficiencies or to promote health in general. Thus, the discussion on hepatotoxicity will be presented in two sections, one focusing on herbal drugs for which adverse hepatic drug reactions have been described and the other describing nutritional supplements that have been found causative for or associated with instances of liver injury.

CAUSALITY ASSESSMENT FOR HEPATOTOXICITY DUE TO HERBALS AND DIETARY SUPPLEMENTS

As is the case for apparent liver injury from conventional medications and xenobiotics, there is no definitive means of diagnosing hepatotoxicity when the injury is thought to be attributable to HDS. Rather, an accurate diagnosis is predicated upon the clinician's diagnostic acumen and on the willingness of the patient to be forthcoming about the use of products. Causality assessment, the process of determining whether there is a reasonable likelihood that a drug or herbal or dietary supplement is the cause of liver injury, is generally performed using one of several methods [129–134]. More importantly, the assessment must be conducted in a carefully defined methodical fashion (Fig. 35-1); the steps are similar whether the suspect is a conventional medication or an herbal or dietary supplement, with only minor modification. First, when liver injury is identified, the initial step is to obtain a thorough medical history surrounding the event that must include information on the contemporaneous receipt of all medications as well as of HDSs. An active inquiry into the use of HDS is critical since, as has already been stated, patients frequently fail to divulge the use of such products. Second, the use of a product must obviously have preceded the onset of injury but, in general, must have been started no more than a year earlier. Third, all other causes of liver injury must be excluded, including viral, autoimmune, hemodynamic/vascular, metabolic, and inherited diseases (Fig. 35-1). Fourth, attribution to a specific medicinal product is supported if there is improvement of the liver injury following cessation of the suspected product, referred to as *dechallenge*, with the caveat that, in rare instances, liver injury can be self-perpetuating. Finally, perhaps the most convincing indicator for attribution of injury to a specific product is if there is recrudescence of the injury following serendipitous or surreptitious resumption of that implicated product (*rechallenge*), often with a more vigorous presentation and more severe outcome. However, because of the possibly greater severity of the reaction, routine intentional rechallenge cannot be advocated.

A characteristic of drug-induced liver injury (DILI) that might be more helpful in implicating herbals than conventional medications is the pattern (hepatocellular, cholestatic, or mixed), duration, or severity of the observed liver injury. For example, bodybuilding supplements have been reported on numerous occasions to typically produce a cholestatic form of liver injury, characterized by protracted jaundice and liver biopsy findings revealing little inflammation but prominent bile pooling [135–137]. Given this extensive clinical experience—the identification of cholestatic liver disease in the setting of bodybuilding supplements—such a presentation permits firmly establishing causation with a high degree of confidence.

LIMITATIONS OF CAUSALITY ASSESSMENT FOR HEPATOTOXICITY DUE TO HERBALS AND DIETARY SUPPLEMENTS

Although several methods have been employed for determining causality for liver injury of conventional

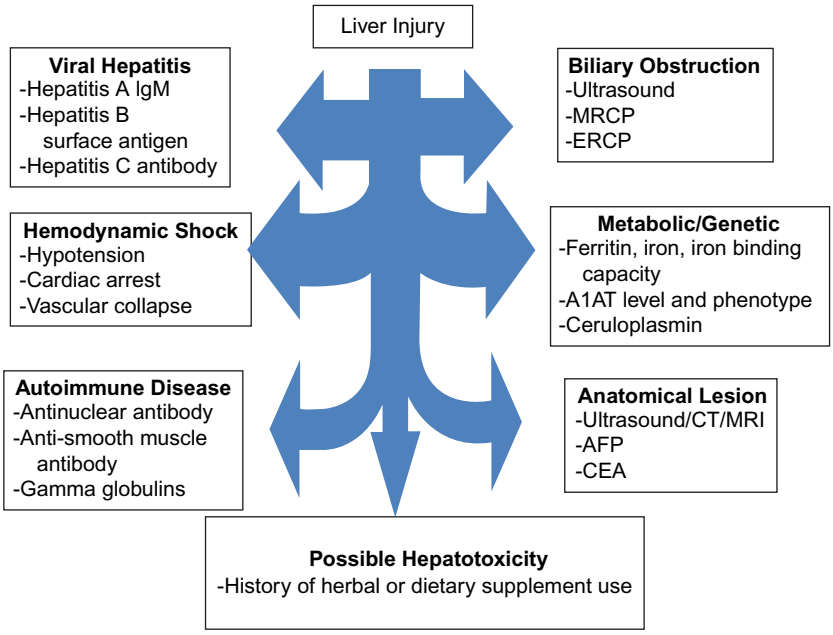

FIGURE 35-1 **The diagnosis of hepatotoxicity due to herbal and dietary supplements depends upon exclusion of other causes.** These include viral hepatitis, hemodynamic-shock, autoimmune disease, biliary obstruction, metabolic and genetic diseases, and anatomical lesions. It is only after taking such an approach, coupled with the appropriate history of herbal or dietary supplement use prior to the onset of injury, that the diagnosis can be made with confidence. A1AT, alpha 1 antitrypsin; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CT, computed tomography; ECRP, endoscopic retrograde cholangiopancreatography; IgM, immunoglobulin M; MRCP, magnetic resonance cholangiography; MRI, magnetic resonance imaging.

medications, there has not been a distinctive or formal method developed to assess causality for liver injury attributable to HDS, although this is an issue of current investigation [138]. Developing a more specific causality assessment tool is important because there are several aspects of HDS use that can confound the process of causality assessment.

One challenging issue faced in performing causality assessment of possible HDS-induced liver injury is the potential for batch-to-batch, seasonal, and geographic variability in the composition of the product under consideration. This can cause the problem of misattribution, even though the causality assessment process suggests impugning a specific product, since the injurious ingredient or combination of ingredients may no longer be present.

Establishing the timing and duration of use of an agent is an important aspect of determining causality. Current methods of causality assessment assign a lower likelihood of attribution if the latency period between starting the product and the first evidence of liver injury is unusually prolonged. Because of the potential for variability of ingredients from batch to batch or for the introduction of new, more potent ingredients at variable times after initiating treatment, a reliance on latency may not always be relevant.

Finally, many HDSs are complex mixtures, containing a multiplicity of ingredients that make it nearly impossible to identify which specific ingredient is the cause of injury. There are also instances in which an ingredient thought to be harmful is excluded from a product, yet injury from this product continues. This occurred when liver injury was attributed to the commercial product Hydroxycut; the toxic ingredient was believed to be ephedra, which was therefore ordered by the FDA to be excluded from its formulations in 2003 [139–144]. However, cases of liver injury continued to occur, finally leading to its complete market recall in 2009. Clearly, improved detection methods are needed to unequivocally identify the toxic ingredient(s) in an herbal mixture responsible for causing the liver injury.

HERBAL PRODUCTS ASSOCIATED WITH LIVER INJURY

Herbals may damage the liver in a manner similar to that attributed to synthetic drugs and the liver injury can be variable, even with the same herbal. As with conventional drugs, there is no uniform mechanism by which injury develops, and risk factors that render an individual susceptible to herbs are known for only a minority of preparations. Hence, clinical signs, symptoms, and findings are identical to those encountered when liver injury is due to synthetic drugs. Clinicians are often misled by not inquiring about the use of herbals and may therefore pursue false lines of suspicion, particularly, if patients do not admit to taking herbals. Liver biopsy may be justified in some instances to assess the type and extent of liver injury, especially when the presentation is that of chronic liver disease, but liver histology lesions specific to herbals are only described for a very few remedies. A careful medication history with specific interrogation for the intake of natural, herbal, or unconventional medication is usually the key investigation, and many

published reports describe delayed recognition of herbals as the true culprit in cases of DILI. A review of herbals that have been associated with liver damage is provided (Table 35-2).

Herbals Containing Pyrrolizidine Alkaloids

Among the first herbals found to occasionally cause severe hepatic injury were those containing pyrrolizidine alkaloids such as echimidine, monocrotaline, retronecine, seneciphylline, and symphytum. Extracts from *Crotalaria*, *Heliotropium*, *Senecio*, and *Symphytum* (comfrey) species are particularly hepatotoxic, with a clear dose dependency. Comfrey (*Symphytum officinale*) is traditionally used to externally treat bruises and joint injuries with tinctures and ointments, but oral preparations are banned in Europe and North America. Exposure of humans to pyrrolizidine alkaloids occurs predominantly via contaminated foodstuffs such as salads, cereals, and honey [145]. As early as 1920, a syndrome of ascites, hepatomegaly, and eventually cirrhosis was described as Senecio disease in South Africa [146], and was followed by reports from Jamaica of children developing a similar disease after the ingestion of bush tea, which contains *Crotalaria* species [147]. Contamination of crops with *Heliotropium* was the reason for a series of pyrrolizidine alkaloid poisonings in India [148,149] and Afghanistan [150], and was followed by instances of liver damage from pyrrolizidine alkaloid intoxication in Arizona, such as in two infants after drinking herbal tea made of *Senecio longilobus* [151,152]. Similar cases have also been seen in Europe and elsewhere [153–155].

The type of liver injury provoked by pyrrolizidine alkaloids is sinusoidal obstruction syndrome (SOS; also known as hepatic venoocclusive disease), a nonthrombotic obliteration of the sinusoids and lumen of the terminal centrilobular hepatic veins. The resulting venous outflow obstruction causes hepatic congestion and parenchymal necrosis resulting in acute liver failure (ALF) or liver fibrosis and cirrhosis [156]. The mechanism of injury involves a direct toxic effect related to biotransformation of pyrrolizidine alkaloids by microsomal cytochrome P450 (CYP) enzymes into pyrrole derivatives, which then form genotoxic protein adducts [157]. Notably, pyrrolizidine alkaloid toxicity can be enhanced by phenobarbital, a potent inducer of CYP3A4, CYP2B6, and several isoenzymes of the 2C family. Acute toxicity is not species specific and an animal model of SOS using monocrotaline has been characterized [158]. Abundant experimental data also point to an oncogenic potential of comfrey and other pyrrolizidine alkaloid-containing herbs [159]. Treatment of affected patients is symptomatic, and spontaneous recovery upon dechallenge to pyrrolizidine alkaloids is possible; however, for those progressing to acute or chronic liver failure, liver transplantation should be considered.

Chinese Herbs

In TCM, the use of herbals dates back as far as 2100 BC and, along with the rising popularity of oriental medicine, their use is increasing worldwide. Most Chinese medicines are mixtures of several different herbs of which one or two are considered the pharmacologically active King herbs, while the remaining constituents enhance the effect of the King herb, alleviate toxicity, or support circumstances considered important for regaining health. More than 13,000 different herbal preparations are used in TCM, which makes it extremely difficult to identify the component responsible for the liver injury. Active or toxic ingredients may vary when plants are harvested during different seasons or extracted through variable procedures. Also, contamination of herbals with microorganisms, pesticides, heavy metals, fungal toxins such as aflatoxin, and synthetic drugs has been described [160].

In the United States, large-scale consumption of Jin Bu Huan (*Lypocodium serratum*) for mild sedative effects has precipitated a total of 11 cases of both acute and chronic hepatitis [161,162]. Unlike many TCM herbal mixtures, Jin Bu Huan is an extract from *Lypocodium serratum* and (–)-tetrahydropalmitine is the active ingredient, with opiate-like properties. The precise mechanism by which liver injury is precipitated is currently unclear, but (–)-tetrahydropalmitine is structurally similar to pyrrolizidine alkaloids (see above). However, liver histology in patients who took Jin Bu Huan showed focal necrosis and portal fibrosis, but no vascular lesions. In all published cases, increased aminotransferase levels have normalized after treatment discontinuation.

A number of dietary products marketed in the United States contain ma huang (*Ephedra* spp.) to support weight reduction. Apart from cardiotoxicity, several published reports provide evidence for the risk of hepatotoxicity following the ingestion of ma huang [163–166]. Typically, acute hepatitis occurs after a short period of intake, sometimes with elevated autoantibodies, suggesting drug-induced autoimmunity. Alternatively, Bajaj et al. have suggested that ma huang hepatotoxicity may be associated with compound heterozygosity for mutation in the *HFE* gene (encoding the hereditary hemochromatosis protein), possibly via enhancing oxidative stress [164].

TABLE 35-2 Herbal Remedies Associated With Liver Damage

Herbal	Application	Toxin	Toxic Mechanism	Clinical Presentation
Pyrrolizidine alkaloids:	Herbal tea, contamination of flour/crop	Toxic pyrroles	Toxification of pyrrolizidine alkaloids by CYP3A4	Sinusoidal obstruction syndrome (venoocclusive disease)
Symphytum officinale				
Crotalaria				
Senecio longilobus				
Heliotropium				
Chinese herbal combinations:				
Paeonia spp.	Immunostimulation, Atopic dermatitis	Unknown	Unknown	Acute and chronic Hepatitis, hepatic failure
Dictamnus dasycarpus				
Jin Bu Huan	Sedative	*Lypocodium serratum*	Contains (−)-tetrahydropalmitine with structural similarities to PA	Acute and chronic cholestatic hepatitis, fibrosis
Ma huang	Weight reduction	*Ephedra sinica* (ephedrine)	Immunoallergic?	Acute hepatitis, autoimmune hepatitis
Shou Wu Pian	Liver tonic, dizziness, hair loss, constipation	*Polygonum multiflorum*	Anthraquinone conversion to hepatotoxin rhein	Acute hepatitis
Onshidou-Genbi-Kounou	Weight reduction	Unknown; contains *Amachazuru* tea leaf, barbaloin, saponins, polyphenols	Unknown	Acute hepatitis, liver failure
Chi R Yun	Venereal diseases, contusion, heart failure, growth retardation	*Breynia officinalis*	Unknown	–
Germander:				
Teucrium chamaedrys	Weight reduction	Neoclerodane diterpenoids	Hepatocyte apoptosis	Acute and chronic hepatitis (including liver failure), fibrosis (when chronic)
Teucrium polium	Antiinflammatory	Unknown	Unknown	–
Chaparral (Greasewood) *Larrea tridentata*	Antioxidant, liver and health tonic, snake bites	Nordihydroguaiaretic acid	Inhibition of COX-1/2 and several cytochrome P450s	Cholestasis, cholangitis, chronic hepatitis, cirrhosis
Atractylis gummifera	Antiemetic, diuretic, chewing gum	Atractylosides	Inhibition of gluconeogenesis through interference with oxidative phosphorylation	Acute hepatitis, liver failure
Callilepis laureola (Impila)	Miscellaneous, Zulu remedy (South Africa)	Atractylosides	Like *Atractylis gummifera*	Like *Atractylis gummifera*
Pennyroyal oil	Abortifacient, pesticide	Menthofuran	Glutathione depletion through electrophilic metabolites	Fulminant hepatic failure
Greater celandine	Irritable bowel syndrome	Unknown	Drug-induced autoimmunity?	Chronic hepatitis, fibrosis cholestatic hepatitis,

(*Continued*)

TABLE 35-2 (Continued)

Herbal	Application	Toxin	Toxic Mechanism	Clinical Presentation
Kava	Anxiolytic, sleeping aid	Kava lactones (kavain, dihydrokavain)?	Idiosyncratic, dose-dependent toxicity?	Acute and chronic hepatitis, cholestasis, liver failure
Black cohosh (*Cimicifuga racemosa*)	Menopausal complaints, joint and muscle pain	Unknown	Liver cell apoptosis via mitochondrial damage	Mild liver enzyme elevations, acute hepatitis, liver failure
Senna (*Cassia angustifolia*)	Laxative	Unknown	Unknown	Cytolytic hepatitis
Cascara sagrada	Laxative	Anthracene glycosides	Cholestatic hepatitis through unknown mechanism	Cholestatic hepatitis
Saw palmetto	Prostatism	*Serenoa repens* or *serrulata*	Unknown	Mild hepatitis
Centella asiatica	Multiple	Unknown	Saponins?	Granulomatous hepatitis, cirrhosis
Noni (*Morinda citrifolia*)	Health tonic	Unknown	Anthraquinones?	Acute cytolytic hepatitis, liver failure
Camphor	Rubefacient	Cyclic terpenes	Unknown	Necrolytic hepatitis
Isabgol	Laxative	Unknown	Unknown	Giant cell hepatitis
Margosa oil (*Azadirachta indica*)	Health tonic	Unknown	Mitochondrial damage	Reye syndrome
Oil of cloves	Dental pain	Eugenol	Dose-dependent hepatotoxin	Hepatic necrosis
Valerian (*Valeriana officinalis*)	Sedative	Unknown	Unknown	Mild hepatitis
Green tea (*Camellia sinensis*)	Standard beverage	(−)-Epigallocatechin gallate or its metabolite (−)-epicatechin gallate	Oxidative stress-related cytotoxicity	Acute hepatitis, cholestasis
Herbalife nutritional supplements (numerous products)	Weight loss, dietary supplement for balanced nutrition	Unknown	Idiosyncrasy?; contamination with bacteria?	Cytolytic and mixed hepatitis, fulminant hepatic failure
Usnic acid	Weight loss	Contains norephedrine hydrochloride, caffeine, diiodothyronine, yohimbine hydrochloride	Unknown; uncoupling of respiratory chain and mitochondrial damage?	Acute liver failure
Hydroxycut	Weight loss, bodybuilding	Contains *Garcinia cambogia* (*Garcinia gummi-gutta*), *Gymnema sylvestre*, chromium polynicotinate, caffeine, green tea	Unknown	Acute cytolytic hepatitis, liver failure

COX, prostaglandin G/H synthase.

Several cases of acute hepatitis and even fulminant hepatic failure have been reported in studies that have investigated the efficacy of Chinese herbal preparations for treating atopic dermatitis [167,168]. The investigators failed to identify the causative agent, but many herbal combinations used to treat eczema have contained *Paeonia* and/or *Dictamnus dasycarpus*. It is noteworthy that of the six cases reported with *D. dasycarpus*, two were fatal [169].

The Shou Wu Pian remedy formulated from the roots and vines of *Polygonum multiflorum* is used as a treatment for dizziness, hair loss, constipation, and, interestingly, as a *liver tonic*. It was first identified in 1996 to have caused acute hepatitis in a 31-year-old pregnant woman, the liver disease subsiding completely after discontinuation of the herb [170]. Following this, there have been additional reports of its potential to cause liver injury [171−175]. Toxicity could be the result of anthraquinones, which are known to be constituents of

P. multiflorum. Anthraquinones are metabolized by colonic bacteria to highly reactive anthrones that, when absorbed and transported to the liver, may cause liver damage [176].

Another herbal marketed for weight loss, Onshidou-Genbi-Kounou, combines several natural compounds (amachazuru, barbaloin, polyphenols, tealeaf, and total saponin), and was the suspected cause of severe acute hepatitis followed by hepatic failure in a woman who took this preparation for several months [177]. Serum levels of liver enzymes were massively elevated to >9,000 IU/L and coagulopathy developed; however, the patient recovered upon cessation of drug intake. Onshidou-Genbi-Kounou contains *N*-nitrosofenfluramine, which has only been associated with valvular heart disease. Possibly, Onshidou-Genbi-Kounou contains further unknown hepatotoxins.

Breynia officinalis is marketed under the Chinese proprietary name, Chi R Yun, and is used to treat conjunctivitis, contusions, growth retardation, heart failure, and venereal diseases, in combination with other TCMs. Following the report to the Poison Control Center of Taiwan of the first two cases of liver injury from this herbal, one involving a 43-year-old women who attempted to commit suicide and developed acute cytolytic hepatitis and the other a 51-year-old woman who used the product to treat her contact dermatitis [178], a case series was described of 19 poisonings that occurred when soup was cooked with *B. officinalis*, accidentally mistaken for a similar plant, *Securinega suffruticosa.* The affected persons developed diarrhea, nausea, vomiting, and hepatocellular liver injury without jaundice within 6 months of consuming the soup [179]. The exact mechanism of liver injury remains undetermined, but the close temporal relationship and a positive dechallenge response identifies *B. officinalis* as the likely cause of liver injury in these cases.

Germander

Germander (*Teucrium chamaedrys*)-containing capsules and tea bag preparations were approved as weight loss remedies in France, although its active ingredients and precise mechanism of action remain unknown. Subsequent widespread use led to several reports to the French Pharmacovigilance Authorities in 1992 about germander-associated acute, chronic, and even fulminant hepatitis [180]. Liver injury usually developed 2 months after intake and, in those with an acute pattern of liver enzyme alterations, acute cytolytic hepatitis was found histologically. Some patients with a chronic course of liver disease showed histological features of chronic hepatitis with fibrosis and even cirrhosis. Causality assessment linking germander and liver damage was confirmed after accidental reexposure led to an immediate relapse of liver injury. However, all patients recovered after discontinuation of the herbal, except for those with cirrhosis. Systematic analysis of germander preparations demonstrated that they contained flavonoids, glycosides, saponins, and several furane-containing neoclerodane diterpenoids [166]. Regarding the latter, animal experiments have demonstrated the formation of toxic and highly reactive epoxides from these diterpenoids, which are potent inducers of hepatocyte apoptosis [181–184]. Formation of epoxides is enhanced by the induction of CYP3A and by glutathione (GSH) depletion, which may occur during weight loss or regular alcohol consumption.

Subsequently, there have been reports of fulminant hepatic failure following the ingestion of *Teucrium polium* used as an antiinflammatory and antimicrobial drug and for the treatment of scars [185,186]. There is also a single report of acute hepatitis with jaundice that occurred in a patient who took a traditional Chinese remedy containing *Teucrium viscidum* for back pain and that resolved spontaneously after the remedy had been stopped [187].

Chaparral

Chaparral (*Larrea tridentata*; commonly referred to as *creosote bush* or *greasewood*) grows in deserts and is a traditional herbal remedy among Native Americans to treat the common cold, bone and muscle pain, and snake bites. Commercial products containing chaparral have been sold for weight reduction and for alleged antiinflammatory, antioxidant, and blood-purifying activities. Furthermore, chaparral has been part of the self-medication taken by patients with HIV infection [188]. In the 1990s, the FDA recorded a series of cases of chaparral-related hepatotoxicity ranging from mild elevations of serum liver enzyme concentrations to fulminant hepatitis, with subsequent liver transplantation for hepatic failure in two cases [189]. Although cholestatic hepatitis accounted for the majority of cases, there were also instances in which cirrhosis developed. *L. tridentata* was found in all preparations, and biochemical and microbial contamination was excluded. A causal relationship was postulated based on the temporal correlation between intake of chaparral and the onset of liver disease, a consistent pattern of hepatic damage, and the observation that reexposure to chaparral or an increased dose led to relapse or aggravation of clinical signs of liver disease. Chaparral toxicity is believed to be due to nordihydroguaiaretic acid, which inhibits prostaglandin G/H synthases (COX enzymes) and CYP [190].

Atractylis gummifera and *Callilepis laureola*

Atractylis gummifera has been traditionally used as a natural antipyretic, diuretic, and emetic in North Africa and the Mediterranean, and a secretion from the plant is occasionally consumed by children as chewing gum [191,192]. Toxic hepatitis with an acute onset is well known and commences a few hours after ingestion, accompanied by abdominal pain, headache, and nausea. It is associated with a syndrome of neurovegetative symptoms, hepatorenal failure, and pronounced hypoglycemia [193]. Death due to fulminant hepatic failure is a possibility. Consumption of *A. gummifera* is particularly dangerous during springtime, when toxins are highly concentrated in roots, or when the plant is confused with wild artichoke.

Callilepis laureola is the major constituent of *Impila*—a traditional herbal remedy used among the Zulu people from South Africa as a multipurpose treatment for stomach problems, impotence, infertility, and to deter *evil spirits*. Paradoxically, *Impila* is the Zulu word for *health*. However, numerous reports provide substantial evidence for potentially fatal nephro- and hepatotoxicity of *C. laureola*[194]. For example, a large series of children were identified retrospectively as having died from *C. laureola* intoxication, presenting with a clinical pattern similar to Reye syndrome with acute hepatorenal failure, hypoglycemia, and multiorgan hemorrhage [195]. Toxicity begins with a sudden onset and mortality is high. Autopsy examinations show centrilobular zonal necrosis of the liver, tubular renal necrosis, and hemorrhages in lungs, skin, and intestine. Despite its well-known toxicity, the underlying mechanism is only partly understood. Studies in rats indicate that atractyloside and carboxy-atractyloside are potent inhibitors of oxidative phosphorylation and other mitochondrial functions, leading to apoptosis [196]. Popat et al. have shown that *Impila* extracts cause a concentration- and time-dependent loss in viability and mitochondrial GSH content in HepG2 cells that is preventable with *N*-acetylcysteine and *S*-adenosyl-L-methionine, which are precursors of GSH [197].

Pennyroyal

Pennyroyal, also referred to as *squawmint oil*, is an herb containing leaves from either *Mentha pulegium* or *Hedeoma pulegioides* that has long been identified as a cause of severe acute liver injury [198]. Its traditional use is as a natural abortifacient and deterrent against fleas. Several reports of fulminant hepatic necrosis due to pennyroyal with lethal outcome have been described [199,200]. Its primary constituents are pulegone and various other monoterpenes characteristically contained in mint species, and particularly in pennyroyal. Hepatotoxicity appears to be due to depletion of GSH by pulegone, subsequently enhanced oxidative stress, and via the primary metabolite of pulegone, menthofuran, which is transformed through CYP into a hepatotoxin [200–203].

Greater Celandine

Drugs containing greater celandine (*Chelidonium majus*) are used in Europe to improve bile flow and irritable bowel syndrome. Greater celandine contains at least 20 different alkaloids, including berberine, chelerythrine, coptisine, and chelidonine, of which the latter serves to standardize the extract [204]. However, the therapeutic efficacy of greater celandine for these indications has never been tested in controlled trials. Several reports from European countries, where commercial drug preparations containing greater celandine alkaloids are widely available, have described potential hepatotoxicity of this herbal [204–207]. The largest series of 10 patients from a single German center revealed cholestatic hepatitis together with low titers of autoantibodies, suggesting drug-induced autoimmunity after variable periods of ingestion of different greater celandine preparations [208]. However, the exact mechanism responsible for injury remains unclear and efforts to replicate hepatotoxicity in experimental animals have thus far failed.

Kava

In industrialized countries, kava-containing preparations are marketed for the treatment of anxiety disorders and depression, while kava root (*Piper methysticum rhizoma*) has long been used as a traditional psychotropic remedy in Hawaii, Polynesia, and the Fiji Islands. Its sedative activity is caused by kavapyrones, including kavain, dihydrokavain, methysticin, and dihydromethysticin, which act as gamma-aminobutyric acid receptor agonists, thus inhibiting activating neurons in the reticular formation and the limbic system [209–210]. A recent systematic review and meta-analysis of randomized, controlled trials with kava for the treatment of anxiety showed a significant anxiolytic effect, as assessed by the Hamilton Rating Scale for Anxiety, as well as good tolerability [211]. More than 100 cases of liver damage have now been associated with the intake of kava worldwide, comparable to numbers that have led to the banning of synthetic drugs [212]. Consequently, the license to distribute kava products was revoked in the United States, Europe, and Australia [213]. A detailed analysis of 29 cases of adverse hepatic reactions due to kava in Germany using a clinical causality

score reported liver injury with both alcoholic and acetonic kava extracts [214]. The large majority of patients were females who developed cytolytic or cholestatic hepatitis, and nine patients who developed fulminant liver failure with subsequent liver transplantation in eight of the patients: three patients died, two following unsuccessful liver transplantation, and the remaining patients recovered completely after the withdrawal of kava. The mechanism by which liver injury is precipitated remains unclear, since no dose-response pattern can be recognized. However, some patients took doses exceeding several times the recommended daily dose of 120 mg. For most other patients, both the cumulative dose and the latency until the hepatotoxic reaction emerged were highly variable, suggesting drug idiosyncrasy. Along this line, a poor-metabolizer phenotype of CYP2D6 was suggested to be a risk factor for developing kava-related liver damage [215]. Another possible basis for its toxicity relates to the mode of kava extraction, with recent in vitro and animal studies confirming that aqueous kava extracts are less cytotoxic than are organic solvent fractions [216,217]. Notably, modern commercial products rely on alcohol or acetone extraction, a process that may extract toxic compounds (e.g., alkaloids) from the plant.

Black Cohosh (*Cimicifuga racemosa*)

Black cohosh, a popular herbal from North America for the treatment of menopausal symptoms, joint pain, and myalgia, has been implicated in a number of case reports on liver injury in Australia and North America [218–220]. Clinical presentation ranges from mild serum aminotransferase elevations to fulminant hepatic failure. In several cases, urgent liver transplantation was necessary. Some patients present with features resembling autoimmune hepatitis, such as elevated autoantibodies or skin rashes. In response to these reports, the Dietary Supplement Information Expert Committee of the US Pharmacopeia's Council of Experts analyzed information from human clinical case reports, adverse event reports, animal pharmacological and toxicological data, historical use, regulatory status, and contemporaneous extent of use associated with black cohosh [221]. All 30 individual reports of liver damage were assigned a causality score of *possible*, but none was labeled as *probable* or *certain*. Based on these results, the Dietary Supplement Information Expert Committee determined that black cohosh products should be labeled with a cautionary statement indicating that hepatotoxicity is a possible adverse outcome. Although meta-analysis of five randomized, controlled clinical trials, including >1,000 patients, revealed no evidence of liver toxicity [222], and reanalysis of individual case report information with liver-specific causality scores raised doubts over black cohosh as being truly hepatotoxic [223], a low incidence of black cohosh hepatotoxicity cannot be excluded by these data. How toxicity may occur is not fully elucidated, but experimental data indicate mitochondrial damage and subsequent apoptosis as a possible molecular mechanism [224].

Miscellaneous

Various other botanicals have been associated with toxic liver damage, such as senna (*Cassia angustifolia*), which is used as a laxative. Senna was identified as the cause of relatively benign hepatitis in a woman taking approximately 10 times the recommended dose [225]. Causality was confirmed by positive rechallenge.

Nadir et al. described a man in whom short-term use of a commercial *Cascara sagrada* product caused cholestatic hepatitis with subsequent portal hypertension, prolonged prothrombin time, and ascites [226]. *C. sagrada* contains anthraquinone glycosides and is recognized as an effective laxative. Other frequent etiologies were excluded, but the patient also took amitriptyline, baclofen, and cimetidine at recommended doses, which can occasionally cause liver injury. Further laboratory tests revealed elevated antinuclear and anti-smooth muscle antibody titers of 1:640 and 1:40, respectively, and liver biopsy showed an eosinophilic infiltrate, suggesting drug-induced autoimmunity.

Also, a combination of herbal ingredients, known as *Prostata*, was suspected to have caused cholestatic hepatitis in a man using this medication for the treatment of benign prostatic hyperplasia [227]. The presumed active ingredient is *Serenoa serrulata*, which exerts estrogenic and antiandrogenic effects. Either hormone may cause liver injury under certain circumstances.

Centella asiatica has been used in Ayurvedic medicine as a psychophysical regenerator and *blood purifier*, and for the treatment of dementia, diabetic microangiopathy, skin defects, and obesity [228]. Recently, three female patients who took this herbal for periods of between 1 and 6 months to lose weight developed severe hepatic injury, including granulomatous hepatitis and cirrhosis [229]. Unintentional reexposure resulted in accelerated recurrence of hepatic lesions in two of the patients. Extracts of this herb contain pentacyclic triterpenic saponosides, including asiaticoside, madecassoside, and centellasaponins. The mechanism by which liver damage is precipitated is uncertain. Treatment with ursodeoxycholic acid at 10 mg/kg/day led to normalization of altered liver biochemistries in

all three patients. Another Ayurvedic herbal preparation, termed Liv.52, is freely available through Internet sources and health food stores across North America and Europe, and is taken to strengthen the liver and to influence the natural course of chronic liver diseases. Liv.52 contains *Achillea millefolium* (yarrow), *Capparis spinosa* (capers), *Cichorium intybus* (wild chicory), *Solanum nigrum* (black nightshade), *Terminalia arjuna* (arjuna), and others. Liv.52 has been suggested as useful for the treatment of human alcohol-related liver cirrhosis after experimental data suggested that it may reduce acetaldehyde production [230]. A European randomized controlled clinical trial in 188 patients with alcoholic liver cirrhosis showed no benefit on survival and on surrogate markers of liver injury in cirrhotics with Child-Pugh class A and B, and the study was prematurely terminated because of increased liver-related mortality among those with Child-Pugh class C [231].

A recent case series of seven patients suggests possible liver toxicity from *Noni* juice (*Morinda citrifolia*), leading to liver failure requiring liver transplantation in one case [232,233]. Other possible causes for the acute hepatitis were ruled out and liver tests rapidly returned to normal after the cessation of Noni intake. Active components within Noni extracts include flavonoids, glycosides, polyunsaturated fatty acids, vitamins, and anthraquinones. The latter can be transformed into rhein by intestinal bacteria and cause mitochondrial damage [234]. However, experimental studies with Noni have failed to reproduce hepatotoxicity in vitro and in vivo [235].

DIETARY SUPPLEMENTS ASSOCIATED WITH LIVER INJURY

Green Tea (*Camellia sinensis*)

Green tea has been consumed for centuries and is currently among the most popular drinks in the world. The first report on liver injury following the ingestion of green tea extracts and preparations was published in 1999 [236] and, since then, there have been numerous cases reported to regulatory agencies worldwide. In response, the US Pharmacopeia performed a systematic review of all reported and published cases from North America, Great Britain, and Australia of liver injury following the ingestion of various different green tea preparations [237]. Thirty-four case reports were retrospectively evaluated, and seven reports pertaining to liver damage were labeled as *probably*, and the remaining seven cases as *possibly* linked to green tea. Subsequently, additional cases were made public and, to date, there have been 58 case reports recorded of hepatotoxicity associated with the consumption of green tea extracts, powdered leaves, green tea infusions, and hydroalcoholic and aqueous extracts [238]. Of particular concern is that these included one lethal case. On histological examination, the livers of patients revealed necroinflammatory changes and cholestasis. However, caution should be exercised about assigning unequivocal blame for the liver injury on green tea in some of the reported cases, since in many instances the patients also took other products that have been implicated in causing hepatotoxicity such as *C. angustifolia* (see above), *Ephedra sinica*, and Hydroxycut (for both, see below). The basis for the toxicity caused by green tea is uncertain but could be due to (−)-epigallocatechin gallate or its metabolite (−)-epicatechin gallate which, under certain conditions such as fasting, can induce liver damage via increasing oxidative stress [239]. In contrast, however, in vitro and in vivo experimental studies have also demonstrated hepatoprotective properties for green teas [240−242], and a recent systematic review of clinical studies aimed at defining the therapeutic effects of *C. sinensis* in humans found overall favorable effects from the tea as reflected by reduced mortality, attenuated steatosis, and a reduced incidence of primary liver cancer [243]. Current evidence suggests a causal relationship between intake of green tea-containing products and hepatotoxicity, and whether the risks from green tea consumption outweigh their benefits remains open to speculation. Consequently, in their systematic review, the US Pharmacopeia included a cautionary statement about green tea that reflects this uncertainty [237].

Herbalife

There are six published reports describing 34 cases from Argentina, Iceland, Israel, Spain, and Switzerland of severe liver injury following consumption of Herbalife nutritional and herbal supplements for weight control and improvement of nutrition [244−249]. The patterns of injury were mostly hepatocellular, but mixed and cholestatic enzyme patterns were also noted, with severity ranging from mild to severe hepatic damage, including evidence of cirrhosis and ALF requiring liver transplantation. Generally accepted liver disease assessment scoring systems were used in evaluating most of the cases, five of which scored as *certain* because of a positive rechallenge, while most of the remainder were judged as *probable*. The cause of liver damage remains speculative, since the patients took up to 17 different Herbalife products at the same time. In addition to the possibility that autoimmune mechanisms played a role in inducing the liver injury among those who had

elevated titers of autoantibodies and plasma cell infiltrates in their liver biopsies, adulteration of individual batches with bacterial pathogens may explain some other cases, in view of a report that two patients were found to have bacterial contamination of several Herbalife products with *Bacillus subtilis* and *Bacillus cereus* [248]. Herbalife runs numerous production sites worldwide, suggesting that spoiled products contaminated with certain germs, chemicals such as softeners, preservatives, and flavor enhancers, pesticides, or heavy metals either added intentionally during the manufacturing process or accidentally contained in the unrefined raw products, i.e., the herb extracts, could have been responsible for local series of cases of hepatotoxicity.

Usnic Acid

Usnic acid extracted from lichens and fungi have been marketed as dietary supplements in the United States to aid in weight loss. Efficacy for this indication was postulated based on its function as an uncoupler of the respiratory chain, which in principle can augment weight loss but also cause mitochondrial damage and subsequent hepatocyte death [250]. Several cases of ALF have been reported requiring liver transplantation following the intake of Lipokinetix, a product containing usnic acid and sold as dietary supplement capsules [165,251–254]. In reacting to these reports, the FDA issued a warning about Lipokinetix in 2001 [255]. Onset of liver injury was usually acute with a maximum latency of 3 months and the injury pattern was hepatocellular with massive elevations of alanine aminotransferase and aspartate aminotransferase. Apart from usnic acid, Lipokinetix contained caffeine, diiodothyronine, norephedrine hydrochloride, and yohimbine hydrochloride, which were confirmed by analyzing the used Lipokinetix lots. None of the ingredients was previously associated with liver damage and inadvertent contamination was excluded. These serious events caused the withdrawal of Lipokinetix from the market.

Hydroxycut

Owing to numerous reports of liver injury, including cases with acute hepatic failure and subsequent liver transplantation, several Hydroxycut products containing caffeine, chromium polynicotinate, *Garcinia cambogia* (*Garcinia gummi-gutta*), *Gymnema sylvestre*, and green tea were withdrawn by the manufacturer following a warning posted by the FDA in May 2009 [140–145,256]. Hydroxycut preparations were sold to support weight loss and muscle building by conventional retailers, through Internet sources, and via direct television marketing. The clinical presentation consisted of an acute onset after several weeks of intake, presenting with high levels of serum aminotransferases in the majority of cases, while others presented with a more insidious, usually cholestatic course.

NATURAL TOXINS

While not ingested intentionally or deliberately added to HDS, certain toxins derived from plants or natural products might contaminate supplements or food during preparation, processing, or storage that may occasionally cause liver injury if ingested accidentally.

Aflatoxins

Humans, particularly those in developing countries with humid climate conditions, such as sub-Saharan Africa and East Asia, may be highly exposed to aflatoxins through consumption of maize (corn), peanuts, rice, and other crops contaminated with *Aspergillus flavus* or *Aspergillus parasiticus*. Acute aflatoxicosis presents with abdominal pain, diarrhea, and vomiting, thus rendering aflatoxin poisoning indistinguishable from acute gastroenteritis. Aflatoxins in doses of 2–50 mg daily have been reported to cause acute toxic hepatitis characterized by jaundice, ascites, portal hypertension, and encephalopathy associated with a high mortality [257–259]. The liver biopsy findings in this situation include fatty infiltration and hepatic necrosis, sometimes accompanied by bile duct injury. In addition to causing acute hepatotoxicity, aflatoxins are potent carcinogens, well known to be associated with the development of primary HCC, but also with cancer of the kidneys and large bowel. Because the incidence of HCC is observed to be high in the same regions in which aflatoxin exposure is common, efforts began in the 1960s to determine whether there was a possible link between the HCC risk and aflatoxin exposure. Not only did epidemiological data confirm this association [260] but early experimental studies of *A. flavus*-contaminated groundnut extracts also demonstrated that aflatoxins are in fact capable of inducing acute liver disease in ducks and liver cancer in rodents [261,262]. Indeed, aflatoxin-related hepatocarcinogenicity occurs not only in humans but also in many other species including dogs, nonhuman primates, rodents, and even fish [263]. Chemically, there are four different naturally occurring aflatoxins: AFB1, AFB2, AFG1, and AFG2. AFB1 and AFG1 possess an unsaturated

bond at the 8,9 position on the terminal furan ring, and epoxidation at this position appears to be critical for their hepatocarcinogenic potency [264].

The metabolism of aflatoxin and the mechanisms of aflatoxin-induced hepatocarcinogenesis are well documented [265]. AFB1 requires metabolic activation to its ultimate carcinogenic form, primarily by the CYP monooxygenase system with the isoenzymes CYP1A2 and CYP3A4 that transform AFB1 to a reactive epoxide (aflatoxin-8,9-epoxide). The epoxide interacts with DNA to generate a promutagenic aflatoxin-*N7*-guanine adduct and, thus, a mutation in codon 249 of the p53 tumor suppressor gene that is considered crucial for the initiation of human hepatocarcinogenesis [266]. Although the epidemiologic pattern of HCC is changing, i.e., beginning to decline in areas of the world of high HBV endemicity with the advent of the hepatitis B vaccine and possibly increasing in areas plagued by the epidemic of obesity and diabetes, the primary causal risks worldwide continue to be both HBV and HCV infections, as well as exposure to aflatoxin [267]. Indeed, aflatoxin exposure is still considered a major cause of the differences in lifetime HCC risks between Western countries and South East Asia and Africa [267].

Ackee Fruit

Ackee fruit (*Blighia sapida*) poisoning has been occasionally reported in different developing countries, including Africa, Latin America, and the West Indies [268–270].

Ackee fruits derive from large green leafy trees of West African origin and are consumed either raw or after boiling in milk or water and served on their own or in meat or fish dishes, such as ackee and salt fish. Ackee fruit is a substantial part of the diet in poor, agricultural areas and its taste resembles that of hazelnut or avocado. Toxicity is related to hypoglycin A and hypoglycin B, the former molecule being more toxic than the latter. The ripe fruit flesh of ackee contains only low quantities of hypoglycins, but concentrations in unripe fruits are 10–100 times greater, depending on the season and exposure to sunlight, which significantly reduces hypoglycin concentrations. In view of several larger series of intoxications in Jamaica in the past, the disease related to ackee fruit poisoning is also termed *Jamaica vomiting sickness*, with a clinical pattern similar to Reye syndrome that includes gastrointestinal symptoms, marked hypoglycemia, and central nervous system abnormalities that typically develop within 6–48 h of ingestion [271]. Lethality is high, particularly in infants and children. Toxicity is believed to be related to methylenecyclopropylacetic acid, a toxic hypoglycin metabolite that interferes with several cofactors [e.g., coenzyme A (CoA) and carnitine] essential to the β-oxidation of long-chain fatty acids and thus inhibits the transport of long-chain fatty acids into the mitochondria. The reduction in fatty acid metabolism causes an increased use of glucose, and the blockade of the substrate for hepatic gluconeogenesis causes hypoglycemia after the depletion of NADH and hepatic glycogen stores [271]. Findings at postmortem examination of fatal ackee fruit intoxications have included massive steatosis of the liver and kidney, depletion of liver glycogen, diffuse hemorrhages, and generalized hyperemia of the internal organs. Diagnosis is based on the patient's history of the use of the product and the clinical presentation, since there are no specific biomarkers. There is no definitive therapy for this poisoning other than the use of symptomatic measures such as fluid and glucose replacement. In the light of these risks, ackee fruit is banned in the United States and other Western countries.

Bacillus cereus

There are several case reports of fulminant liver failure attributed to *Bacillus cereus* food poisoning [272–274]. *B. cereus* is a ubiquitous, endospore-forming, aerobic, gram-positive bacterium known for precipitating a type of toxin-mediated food poisoning in the Far East, typically after the ingestion of cooked rice. Although instances of fulminant hepatic failure are extremely rare, those reported have been well characterized, describing acute-onset hepatic failure complicated by lactic acidosis, rhabdomyolysis, cerebral edema, and death in some cases, despite maximal medical care. Certain strains of this bacterium secrete a cyclic peptide toxin, cereulide, which causes vomiting in humans and animals but may also act as a mitochondrial toxin that interferes with fatty acid metabolism, leading to the breakdown of mitochondria derived energy supply [274,275]. Thus, the pathophysiology of *B. cereus*-related liver failure is similar to that observed with ackee fruit, aflatoxin (see above), Reye syndrome, and fatty liver of pregnancy [276]. Diagnosis is based on the coexistence of fulminant hepatic failure, hypoglycemia, lactic acidosis, hyperammonemia, and central nervous system symptoms and should prompt immediate referral to a liver transplant center, since liver transplantation may be the only therapeutic option for some patients.

Microcystins

Water contaminated with cyanobacterial hepatotoxic heptapeptides, i.e., microcystins, has been recognized as a possible cause of an outbreak of ALF at a dialysis

center in Caruaru, Brazil [277]. At the clinic, 116 out of 131 patients (89%) experienced visual disturbances, nausea, and vomiting after routine hemodialysis treatment. Subsequently, 100 patients developed ALF and, of these, 76 died. The observed syndrome was thus termed the Caruaru syndrome. Examination of phytoplankton from the dialysis clinic's water source and in-depth analyses of the clinic's water treatment system, together with studies on serum and liver tissue of clinic patients, led to the identification of two groups of cyanobacterial toxins: the hepatotoxic cyclic peptide microcystins and the hepatotoxic alkaloid cylindrospermopsin. Authors of this and subsequent analyses concluded that the likely cause of liver injury were microcystins, specifically microcystin-YR, -LR, and -AR [278]. Cyanotoxins—to which class microcystins belong—are also implicated in animal poisoning, human gastroenteritis, dermal contact irritations, and primary liver cancer in humans [279,280]. The (geno) toxic mechanism of microcystins is to act as potent inhibitors of protein phosphatase 1 and 2A, thus leading to increased protein phosphorylation causing cytotoxicity and tumor promotion [281].

CONCLUSIONS

HDS use is extensive, rivaling and often exceeding that of conventional medications. There is general belief that because they have been used for centuries and are pure, they must be effective and safe. Unfortunately, neither of these generalizations is accurate. Efficacy for most herbal products has not been scientifically proven and they are certainly no safer than conventional medications; some of them are less safe. Safety would be enhanced if there were greater oversight of their production and distribution to ensure that they do not contain potentially toxic or otherwise dangerous contents. Asking about their use is an essential component of causality assessment when liver dysfunction is identified with the suspicion that the cause might be DILI.

DISCLAIMER

The views expressed herein are those of the author and not the US Food and Drug Administration.

References

[1] Winslow LC, Kroll DJ. Herbs as medicine. Arch Intern Med 1998;158:2192–9.

[2] Ernst E, Hung SK. Great expectations: what do patients using complementary and alternative medicine hope for? Patient 2011;4:89–101.

[3] Eisenberg DM, Kessler RC, Foster C, et al. Unconventional medicine in the United States: prevalence, costs, and patterns of use. NEJM 1993;328:246–52.

[4] Kessler RC, Davis RB, Foster DF, et al. Long-term trends in the use of complementary and alternative medical therapies in the United States. Ann Intern Med 2001;135:262–8.

[5] Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national study. JAMA 1998;280:1569–75.

[6] Block G, Cox D, Madans J, et al. Vitamin supplement use, by demographic characteristics. Am J Epidemiol 1988;127:297–309.

[7] Koplan JP, Annest JL, Layde PM, et al. Nutrient intake and supplementation in the United States (NHANES II). Am J Public Health 1986;76:287–9.

[8] Ervin RB, Wright JD, Kennedy-Stephenson J. Use of dietary supplements in the United States, 1988–1994. Vital Health Stat 11 1999;(244):1–14.

[9] Radimer K, Bindewald B, Hughes J, et al. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999–2000. Am J Epidemiol 2004;160:339–49.

[10] Ni H, Simile C, Hardy AM. Utilization of complementary and alternative medicine by United States adults: results from the 1999 National Health Interview Survey. Med Care 2002;40:353–8.

[11] Kennedy J. Herb and supplement use in the US adult population. Clin Ther 2005;27:1847–58.

[12] Timbo BB, Ross MP, McCarthy PV, et al. Dietary supplements in a national survey: prevalence of use and reports of adverse events. J Am Diet Assoc 2006;106:1966–74.

[13] Molassiotis A, Fernandez-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a European survey. Ann Oncology 2005;16:655–63.

[14] Colebunders R, Dreezen C, Florence E, et al. The use of complementary and alternative medicine by persons with HIV infection in Europe. Int J STD AIDS 2003;14:672–4.

[15] Bucker B, Groenewold M, Schoefer Y, et al. The use of complementary alternative medicine (CAM) in 1001 German adults: results of a population-based telephone survey. Gesundheitswesen 2008;70:e29–36.

[16] Menniti-Ippolito F, Gargiulo L, Bologna E, et al. Use of unconventional medicine in Italy: a nation-wide survey. Eur J Clin Pharmacol 2008;58:61–4.

[17] Landstrom E, Kolvist Hursti U-K, Becker W, et al. Use of functional foods among Swedish consumers is related to health-consciousness and perceived effect. Brit J Nutr 2007;98u:1058–69.

[18] Garcia-Cortez M, Borraz Y, Lucena MI, et al. Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish liver toxicity registry. Rev Esp Enferm Di 2000;100:688–95.

[19] Afifi FU, Wazaify M, Jabr M, et al. The use of herbal preparations as complementary and alternative medicine (CAM) in a sample of patients with cancer in Jordan. Complement Ther Clin Pract 2010;16:208–12.

[20] AlBarai FA, Rutter PM, Brown D. A cross-sectional survey of herbal remedy taking by United Arab Emirate (UEA) citizens in Abu Dhabi. Pharmacoepidemiol Drg Saf 2008;17:725–32.

[21] Malak AT, Karayurt O, Demir E, et al. Complementary and alternative medicine in cancer patients—analysis of influencing factor in Turkey. Asian Pac J Cancer Prev 2009;10:1083–7.

[22] Ben-Arye E, Karkabi S, Shapira C, et al. Complementary medicine in the primary care setting: results of a survey of gender and cultural patterns in Israel. Gend Med 2009;6:384–97.

[23] Watanabe K, Matsuura K, Gao P, et al. Traditional Japanese kampo medicine: clinical research between modernity and

traditional medicine—the state of research and methodologic suggestions for the future. Evid Based Complement Altern Med 2011;2011:513842.
[24] Chen FP, Kung YY, Chen YC, et al. Frequency and pattern of Chinese herbal medicine prescriptions for chronic hepatitis in Taiwan. J Ethnopharmacol 2008;117:84–91.
[25] Siti ZM, Tahir A, Ida Farah A, et al. Use of traditional and complementary medicine in Malaysia: a baseline study. Complement Therap Med 2009;(17):292–9.
[26] Saokaew S, Uwankesawong W, Permsuwan U. Safety of herbal products in Thailand: an analysis of reports in the Thai Health Product Vigilance Center database from 2000 to 2008. Drug Saf 2011;34:339–50.
[27] Lamorde M, Tabuti JRS, Obua C, et al. Medicinal plants used by traditional medicine practitioners for the treatment of HIV/AIDS and related conditions in Uganda. J Ethnopharmacol 2010;130:43–53.
[28] Rybicki EP, Chikwamba R, Koch M, et al. Plant-made therapeutics: an emerging platform in South Africa. Biotechnol Adv 2012;30(2):449–59.
[29] Kuete V, Efferth T. Pharmacogenomics of Cameroonian traditional herbal medicine for cancer therapy. J Ethnopharmacol 2011;137:752–66.
[30] Wambugu SN, Mathiu PM, Gakuya DW, et al. Medicinal plants used in the management of chronic joint pains in Machakos and Makueni counties, Kenya. J Ethnopharmacol 2011;137:945–55.
[31] Shorofi SA, Arbon P. Complementary and alternative medicine (CAM) among hospitalized patients: an Australian study. Complement Ther Clin Pract 2010;116:86–91.
[32] WHO. Traditional medicine. Fact sheet no. 134, December 2008.
[33] Metcalfe A, Williams J, McChesney J, et al. Use of complementary and alternative medicine by those with a chronic disease and the general population—results of a national population based survey. BMC Complement Altern Med 2010;10:58.
[34] Sparber A, Wootton JC, Bauer L, et al. Use of complementary medicine by adult patients participating in HIV/AIDS clinical trial. J Altern Complement Med 2000;6:415–22.
[35] Marcus DM. Therapy: herbals and supplements for rheumatic diseases. Nat Rev Rheumatol 2009;8(5):299–300.
[36] Naing A, Stephen SK, Frenkel M, et al. Prevalence of complementary use in a phase 1 clinical trials program: the MD Anderson Cancer Center experience. Cancer 2011;117(22):5142–50.
[37] Konvicka JJ, Meyer TA, McDavid AJ, et al. Complementary/alternative medicine use among chronic pain clinic patients. J Perianesth Nurs 2008;23:17–23.
[38] Bin YS, Kiat H. Prevalence of dietary supplement use in patients with proven or suspected cardiovascular disease. Evid Based Complement Alternat Med 2011. doi: 10.1155/2011/632829.
[39] Garrow D, Egede LE. National patterns and correlates of complementary and alternative medicine use in adults with diabetes. J Altern Med 2006;12:895–902.
[40] Seeff LB, Lindsay KL, Bacon BR, et al. Complementary and alternative medicine in chronic liver disease. Hepatology 2001;34:595–603.
[41] Strader DB, Bacon BR, Lindsay KL, et al. Use of complementary and alternative medicine in patients with liver disease. Am G Gastroenterol 2002;97:2391–7.
[42] Seeff LB, Curto TM, Szabo G, et al. Herbal product use by persons enrolled in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial. Hepatology 2008;47:605–12.
[43] Stickel F, Schuppan D. Herbal medicine in the treatment of liver diseases. Dig Liver Dis 2007;39:293–304.
[44] 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;12:285–95.
[45] Richmond JA, Bailey DE, Patel K, et al. The use of complementary and alternative medicine by patients with chronic hepatitis C. Complement Ther Clin Pract 2010;16:124–31.
[46] Ferrucci LM, Bell BP, Dhotre KB, et al. Complementary and alternative medicine use in chronic liver disease patients. J Clin Gastroenterol 2010;44:e41–5.
[47] Nahin RL, Barnes PM, Stussman BJ, et al. [National health statistics reports; no 18] Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. Hyattsville, MD: National Center for Health Statistics; 2009.
[48] Cavaliere C, Rea P, Lynch ME, Blumenthal M. Herbal supplement sales rise in all channels in 2009. HerbalGram 2010;86:62–5.
[49] Saper RB, Phillips RS, Sehgal A, et al. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold over the Internet. JAMA 2008;300:915–23.
[50] Kneifel W, Czech E, Kopp B. Microbial contamination of medicinal plants. Planta Med 2000;68:5–15.
[51] Stickel F, Droz S, Patsenker E, et al. Severe hepatotoxicity following ingestion of Herbalife contaminated with *Bacillus subtilis*. J Hepatol 2009;50:111–7.
[52] Gray SL, Lackey BR, Tate PL, et al. Mycotoxins in root extracts of American and Asian ginseng bind estrogen receptors alpha and beta. Exp Biol Med 2004;229:560–8.
[53] Wong MK, Tan P, Wee YC. Heavy metals in some Chinese herbal plants. Biol Trace Elem 1993;36:135–42.
[54] Koh HL, Woo SO. Chinese propriety medicine in Singapore: regulatory control of toxic heavy metals and undeclared drugs. Drug Saf 2000;23:351–62.
[55] Au AM, Ko R, Boo FO, et al. Screening methods for drugs and heavy metals in Chinese patent medicines. Bull Environ Contam Toxicol 2000;65:112–9.
[56] Ernst E. Heavy metals in traditional Indian remedies. Eur J Clin Pharmacol 2002;57:891–6.
[57] Chan K. Some aspects of toxic contaminants in herbal medicines. Chemosphere 2003;52:1361–71.
[58] Centers for Disease Control and Prevention. Lead poisoning associated with use of Ayurvedic medication—five states. 2000–2003. MMWR Morb Mortal Wkly Rep 2004;53:582–4.
[59] Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J Intern Med 2002;252:107–13.
[60] Miller GM, Streipp R. A study of western pharmaceuticals contained within samples of Chinese herbal/patent medicines collected from New York City's Chinatown. Legal Med 2007;9:258–64.
[61] Shaw D, Leon C, Kolev S, et al. Traditional remedies and food supplements. A 5-year toxicological study (1991–1995). Drug Saf 1997;17:342–56.
[62] Guns ES, Goldenberg SL, Brown PN. Mass spectral analysis of PC-SPES confirms the presence of diethylstilbestrol. Can J Urol 2002;9:1684.
[63] Oh WK, Small EJ. Complementary and alternative therapies in prostate cancer. Semin Oncol 2002;29:575.
[64] Sovak M, Seligson AL, Konas M, et al. Herbal composition of PC-SPES for management of prostate cancer: identification of active principles. J Natl Cancer Inst 2002;94:1275.
[65] Fleshler N, Harvey M, Adomat H, et al. Evidence for contamination of herbal erectile dysfunction products with phosphodiesterase type 5 inhibitors. J Urol 2005;174:636–41.

[66] Buettner C, Mukamal KJ, Gardiner P, et al. Herbal supplement use and blood lead levels of United States adults. J Gen Intern Med 2009;24:1175–82.
[67] Blendon RJ, DesRoches CM, Benson JM, et al. Americans' views on the use and regulation of dietary supplements. Arch Intern Med 2001;161:805–10.
[68] Denham BE. Dietary supplements–regulatory issues and implications for public health. JAMA 2011;306:428–9.
[69] <http://ec.europa.eu/health/human-use/herbal-medicines/undex_ en.htm> [accessed 25.11.2011].
[70] <http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/HerbalMedicinesAdvisoryCommittee/index.htm> [accessed 25.11.2011].
[71] <http:/mhra.gov.uk/groups/pl-p/documents/websitesources/con2030651.pdf> [accessed 25.11.2011].
[72] <http://apps.who.int/medicinedocs/en> [accessed 25.11.2011].
[73] Kaptchuck TJ, Eisenberg DM. Varieties of healing. 2:a taxonomy of unconventional healing practices. Ann Intern Med 2001;135:196–204.
[74] Modi AA, Wright EC, Seeff LB. Complementary and alternative medicine (CAM) for the treatment of chronic hepatitis B and C: a review. Antiviral Therap 2007;12:285–95.
[75] Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA 1996;276:637–9.
[76] Gagnier JJ, Boon H, Rochon P, et al. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. Ann Intern Med 2006;144:364–7.
[77] Gagnier JJ, Boon H, Rochon P, et al. Recommendations for reporting randomized controlled trials of herbal interventions: explanation and elaboration. J Clin Epidemiol 2006;59:1134–49.
[78] Floersheim GL. Treatment of human amatoxin poisoning: myths and advances in therapy. Med Toxicol Advers Drug Exp 1987;2:1–9.
[79] Mulrow C, Lawrence V, Jacobs B, et al. Milk thistle: effects on liver disease and cirrhosis and clinical adverse effects. AHRQ evidence reports and summaries 2000;21:1–3.
[80] Dehmlow C, Erhard J, de Groot H. Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin. Hepatology 1996;23:749–54.
[81] Boigk G, Stroedter L, Herrbst H, et al. Silymarin retards collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct obliteration in rats. Hepatology 1997;26:643–9.
[82] Ferenci P, Dragosics B, Dittrich H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. J Hepatol 1989;9:105–13.
[83] Pares A, Planas R, Torres M, et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. J Hepatol 1998;28:615–21.
[84] Rambaldi A, Jacobs BP, Iaquinto G, et al. Milk thistle for alcoholic and/or hepatitis B or C liver disease—a systematic Cochrane hepato-biliary group review with meta-analyses of randomized clinical trial. Am J Gastroenterol 2005;100:2583–91.
[85] Polyak SJ, Morishima C, Shuhart MC, et al. Inhibition of T-cell inflammatory cytokines, hepatocyte NF-κB signaling, and HCV infection by standardized silymarin. Gastroenterology 2007;132:1925–36.
[86] Ferenci P, Scherzer T-M, Kerschner H, et al. Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy. Gastroenterology 2008;135:1561–7.
[87] Payer BA, Reiberger T, Ritter K, et al. Successful eradication and inhibition of HIV replication by intravenous silibinin in an HIV-HCV coinfected patient. J Clin Virol 2010;49:131–3.
[88] Neumann UP, Biermer M, Eurich D, et al. Successful prevention of hepatitis C virus (HCV) liver graft reiinfection by silibinin mono-therapy. J Hepatol 2010;52:951.
[89] Wagoner J, Negash A, Kane OJ, et al. Multiple effects of silymarin on the hepatitis C virus lifecycle. Hepatology 2010;51:1912–21.
[90] Ahmed-Belkacem A, Ahnou N, Barbotte L, et al. Silibinin and related compounds are direct inhibitors of hepatitis C virus RNA-dependent RNA polymerase. Gastroenterology 2010;138:1112–22.
[91] Polyak SJ, Morishima C, Lohman V, et al. Identification of hepatoprotective flavonolignans from silymarin. PNAS 2010;107:5995–9.
[92] Patel N, Joseph C, Corcoran GB, et al. Silymarin modulated doxorubicin-induced oxidative stress, Bcl-xL and p53 expression while preventing apoptotic and necrotic cell death in the liver. Toxico Appl Pharmacol 2010;245:143–52.
[93] Hawke RL, Schrieber SJ, Soule TA, et al. Silymarin ascending multiple oral dosing phase I study in noncirrhotic patients with chronic hepatitis C. J Clin Pharmacol 2010;50:434–49.
[94] Fried MW, Navarro VJ, Afdahl NH, Wahed AS, Hawke RL, Belle SH, et al. A randomized placebo-controlled trial of oral silymarin (milk thistle) for chronic hepatitis C: final results of the SyNCH multicenter study. Hepatology 2011;54(Suppl. 4):119A.
[95] Loguercio C, Festi D. Silybin and the liver: from basic research to clinical practice. World J Gastroenterol 2011;17:2288–301.
[96] Kumada H. Long-term treatment of chronic hepatitis C with glycyrrhizin [stronger neominophagen C (SNMC)] for preventing liver cirrhosis and hepatocellular carcinoma. Oncology 2002;62(Suppl. 1):94–100.
[97] Hidaka I, Hino K, Korenaga M, et al. Stronger Neominophagen C, a glycyrrhizin-containing preparation, protects liver against carbon tetrachloride-induced oxidative stress in transgenic mice expressing the hepatitis C virus polyprotein. Liver Int 2007;27:845–53.
[98] Yoshikawa M, Matsui Y, Kawamoto H, et al. Effects of glycyrrhizin on immune mediated cytotoxicity. J Gastroenterol Hepatol 1997;12:243–8.
[99] Shiki Y, Shirai K, Saito Y, et al. Effect of glycyrrhizin on lysis of hepatocyte membranes induced by anti-liver cell membrane antibody. J Gastroenterol Hepatol 1992;7:12–6.
[100] Borchers AT, Sakai S, Hendeson GL, et al. Shosaiko-to and other Kampo (Japanese herbal) medicines: a review of their immunomodulatory activities. J Ethnopharmacol 2000;73:1–13.
[101] Yamashiki M, Nishimura A, Huang XX, et al. Effects of the Japanese herbal medicine "Sho-saiko-to" (TJ-9) on interleukin-12 production in patients with HCV-positive liver cirrhosis. Dev Immunol 1999;7:17–22.
[102] Cyong JC, Ki SM, Iijima K, et al. Clinical and pharmacological studies on liver diseases treated with Jampo herbal medicine. Am J Chin Med 2000;28:351–60.
[103] Chen MH, Chen JC, Tsai CC, et al. Sho-saiko-to prevents liver fibrosis induced by bile duct ligation in rats. Am J Chin Med 2004;32:195–207.
[104] Sakaida I, Hironaka K, Kimura T, et al. Herbal medicine Sho-saiko-to (TJ-9) increases expression matrix metalloproteinases (MMPs) with reduced expression of tissue inhibitor of metaloproteinases (TIMPs) in rat stellate cells. Life Sci 2004;74:2251–63.
[105] Shimizu I, Ma YR, Mizobuchi Y, et al. Effects of Sho-saiko-to, a Japanese herbal medicine, on hepatic fibrosis in rats. Hepatology 1999;29:149–60.

[106] Sakaida I, Matsumuru Y, Akiyama S, et al. Herbal medicine Sho-saiko-to (TJ-9) prevents liver fibrosis and enzyme altered lesions in rat liver cirrhosis induced by choline-deficient L-amino acid-defined diet. J Hepatol 1998;28:298–306.
[107] Hirayama C, Okomura M, Tanikawa K, et al. A multicenter randomized controlled clinical trial of Shosaiko-to in chronic active hepatitis. Gastroenterol Jpn 1989;24:713–9.
[108] Tajiri H, Kozaiwa K, Ozaki Y, et al. Effect of sho-saiko-to (xiao-chai-hu-tang) on HBeAg clearance in children with chronic hepatitis B virus infection and with sustained liver disease. Am J Chin Med 1991;19:121–9.
[109] Oka H, Yamamoto S, Kuroki T, et al. Prospective study of chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). Cancer 1995;76:743–9. Cohen MR. Herbal and complementary and alternative medicine therapies for liver disease. A focus on Chinese traditional medicine in hepatitis C virus. Clin Liver Dis 2001;5:461–78.
[110] Kiguchi T, Kimura F, Katayama Y, et al. Acute thrombocytopenic purpura after ingestion of Sho-saiko-yo for hepatitis. Liver 2000;20:491.
[111] Kamiyama T, Nouchi T, Kojima S, et al. Autoimmune hepatitis triggered by administration of an herbal medicine. Am J Gastroenterol 1997;92:703–4.
[112] Hsu IM, Huang YS, Tsay SH, et al. Acute hepatitis induced by Chinese hepatoprotective herb, xiao-chai-hu-tang. J Chin Med Assoc 2006;69:86–8.
[113] Chen TS, Chen PS. Liver in traditional Chinese medicine. J Gastroenterol Hepatol 1998;13:437–42.
[114] Jia JD, Wang BE, Dong Z, et al. The effect of herbal compound 861 on mRNA levels for type I, III, and IV collagens and TGF in immune complex of rat liver fibrosis. Chin J Hepatol 1996;4:142–4.
[115] Wang TL, Wang BE, Zhang HH, et al. Pathological study of the therapeutic effect on HBV-related liver fibrosis with herbal compound 861. Chin J Gastroenterol Hepatol 1998;7:148–53.
[116] Batey RG, Bensoussan A, Fan YY, et al. Preliminary report of a randomized, double-blind placebo-controlled trial of a Chinese herbal medicine preparation CH-100 in the treatment of chronic hepatitis C. J Gastroenterol Hepatol 1998;13:244–7.
[117] Mollison L, Totten L, Flexman J, et al. Randomized double-blind placebo-controlled trial of a Chinese herbal therapy (CH-100) in chronic hepatitis C. J Gastroenterol Hepatol 2006;21:1184–8.
[118] Wu P, Dugoua JJ, Eyawo O, et al. Traditional Chinese medicines in the treatment of hepatocellular cancers: a systematic review and meta-analysis. J Exp Clin Cancer Res 2009;28:112–25.
[119] Liu J, Lin H, McIntosh H. Genus *Phyllanthus* for chronic hepatitis B virus infection: a systematic review. J Viral Hepat 2001;8:358–66.
[120] Ott M, Thyagarajan SP, Gupta S. *Phyllanthus amarus* suppresses hepatitis B virus by interrupting interactions between HBV enhancer I and cellular transcription factors. Eur J Clin Invest 1997;27:908–15.
[121] Venkateswaran PS, Millman I, Blumberg BS. Effects of an extract from *Phyllanthus niruri* on hepatitis B and woodchuck hepatitis viruses: in vitro and in vivo studies. Proc Natl Acad Sci USA 1987;84:274–8.
[122] Lee CD, Ott M, Thyagarajan SP, et al. *Phyllanthus amarus* down-regulates hepatitis B virus mRNA transcription and replication. Eur J Clin Invest 1996;26:1069–76.
[123] Thygarajan SP, Subramanian S, Thirunalasundari T, et al. Effect of *Phyllanthus amarus* on chronic carriers of hepatitis B virus. Lancet 1988;2:764–6.
[124] Thamlikitkul V, Wasuwat S, Kanchanapee P. Efficacy of *Phyllanthus amarus* for eradication of hepatitis B virus in chronic carriers. J Med Assoc Thai 1991;74:381–5.
[125] Leelarasamee A, Trakulsomboon S, Maunwongyathi P, et al. Failure of *Phyllanthus amarus* to eradicate hepatitis B surface antigen from symptomless carriers. Lancet 1990;335:1600–1.
[126] Milne A, Hopkirk N, Lucas CR, et al. Failure of New Zealand hepatitis B carriers to respond to *Phyllanthus amarus*. NZ Med J 1994;107:243.
[127] Coon JT, Ernst E. Complementary and alternative therapies in the treatment of chronic hepatitis C: a systematic review. J Hepatol 2004;40:491–500.
[128] Girish C, Pradhan ASC. Drug development for liver diseases: focus on picrolov, ellagic acid and curcumin. Fundam Clin Pharmacol 2008;22:623–32.
[129] Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993;46:1323–30.
[130] Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol 1993;46:1331–6.
[131] Maria VAJ, Victorino RMM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology 1997;26:664–9.
[132] Aithal GP, Rawlins MD, Day CP. Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. J Hepatol 2000;33:949–52.
[133] Lucena MI, Camargo R, Andrade RJ, Perez-Sanchez CJ, de la Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity. Hepatology 2001; 33:123–30.
[134] Rochon J, Protiva P, Seeff LB, et al. Drug-induced Liver Injury Network (DILIN): reliability of the Roussel Uclaf causality assessment method for assessing causality in drug-induced liver injury. Hepatology 2008;48:1175–82.
[135] Zimmerman HJ. Hormonal derivatives and related drugs. In: Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott; 1999 p. 556–588.
[136] Schaffner F, Popper H, Chesrow E. Cholestasis produced by the administration of norethandrelone. Am J Med 1959;26:249–54.
[137] Ishak KG, Zimmerman HJ. Hepatotoxic effects of anabolic/androgenic steroids. Semin Liver Dis 1967;7:230–6.
[138] Teschke R, Schwarzenboek A, Hennermann KH. Causality assessment in hepatotoxicity by drugs and dietary supplements. Br J Clin Pharmacol 2008;66:755–66.
[139] Steven T, Qadri A, Zein NN. Two patients with acute liver injury associated with the use of the herbal weight-loss supplement Hydroxycut. Ann Intern Med 2005;142:477–8.
[140] Jones FP, Andrews AH. Acute liver injury associated with the herbal supplement Hydroxycut in a soldier deployed to Iraq. Am J Gastroenterol 2007;102:2357.
[141] Dara L, Hewett J, Lim JK. Hydroxycut hepatotoxicity: a case series and review of liver toxicity from herbal weight loss supplements. World J Gastroenterol 2008;14:6999–7004.
[142] Shim M, Saab S. Severe hepatotoxicity due to Hydroxycut: a case report. Dig Dis Sci 2009;54:406–8.
[143] Fong T, Klontz KC, Canas-Coto A, Casper SJ, Durazo FA, Davern TJ, et al. Hepatotoxicity due to Hydroxycut: a case series. Am J Gastroenterol 2010;105:1561–6.
[144] <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149575.htm> [accessed 21.11.2011].

[145] Prakash AS, Pereira TN, Reilly PE, Seawright AA. Pyrrolizidine alkaloids in human diet. Mutat Res 1999;443:53–67.
[146] Wilmot FC, Robertson GW. Senecio disease or cirrhosis of the liver due to senecio poisoning. Lancet 1920;II:828–9.
[147] Bras G, Jeliffe DB, Stuart KL. Veno-occlusive disease of the liver with non-portal type of cirrhosis occurring in Jamaica. Arch Pathol 1954;57:285.
[148] Tandon BN, Tandon RK, Tandon HD, Narndranathan M, Joshi YK. An epidemic of veno-occlusive disease of liver in Central India. Lancet 1976;2:271–2.
[149] Datta DV, Khuroo MS, Mattocks AR, Aikat BK, Chhuttani PN. Herbal medicine and veno-occlusive disease in India. Postgrad Med J 1978;54:511–5.
[150] Kakar F, Akbarian Z, Leslie T, Mustafa ML, Watson J, Van Egmond HP, et al. An outbreak of hepatic veno-occlusive disease in Western Afghanistan associate with exposure to wheat flour contaminated with pyrrolizidine alkaloids. J Toxicol 2010:313280 [Epub 2010 June 28].
[151] Stillman AE, Huxtable RJ, Consroe P, Kohnen P, Smith S. Hepatic veno-occlusive disease due to pyrrolizidine (*Senecio*) poisoning in Arizona. Gastroenterology 1977;73:349–52.
[152] Fox DW, Hart MC, Bergeson PS, Jarrett PB, Stillman AE, Huxtable RJ. Pyrrolizidine (*Senecio*) intoxication mimicking Reye's syndrome. J Pediatr 1978;93:980–2.
[153] Weston CFM, Cooper BT, Davies JD, Levine DF. Veno-occlusive disease of the liver secondary to ingestion of comfrey. Brit Med J 1987;295:183.
[154] Roulet M, Laurini R, Rivier L, Calame A. Hepatic veno-occlusive disease in a newborn infant of a woman drinking herbal tea. J Pediatr 1988;112:433–6.
[155] Sperl W, Stuppner H, Gassner I, Judmaier W, Dietze O, Vogel W. Reversible hepatic veno-occlusive disease in an infant after consumption of pyrrolizidine-containing herbal tea. Eur J Pediatr 1995;154:112–6.
[156] DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). Semin Liver Dis 2002;22:27–42.
[157] Lin G, Wang JY, Li N, Li M, Gao H, Ji Y, et al. Hepatic sinusoidal obstruction syndrome associated with consumption of *Gynura segetum*. J Hepatol 2011;54:666–73.
[158] DeLeve LD, McCuskey RS, Wang X, Hu L, McCuskey MK, Epstein RB, et al. Characterization of a reproducible rat model of hepatic veno-occlusive disease. Hepatology 1999;29:1779–91.
[159] Mei N, Guo L, Fu PP, Fuscoe JC, Luan Y, Chen T. Metabolism, genotoxicity, and carcinogenicity of comfrey. J Toxicol Environ Health B Crit Rev 2010;13:509–26.
[160] Shaw D. Toxicological risks of Chinese herbs. Planta Med 2010;76:2012–8.
[161] Woolf GM, Petrovic LM, Roiter SE, et al. Acute hepatitis associated with the Chinese herbal product Jin Bu Huan. Ann Intern Med 1994;10:729–35.
[162] Piciotto A, Campo N, Brizzolara R, et al. Chronic hepatitis induced by Jin Bu Huan. J Hepatol 1998;28:165–7.
[163] Nadir A, Agrawal S, King PD, Marshall JB. Acute hepatitis associated with the use of a Chinese herbal product, Ma-Huang. Am J Gastro 1996;91:1436–8.
[164] Bajaj J, Knox JF, Komorowski R, Saeian K. The irony of herbal hepatitis: Ma-Huang-induced hepatotoxicity associated with compound heterozygosity for hereditary hemochromatosis. Dig Dis Sci 2003;48:1925–8.
[165] Neff GW, Reddy KR, Durazo FA, Meyer D, Marrero R, Kaplowitz N. Severe hepatotoxicity associated with the use of weight loss diet supplements containing ma huang or usnic acid. J Hepatol 2004;41:1062–4.
[166] Vigano M, Lampertico P, Colombo M. Acute hepatitis following assumption of a herbal remedy. Europ J Gastroenterol Hepatol 2008;20:364–5.
[167] Kane JA, Kane SP, Jain S. Hepatitis induced by traditional Chinese herbs; possible toxic components. Gut 1995;36:146–7.
[168] Yoshida EM, McLean CA, Cheng ES, Blanc PD, Somberg KA, Ferrell LD, et al. Chinese herbal medicine, fulminant hepatitis and liver transplantation. Am J Gastro 1996;12:2647–8.
[169] McRae CA, Agarwal K, Mutimer D, Bassendine MF. Hepatitis associated with Chinese herbs. Europ J Gastroenterol Hepatol 2002;14:559–62.
[170] But PP, Tomlinson B, Lee KL. Hepatitis related to the Chinese medicine Shou-wu-pian manufactured from *Polygonum multiflorum*. Vet Hum Toxicol 1996;38:280–2.
[171] Park GJ, Mann SP, Ngu MC. Acute hepatitis induced by Shou-Wu-Pian, a herbal product derived from *Polygonum multiflorum*. J Gastroenterol Hepatol 2001;16:115–7.
[172] Mazzanti G, Battinelli L, Daniele C, et al. New case of acute hepatitis following the consumption of Shou Wu Pian, a Chinese herbal product derived from *Polygonum multiflorum*. Ann Intern Med 2004;140:W30.
[173] Panis B, Wong DR, Hooymans PM, et al. Recurrent toxic hepatitis in a Caucasian girl related to the use of Shou-Wu-Pian, a Chinese herbal preparation. J Pediatr Gastroenterol Nutr 2005;41:256–8.
[174] Cárdenas A, Restrepo JC, Sierra F, et al. Acute hepatitis due to Shen-Min, a herbal product derived from *Polygonum multiflorum*. J Clin Gastroenterol 2006;40:629–32.
[175] Laird AR, Ramchandani N, deGoma EM, Avula B, Khan IA, Gesundheit N. Acute hepatitis associated with the use of an herbal supplement (*Polygonum multiflorum*) mimicking iron-overload syndrome. J Clin Gastroenterol 2008;42:861–2.
[176] Tolman KG, Hammar S, Sannella JJ. Possible hepatotoxicity of doxidan. Ann Intern Med 1976;84:290–2.
[177] Kanda T, Yokosuka O, Okada O, Suzuki Y, Saisho H. Severe hepatotoxicity associated with Chinese diet product "Onshidou-Genbi-Kounou". J Gastroenterol Hepatol 2003;18:354–5.
[178] Lin TJ, Tsai MS, Chiou NM, Deng JF, Chiu NY. Hepatotoxicity caused by *Breynia officinalis*. Vet Hum Toxicol 2002;44:87–8.
[179] Lin TJ, Su CC, Lan CK, Jiang DD, Tsai JL, Tsai MS. Acute poisonings with *Breynia officinalis*—an outbreak of hepatotoxicity. J Toxicol Clin Toxicol 2003;41:591–4.
[180] Larrey D, Vial T, Pauwels A, Castot A, Biour M, David M, et al. Hepatitis after germander (*Teucrium chamaedrys*) administration: another instance of herbal medicine hepatotoxicity. Ann Intern Med 1992;117:129–32.
[181] Loeper J, Descatoire V, Letteron P, Moulis C, Degott C, Dansette P, et al. Hepatotoxicity of germander in mice. Gastroenterology 1994;106:464–72.
[182] Kouzi SA, McMurty RJ, Nelson SD. Hepatotoxicity of germander (*Teucrium chamedrys L.*) and one of its constituent neoclerodane diterpenes, teucrin A in the mouse. Chem Res Toxicol 1994;7:850–6.
[183] Lekehal M, Pessayre D, Lereau JM, Moulis C, Fourasté I, Fau D. Hepatotoxicity of the herbal medicine, germander. Metabolic activation of its furano diterpenoids by cytochrome P450 3A depletes cytoskeleton-associated protein thiols and forms plasma membrane blebs in rat hepatocytes. Hepatology 1996;24:212–8.
[184] Fau D, Lekehal M, Farrell G, Moreau A, Moulis C, Feldmann G, et al. Diterpenoids from germander, an herbal medicine, induce apoptosis in isolated rat hepatocytes. Gastroenterology 1997;113:1334–46.

[185] Mattei A, Rucay P, Samuel D. Liver transplantation for severe acute liver failure after herbal medicine (*Teucrium polium*) administration. J Hepatol 1995;22:597.
[186] Savvidou S, Goulis J, Giavazis I, Patsiaoura K, Hytiroglou P, Arvanitakis C. Herb-induced hepatitis by *Teucrium polium* L.: report of two cases and review of the literature. Eur J Gastroenterol Hepatol 2007;19:507–11.
[187] Poon WT, Chau TL, Lai CK, Tse KY, Chan YC, Leung KS, et al. Hepatitis induced by *Teucrium viscidum*. Clin Toxicol (Phila) 2008;46:819–22.
[188] Kassler WJ, Blanc P, Greenblatt R. The use of medicinal herbs by human immunodeficiency virus-infected patients. Arch Intern Med 1991;151:2281–8.
[189] Sheikh NM, Philen RM, Love LA. Chaparral-associated Hepatotoxicity. Arch Intern Med 1997;157:913–9.
[190] Agarwal R, Wang ZY, Bik DP, Mukhtar H. Nordihydroguaiaretic acid, an inhibitor of lipoxygenase, also inhibits cytochrome P-450-mediated monooxygenase activity in rat epidermal and hepatic microsomes. Drug Metab Dispos 1991;19:620–4.
[191] Georgiou M, Sianidou L, Hatzis T, Papadatos J, Koutselinis A. Hepatotoxicity due to *Atractylis gummifera*-L. J Toxicol Clin Toxicol 1988;26:487–93.
[192] Larrey D. Hepatotoxicity of herbal remedies. J Hepatol 1997;26:47–54.
[193] Hamouda C, Hédhili A, Ben Salah N, Zhioua M, Amamou M. A review of acute poisoning from *Atractylis gummifera* L. Vet Hum Toxicol 2004;46:144–6.
[194] Popat A, Shear NH, Malkiewicz I, Stewart MJ, Steenkamp V, Thomson S, et al. The toxicity of *Callilepis laureola*, a South African traditional herbal medicine. Clin Biochem 2001;34:229–36.
[195] Watson AR, Coovadia HM, Bhoola KD. The clinical syndrome of Impila (*Callilepis laureola*) poisoning in children. S Afr Med J 1979;55:290–2.
[196] Stewart MJ, Steenkamp V, van der Merwe S, Zuckerman M, Crowther NJ. The cytotoxic effects of a traditional Zulu remedy, impila (*Callilepis laureola*). Hum Exp Toxicol 2002;21:643–7.
[197] Popat A, Shear NH, Malkiewicz I, Thomson S, Neuman MG. Mechanism of Impila (*Callilepis laureola*)-induced cytotoxicity in Hep G2 cells. Clin Biochem 2002;35:57–64.
[198] Sullivan Jr JB, Rumack BH, Thomas Jr H, Peterson RG, Bryson P. Pennyroyal oil poisoning and hepatotoxicity. J Am Med Assoc 1979;242:2873–4.
[199] Anderson IB, Mullen WH, Meeker JE, Khojasteh-Bakht SC, Oishi S, Nelson SD, et al. Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. Ann Intern Med 1996;124:726–34.
[200] Bakerink JA, Gospe SM, Dimand RJ, Eldridge MW. Multiple organ failure after ingestion of pennyroyal oil from herbal tea in two infants. Pediatrics 1996;98:944–7.
[201] Thomassen D, Slattery JT, Nelson SD. Menthofuran-dependent and independent aspects of pulegone hepatotoxicity: roles of glutathione. J Pharmacol Exp Ther 1990;253:567–72.
[202] Thomassen D, Knebel N, Slattery JT, McClanahan RH, Nelson SD. Reactive intermediates in the oxidation of menthofuran by cytochromes P-450. Chem Res Toxicol 1992;5:123–30.
[203] Gordon WP, Huitric AC, Seth CL, McClanahan RH, Nelson SD. The metabolism of the abortifacient terpene, (R)-(+)-pulegone, to a proximate toxin, menthofuran. Drug Metab Dispos 1987;15:589–94.
[204] Colombo ML, Bosisio E. Pharmacological activities of *Chelidonium majus* L. (Papaveraceae). Pharmacol Res 1996;33:127–34.
[205] Stickel F, Pöschl G, Seitz HK, Waldherr R, Hahn EG, Schuppan D. Acute hepatitis induced by greater celandine (*Chelidonium majus*). Scand J Gastroenterol 2003;38:565–8.
[206] Hardeman E, Van Overbeke L, Ilegems S, Ferrante M. Acute hepatitis induced by greater celandine (*Chelidonium majus*). Acta Gastroenterol Belg 2008;71:281–2.
[207] Moro PA, Cassetti F, Giugliano G, Falce MT, Mazzanti G, Menniti-Ippolito F, et al. Hepatitis from greater celandine (*Chelidonium majus* L.): review of literature and report of a new case. J Ethnopharmacol 2009;15(124):328–32.
[208] Benninger J, Schneider HT, Schuppan D, Kirchner T, Hahn EG. Acute hepatitis induced by greater celandine (*Chelidonium majus*). Gastroenterology 1999;117:1234–7.
[209] Davies LP, Drew CA, Duffield P, Johnston GA, Jamieson DD. Kavapyrones and resin: studies on $GABA_A$, $GABA_B$ and benzodiazepine binding sites in rodent brain. Pharmacol Toxicol 1992;71:120–6.
[210] Jussofie A, Schmiz A, Hiemke C. Kavapyrone enriched extract from *Piper methysticum* as modulator of the GABA binding site in different regions of rat brain. Psychopharmacol 1994;116:469–74.
[211] Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. J Clin Psychopharmacol 2000;20:84–9.
[212] Ernst E. Re-evaluation of kava (*Piper methysticum*). Br J Clin Pharmacol 2007;64:415–7.
[213] Centers for Disease Control and Prevention. Hepatic toxicity possibly associated with kava-containing products—United States, Germany, and Switzerland. J Am Med Assoc 2003;289:36–7.
[214] Stickel F, Baumüller HM, Seitz KH, Vasilakis D, Seitz G, Seitz HK, et al. Hepatitis induced by Kava-Kava (*Piper methysticum rhizoma*). J Hepatol 2003;39:62–7.
[215] Russmann S, Lauterburg BH, Helbling A. Kava hepatotoxicity. Ann Intern Med 2001;135:68–9.
[216] Jhoo J-W, Freeman JP, Heinze TM, Moody JD, Schnackenberg LK, Beger RD, et al. In vitro cytotoxocity of nonpolar constituents from different parts of kava plant (*Piper methysticum*). J Agric Food Chem 2006;54:3157–62.
[217] Sorrentino L, Capasso A, Schmidt M. Safety of ethanolic kava extract: results of a study of chronic toxicity in rats. Phytomedicine 2006;13:542–9.
[218] Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. Med J Aust 2002;177:440–3.
[219] Levitsky J, Alli TA, Wisecarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. Dig Dis Sci 2005;50:538–9.
[220] Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. Liver Transpl 2006;12:989–92.
[221] Mahady GB, Low Dog T, Barrett ML, Chavez ML, Gardiner P, Ko R, et al. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. Menopause 2008;15:628–38.
[222] Naser B, Schnitker J, Minkin MJ, de Arriba SG, Nolte KU, Osmers R. Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract. Menopause 2011;18:366–75.
[223] Teschke R. Black cohosh and suspected hepatotoxicity: inconsistencies, confounding variables, and prospective use of a diagnostic causality algorithm. A critical review. Menopause 2010;17:426–40.

[224] Lüde S, Török M, Dieterle S, Knapp AC, Kaeufeler R, Jäggi R, et al. Hepatic effects of *Cimicifuga racemosa* extract in vivo and in vitro. Cell Mol Life Sci 2007;64:2848–57.
[225] Beuers U, Spengler U, Pape G. Hepatitis after chronic abuse of senna. Lancet 1992;337:372–3.
[226] Nadir A, Reddy D, Van Thiel DH. *Cascara sagrada*-induced intrahepatic cholestasis causing portal hypertension: case report and review of herbal hepatotoxicity. Am J Gastroenterol 2000;95:3634–7.
[227] Hamid S, Rojter S, Vierling J. Protracted cholestatic hepatitis after the use of prostata. Ann Intern Med 1997;127:169.
[228] Brinkhaus B, Lindner M, Schuppan D, Hahn EG. Chemical, pharmacological and clinical profile of the East Asian plant *Centella asiatica*. Phytomedicine 2000;7:427–48.
[229] Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of *Centella asiatica*. Rev Esp Enferm Dig 2005; 97:115–24.
[230] Chauhan BL, Kulkarni RD. Effect of LIV.52, a herbal preparation, on absorption and metabolism of ethanol in humans. Eur J Clin Pharmacol 1991;40:189–91.
[231] Fleig WW, Morgan MY, Hölzer MA, a European multicenter study group. The ayurvedic drug LIV.52 in patients with alcoholic cirrhosis. Results of a prospective, randomized, double-blind, placebo-controlled clinical trial (abstract). J Hepatol 1997;26(Suppl. 1):127.
[232] Stadlbauer V, Weiss S, Payer F, Stauber RE. Herbal does not at all mean innocuous: the sixth case of hepatotoxicity associated with *Morinda citrifolia* (Noni). Am J Gastroenterol 2008;103:2406–7.
[233] Yu EL, Sivagnanam M, Ellis L, Huang JS. Acute hepatotoxicity after ingestion of *Morinda citrifolia* (Noni berry) juice in a 14-year-old boy. J Pediatr Gastroenterol Nutr 2011;52:222–4.
[234] West BJ, Su CX, Jensen CJ. Hepatotoxicity and subchronic toxicity tests of *Morinda citrifolia* (Noni) fruit. J Toxicol Sci 2009;34:581–5.
[235] Bironaite D, Ollinger K. The hepatotoxicity of rhein involves impairment of mitochondrial functions. Chem Biol Interact 1997;103:35–50.
[236] Gavilan JC, Bermudez FJ, Salgado F, Pena D. Phytotherapy and hepatitis. Rev Clin Esp 1999;199:693–4.
[237] Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts. A systematic review by the US Pharmacopeia. Drug Saf 2008;31:469–84.
[238] Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. Liver Int 2011;31:595–605.
[239] Galati G, Lin A, Sultan AM, O'Brien PJ. Cellular and in vivo hepatotoxicity caused by green tea phenolic acids and catechins. Free Radic Biol Med 2006;40:570–80.
[240] Lin BR, Yu CJ, Chen WC, et al. Green tea extract supplement reduces D-galactosamine-induced acute liver injury by inhibition of apoptotic and proinflammatory signaling. J Biomed Sci 2009;16:35.
[241] Kobayashi H, Tanaka Y, Asagiri K, et al. The antioxidant effect of green tea catechin ameliorates experimental liver injury. Phytomedicine 2010;17:197–202.
[242] Zhong Z, Froh M, Lehnert M, et al. Polyphenols from *Camellia sinenesis* attenuate experimental cholestasis-induced liver fibrosis in rats. Am J Physiol Gastrointest Liver Physiol 2003;285:G1004–13.
[243] Jin X, Zheng RH, Li YM. Green tea consumption and liver disease: a systematic review. Liver Int 2008;28:990–6.
[244] Elinav E, Pinsker G, Safadi R, et al. Association between consumption of Herbalife® nutritional supplements and acute hepatotoxicity. J Hepatol 2007;47:514–20.
[245] Schoepfer AM, Engel A, Fattinger K, et al. Herbal does not mean innocuous: 10 cases of severe hepatotoxicity associated with dietary supplements from Herbalife® products. J Hepatol 2007;47:521–6.
[246] Duque JM, Ferreiro J, Salgueiro E, Manso G. Hepatotoxicity associated with the consumption of herbal slimming products. Med Clin (Barc) 2007;128:238–9.
[247] Chao S, Anders M, Turbay M, Olaiz E, Mc Cormack L, Mastai R. Toxic hepatitis by consumption of Herbalife products: a case report. Acta Gastroenterol Latinoam 2008;38:274–7.
[248] Stickel F, Droz S, Patsenker E, Boegli-Studer K, Aebi B, Leib SL. Severe hepatotoxicity following ingestion of Herbalife® nutritional supplements contaminated with *Bacillus subtilis*. J Hepatol 2009;50:111–7.
[249] Johannsson M, Ormarsdottir S, Olafsson S. Hepatotoxicity associated with the use of Herbalife. Laeknabladid 2010;96:167–72.
[250] Han D, Matsumaru K, Rettori D, Kaplowitz N. Usnic acid-induced necrosis of cultured mouse hepatocytes: inhibition of mitochondrial function and oxidative stress. Biochem Pharmacol 2004;67:439–51.
[251] Favreau JT, Ryu ML, Braunstein G, et al. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. Ann Intern Med 2002;136:590–5.
[252] Durazo FA, Lassman C, Han SB, et al. Fulminant liver failure due to usnic acid for weight loss. Am J Gastroenterol 2004;99:950–2.
[253] Neff GW, Reddy KR, Durazo FA, Meyer D, Marrero R, Kaplowitz N. Severe hepatotoxicity associated with the use of weight loss diet supplements containing ma huang or usnic acid. J Hepatol 2004;41:1062–4.
[254] Yellapu RK, Mittal V, Grewal P, Fiel M, Schiano T. Acute liver failure caused by "fat burners" and dietary supplements: a case report and literature review. Can J Gastroenterol 2011;25:157–60.
[255] <http://www.cfsan.fda.gov/~dms/ds-lipo.html> [accessed 31.12.2011].
[256] Lobb A. Hepatotoxicity associated with weight-loss supplements: a case for better post-marketing surveillance. World J Gastroenterol 2009;15:1786–7.
[257] Probst C, Njapau H, Cotty PJ. Outbreak of an acute aflatoxicosis in Kenya in 2004: identification of the causal agent. Appl Environ Microbiol 2007;73:2762–4.
[258] Lye MS, Ghazali AA, Mohan J, Alwin N, Nair RC. An outbreak of acute hepatic encephalopathy due to severe aflatoxicosis in Malaysia. Am J Trop Med Hyg 1995;53:68–72.
[259] Krishnamachari KA, Bhat RV, Nagarajan V, Tilak TB. Hepatitis due to aflatoxicosis. An outbreak in Western India. Lancet 1975;1:1061–3.
[260] Bosch FX, Munoz N. Prospects for epidemiological studies on hepatocellular cancer as a model for assessing viral and chemical interactions. IARC Sci Publ 1988;89:427–38.
[261] Lancaster MC, Jenkins FP, Philp JM. Toxicity associated with certain samples of groundnuts. Nature 1961;192:1095–6.
[262] Sargeant K, Sheridan A, O'Kelly J, Carnaghan RBA. Toxicity associated with certain samples of groundnuts. Nature 1961;192:1096–7.
[263] Eaton DL, Groopman JD. The toxicology of aflatoxins: human health, veterinary, and agricultural significance. San Diego, CA: Academic Press, Inc.; 1994.
[264] Groopman JD, Kensler TW. Role of metabolism and viruses in aflatoxin-induced liver cancer. Toxicol Appl Pharmacol 2005;206:131–7.
[265] Hussain SP, Schwank J, Staib F, Wang XW, Harris CC. TP53 mutations and hepatocellular carcinoma: insights into the

etiology and pathogenesis of liver cancer. Oncogene 2007;26:2166–76.
[266] Aguilar F, Hussain SP, Cerutti P. Aflatoxin B1 induces the transversion of G > T in codon 249 of the p53 tumor suppressor gene in human hepatocytes. Proc Natl Acad Sci USA 1993;90:8586–90.
[267] Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. Dig Liver Dis 2010;42(Suppl. 3):S206–14.
[268] Gaillard Y, Carlier J, Berscht M, Mazoyer C, Bevalot F, Guitton J, et al. Fatal intoxication due to ackee (*Blighia sapida*) in Suriname and French Guyana. GC-MS detection and quantification of hypoglycin-A. Forensic Sci Int 2011;206:e103–7.
[269] Joskow R, Belson M, Vesper H, Backer L, Rubin C. Ackee fruit poisoning: an outbreak investigation in Haiti 2000–2001, and review of the literature. Clin Toxicol (Phila) 2006;44:267–73.
[270] Meda HA, Diallo B, Buchet JP, Lison D, Barennes H, Ouangré A, et al. Epidemic of fatal encephalopathy in preschool children in Burkina Faso and consumption of unripe ackee (*Blighia sapida*) fruit. Lancet 1999;353:536–40.
[271] Barceloux DG. Akee fruit and Jamaican vomiting sickness (*Blighia sapida Köenig*). Dis Mon 2009;55:318–26.
[272] Saleh M, Al Nakib M, Doloy A, Jacqmin S, Ghiglione S, Verroust N, et al. *Bacillus cereus*, an unusual cause of fulminant liver failure: diagnosis may prevent liver transplantation. J Med Microbiol 2012;61:743–5.
[273] Dierick K, Van Coillie E, Swiecicka I, Meyfroidt G, Devlieger H, Meulemans A, et al. Fatal family outbreak of *Bacillus cereus*-associated food poisoning. J Clin Microbiol 2005;43:4277–9.
[274] Mahler H, Pasi A, Kramer JM, Schulte P, Scoging AC, Bär W, et al. Fulminant liver failure in association with the emetic toxin of *Bacillus cereus*. N Engl J Med 1997; 336:1142–8.
[275] Sakurai N, Koike KA, Irie Y, Hayashi H. The rice culture filtrate of *Bacillus cereus* isolated from emetic-type food poisoning causes mitochondrial swelling in a HEp-2 cell. Microbiol Immunol 1994;38:337–43.
[276] Schafer DF, Sorrell MF. Power failure, liver failure. N Engl J Med 1997;336:1173–4.
[277] Jochimsen EM, Carmichael WW, An JS, Cardo DM, Cookson ST, Holmes CE, et al. Liver failure and death after exposure to microcystins at a hemodialysis center in Brazil. N Engl J Med 1998;338:873–8.
[278] Carmichael WW, Azevedo SM, An JS, Molica RJ, Jochimsen EM, Lau S, et al. Human fatalities from cyanobacteria: chemical and biological evidence for cyanotoxins. Environ Health Perspect 2001;109:663–8.
[279] Ding WX, Shen HM, Zhu HG, Lee BL, Ong CN. Genotoxicity of microcystic cyanobacteria extract of a water source in China. Mutat Res 1999;442:69–77.
[280] Nishiwaki-Matsushima R, Ohta T, Nishiwaki S, Suganuma M, Kohyama K, Ishikawa T, et al. Liver tumor promotion by the cyanobacteria cyclic peptide toxin microcystin-LR. J Cancer Res Clin Oncol 1992;118:420–4.
[281] Yoshizawa S, Matsushima R, Watanabe MF, Harada KI, Carmichael WW, Fujiki H. Inhibition of protein phosphatases by microcystins and nodularin associated with hepatotoxicity. J Cancer Res Clin Oncol 1990;116:609–14.