Hepatotoxicity of botanicals†

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Abstract

Objective: Hepatic impairment resulting from the use of conventional drugs is widely acknowledged, but there is less awareness of the potential hepatotoxicity of herbal preparations and other botanicals, many of which are believed to be harmless and are commonly used for self-medication without supervision. The aim of this paper is to examine the evidence for hepatotoxicity of botanicals and draw conclusions regarding their pathology, safety and applications.

Design: Current literature on the hepatotoxicity of herbal drugs and other botanicals is reviewed. The aetiology, clinical picture and treatment of mushroom (*Amanita*) poisoning are described.

Results: Hepatotoxic effects have been reported for some Chinese herbal medicines (such as Jin Bu Huan, Ma-Huang and Sho-saiko-to), pyrrolizidine alkaloid-containing plants, germander (*Teucrium chamaedrys*), chaparral (*Larrea tridentata*), *Atractylis gummifera*, *Callilepsis laureola*, and others. The frequency with which botanicals cause hepatic damage is unclear. There is a lack of controlled treatment trials and the few studies published to date do not clarify the incidence of adverse effects. Many plant products do not seem to lead to toxic effects in everyone taking them, and they commonly lack a strict dose-dependency. For some products, such as Sho-saiko-to, the picture is confused further by demonstrations of hepatoprotective properties for some components. Mushroom poisoning is mostly due to the accidental consumption of *Amanita* species. Treatment with silymarin, thioctic acid, penicillin and liver transplantation have been shown to be effective but require early diagnosis.

Conclusions: Severe liver injury, including acute and chronic abnormalities and even cirrhotic transformation and liver failure, has been described after the ingestion of a wide range of herbal products and other botanical ingredients, such as mushrooms. It is concluded that in certain situations herbal products may be just as harmful as conventional drugs.

Keywords
Herbal medicine
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Chaparral
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Amanita
Mushroom poisoning
Toxic liver injury

Hepatotoxicity of xenobiotics has been extensively documented and presents an everyday problem to medical staff[1]. Drugs and foreign chemicals can induce many liver abnormalities, sometimes imitating naturally occurring liver diseases. It is assumed that almost 2% of all jaundiced patients suffer from drug-induced hepatopathy. There are large interindividual differences in the capability of subjects to metabolize drugs and other chemicals. The biotransformation of exogenous compounds depends mainly on drug-metabolizing enzyme systems, of which the most important represent the group of cytochrome P450s, mixed-function mono-oxygenases and cytochrome C reductase. All these systems are located in microsomes, each of them responsible for the degradation of one specific or a few foreign substances. More than 150 different cytochrome P450s have been detected and there are probably many more[2]. Enzymes can be enhanced as well as downregulated depending primarily on the availability of the specific substrate. Especially in the setting of enzyme induction, this may lead to the formation of toxic metabolites either from the specific substrate or other exogenously administered compounds which are metabolized by the same enzyme system. For example, co-carcinogenicity of alcohol is assumed to be a result of the formation of carcinogens through alcohol-induced P450 2E1. Thus, differences in enzyme activities are an important reason for interindividual variability in the capacity to handle foreign chemicals.

Hepatic impairment due to conventional drugs is widely acknowledged and most physicians are well aware of these drugs. Due to these potentially toxic effects and, of course, other reasons, patients seek help in alternative 'natural' treatments believing that side effects do not

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exist. In this sense, herbal medication has gained increasing attention among the health aware and those who may have been disappointed by scientific medicine[3–5]. Herbal preparations do, however, contain substantial amounts of pharmaceutically active ingredients whose mechanisms of action and adverse effects are mostly unknown. Difficulties arise especially in those preparations that contain a number of different ingredients which makes the identification of the crucial toxin almost impossible and sometimes scapegoats the wrong herbal candidate. Studies evaluating the effectiveness and safety of most herbal preparations have not been undertaken although it increasingly seems that evidence of the health hazards of herbal drugs outnumber those indicating beneficial effects. Additionally, these medicaments are sold over the counter without prescription or are handed out to patients by herb practitioners with questionable expertise, particularly with regard to pharmacodynamics and safety[6]. Frequently, patients omit the intake of herbal products, even on repeated questioning, either assuming their safety or fearing not to be taken seriously for using herbs. Self-medication is frequent and sometimes patients even increase the dosage when symptoms of liver disease resume. Another problem with herbal medication is the often great number of herbal extracts in a single preparation, as well as the dangers of contamination, misidentification and improper storage[7]. A health control laboratory in Sweden raised the issue that adverse liver abnormalities due herbal medication occur with a high incidence by showing that discontinuing herbal drugs normalized liver enzyme tests in a high percentage of subjects[8].

The aim of this paper is to summarize the current knowledge about potentially hepatotoxic herbal drugs and other botanicals. The current literature on this topic is reviewed and conclusions about pathology, safety and applications are drawn. A list of plants with known or assumed hepatotoxic effects is given in Table 1.

Chinese herbal medicine

In the recent past, Far Eastern medicine has gained increasing attention and, especially among the health aware, use of traditional Chinese herbal medicines has become very fashionable. Due to the fact that Chinese herbs – being natural compounds – have sometimes been use for thousands of years for various diseases and ailments, these remedies are considered by definition as completely innocuous. However, evidence has lately accumulated that this assumption is naive after numerous reports have raised doubts about their safety and have proved potential toxicity, particularly to the liver.

The difficulty with traditional Chinese herbal preparations is rooted in its heterogenity. Some 7000 different plant species are used in China and preparations may vary extremely with regard to composition and dosage[9]. An intense discussion of Chinese herbal medicine resulted from the examination of the efficacy of treatment of atopic dermatitis[10,11]. In a reaction to dermatological studies, a number of reports were published showing acute hepatitis after the treatment of eczema with Chinese herbal decoctions containing various plant extracts[12–16]. Two cases of fulminant hepatic failure occurred[14,15] after which one individual died and the other was rescued by immediate orthotopic liver transplantation (OLT). Apparently, liver abnormalities due to Chinese herbal remedies are quite frequent and are simply overseen since many patients are not properly scrutinized for this aetiology of the presenting liver disease.

At present, hepatotoxicity associated with Chinese herbal medication can be classified into two main groups: where the toxicity can be ascribed to a single component, and where there are several toxic agents. In the first group belongs a substance which has recently been incriminated as causing both acute and chronic hepatitis: Jin Bu Huan, a tablet product taken for alleged sedative and analgesic properties. Its active ingredient is a

Table 1 Ascertained and suspected hepatotoxic herbal components

Chinese herbal medication	Germander	Pyrrolizidine alkaloids	Atractylosides	Chaparral	Miscellaneous
Lypocodium serratum (Jin Bu Huan) Ma-Huang Sho-saiko-to *Paeonia* spp. *Dictamnus* spp.	*Teucrium chamaedrys* *Teucrium polium*	*Crotalaria* *Heliotropium* *Senecio* *Symphytum officinale* (comfrey) *Symphytum longilobus* Maté (Paraquay)	*Atractylis gummifera* *Callilepsis laureola*	*Larrea tridentata*	Senna (*Cassia angustifolia*) Mistletoe (*Viscum album*) Valerian (*Valeriana officinalis*) *Scutellaria* spp. (scullcap) Pennyroyal (*Mentha pulegium*) Margosa oil (*Azadirachza indica*) Sassafras (*Sassafras albidum*) Prostata

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plant extract from *Lypocodium serratum* which is taken on a three times per day basis. While a case report from 1994 described acute hepatitis after ingestion of Jin Bu Huan[17], recently this herbal drug was also found to induce chronic hepatitis after a period as short as 1 year of intake. In the latter patient, focal hepatocellular necrosis and moderate fibrosis had developed and it remains speculative whether prolonged treatment would have even lead to cirrhosis and liver failure[18].

Another single agent preparation that emerged as liver toxic in the literature is the ephedrine-containing Chinese herb product Ma-Huang[19]. This remedy is frequently added to overweight treatment regimens in the United States for its acclaimed weight-reducing and energizing effects[20]. In the published report, the female patient developed acute hepatitis with no other evident cause of liver disease after only 3 weeks of intake of Ma-Huang. Nevertheless, scepticism remains about whether Ma-Huang was responsible or whether the occurrence of hepatitis following administration of the drug was simply coincidental. Ephedrine has been used in western medicine for a long time and reports about liver toxic side effects are completely lacking. In this patient, hepatitis resolved gradually after discontinuation of treatment and re-exposure was not instigated, although this would have proven a causal relationship[21]. This incident pinpoints once again a major problem with the evaluation of Chinese herbal medication – misidentification, manufacturing inconsistencies and contamination may occur which jeopardize the detection of detrimental components[22,23].

Apart from preparations containing only one active component, mixtures of numerous herbs are frequently administered. In fact, composing an individually tailored preparation is part of the medication philosophy in traditional Chinese medicine[9]. This obviously makes the assessment of safety profiles of Chinese herbal products based on western standards extremely difficult. With respect to medications used for the treatment of psoriasis and eczema, compositions have recently been analysed and the ingredients of five preparations are listed in Table 2. Although the preparations were used for the same kind of skin disease, compositions vary substantially. However, products that were shown to be hepatotoxic share a similarity with respect to the combination of ingredients. As can be seen from the lists of plant extracts, one species appears in all five listed recipes, namely *Paeonia*, while *Dictamnus* and *Rhemannia* extracts are missing in at least one of the preparations. Whether this points to *Paeonia* as the crucial plant remains to be investigated, particularly since it is *Paeonia* that is believed to be the effective compound with regard to treating psoriasis[24].

Nevertheless, Chinese herbal medicine cannot generally be accused of being harmful to the liver, as shown in various reports with regard to hepatocarcinogenesis and fibrosis. In this area, reports referring to a herbal preparation named Sho-saiko-to are conflicting. While Itoh *et al.* attributed the observed hepatotoxicity of this herbal composition to *Scutellaria* (skullcap)[25], others have even suggested beneficial properties with regard to the liver. It has been shown lately in both human and animal studies that Sho-saiko-to is capable of preventing hepatocellular carcinoma and fibrosis in humans, an observation which was consecutively supported by experimental data from *in vivo* and *in vitro* studies[26–28].

Similarly, cell culture work on interleukin-10 production in patients with chronic hepatitis C indicates that this may halt the progression of the disease[29]. Other work suggests a positive effect of another Chinese herbal preparation on the course of chronic hepatitis C[30]. Batey *et al.* found a preparation containing as many as 19 different herbal extracts to be effective in reducing elevated alanine aminotransferase levels in patients with hepatitis C. However, no patient effectively cleared the virus[30].

The frequency with which Chinese herbs evoke adverse effects in the liver is unclear since, so far, reports about toxicity have largely been case reports. Increasing awareness of their toxic properties will lead to data on safety and dose dependence which will draw a clearer picture in the near future. Thus, it seems that traditional

Table 2 Herbal ingredients in hepatotoxic Chinese herbal preparations for psoriasis and eczema

Case 1 (Perharic-Walton & Murray)[14]	Case 2 (Kane *et al.*)[15]	Case 3 (Kane *et al.*)[15]	Case 4 (Davies *et al.*)	Case 5 (Yoshida *et al.*)[16]
Paeonia spp.	*Paeonia suffructicosa*	*Paeonia suffructicosa*	*Paeonia suffructicosa*	*Paeonia* spp.
Dictamnus dasycarpus	*Dictamnus dasycarpus*	*Dictamnus dasycarpus*	*Paeonia lactiflora*	*Glycirrhiza* spp.
Rhemannia glutinosa	*Shisandra chinensis*	*Rhemannia glutinosa*	*Rhemannia glutinosa*	*Artemisia capillaris*
Cocculus trilobus	*Angelica sinensis*	*Hedyotis diffusa*	*Dictamnus dasycarpus*	*Bupleurum* spp.
Erysolen gracilis	*Bupleurum chinese*	*Sophora subprostata*	*Tribulus terrestris*	*Gentiana scabrae*
Glycyrrhiza spp.	*Phellodendraon chinese*	*Gentiana scabra*	*Glycyrrhiza wralensis*	*Magnolia* spp.
Lophaterum spp.	*Tribulus terrestris*	*Smilax glabra*	*Akebia trifoliata*	*Crysanthemum morifolium*
Potentilla spp.	*Shizinepeta tenuifolia*	*Paria polyphylla*	*Lophaterum gracile*	*Circuma* spp.
	Saposhnikovia divaricata		*Ledbouriella divaricata*	*Saussurea lappa*
			Viola chinensis	*Plantago asiatica*
			Viola grypoceras	*Gardinia jasminoidis*
			Viola inconspicua	*Alisma plantago aquatica*
			Viola patrinii	
			Viola yedoensis	

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Chinese medicine must meet requirements similar to those of western medical treatments: effectiveness has to be assessed, safety profiles have to be explored, dosage finding studies have to be performed, and surveillance of use has to be established.

Pyrrolizidine alkaloids

Hepatotoxicity of pyrrolizidine alkaloids has been clearly recognized for more than 70 years, since *Senecio* 'disease' was first described in South Africa[31]. Reports from Jamaica about children developing ascites, hepatomegaly and eventually cirrhosis after the ingestion of 'bush tea' followed. Liver disease was related to the large content of *Crotalaria* species in tea leaves[32]. Later, epidemics of pyrrolizidine alkaloid poisoning took place in India[33] and Afghanistan[34]. In the latter, cereal contaminated with *Heliotropium* alkaloids had caused an endemic outbreak of herb-associated liver disease.

The main liver injury evoked by pyrrolizidine alkaloids is veno-occlusive disease (VOD). Other known or supposed aetiologies of hepatic VOD are systemic lupus erythematosus, azathioprine medication in renal transplant patients, radiotherapy, alcoholic hepatitis, oral contraceptives and a number of cytostatics[1,35]. In western countries it was in the 1970s that the first cases of pyrrolizidine alkaloid intoxication were noticed. In Arizona two infants exposed to herbal tea containing *Senecio longilobus* were diagnosed as having hepatic VOD[36,37]. Briefly afterwards, similar cases were also reported from Europe and elsewhere[38–41]. Pyrrolizidine content may vary in particular plants, and clinical courses show striking differences due to varying amounts of ingested toxins. While high doses over a short time account for acute clinical pictures, a more prolonged intake of small portions appears to cause rather insidious liver disease[42]. About 20% of all patients with an acute form of VOD present with a fatal disease and a considerable percentage develop cirrhosis[43,44]. Pathologically, in VOD a non-thrombotic obliteration of the lumen of terminal centrilobular veins occurs which resembles Budd–Chiari syndrome. Accordingly, portal vein wedge pressure is elevated as well as corrected sinusoidal pressure indicating the presence of a post-sinusoidal block. This results in hepatic congestion and eventually in centrilobular necrosis[42,45]. Subsequently, fibrosis may develop. Its distribution pattern is characterized by 'reversed lobulation' showing fibrotic septa extending from perivenular areas rather than from the portal tracts. Signs of inflammation are usually lacking[45].

There is agreement that pyrrolizidines of the *Heliotropium*, *Senecio* and *Crotalaria* species, as well as maté tea, are especially toxic. However, *Symphytum* (comfrey) leaves and roots, the extracts of which are widely sold in the USA, were also noticed to cause liver injury[46]. This probably occurs because of at least nine different hepatotoxic pyrrolizidine alkaloids it contains[47]. The mechanism by which pyrrolizidine alkaloids enact hepatotoxicity are not yet fully elucidated but it probably involves a toxic rather than an immunological mechanism. Acute toxicity is reproducible in animals[48] and it seems to be related to biotransformation of alkaloids by cytochrome P450s. Pyrrole derivatives are formed which serve as alkylating agents and it was shown that unbound pyrroles may act as highly reactive hepatocarcinogens in animal studies[49,50]. Interestingly, toxicity of pyrrolizidines can be increased by co-medication with phenobarbital which is a potent inducer of cytochromes[51]. A standard treatment does not exist except for stopping the intake. As soon as chronic or acute liver failure is imminent, OLT may offer a therapeutic perspective but data about the outcome are lacking. Hepatotoxicity of pyrrolizidines is well documented and it is therefore difficult to understand why their use is not regulated. The sale of comfrey is banned in Germany and Canada, but it is still freely available in the USA[52].

Taking all this into consideration, patients and medical professionals should follow the simple guidelines recently issued by Huxtable: do not use herbal drugs in infants and children; avoid medication with herbal remedies during pregnancy and while nursing; do not take herbs on a regular basis; and lastly, beware of taking comfrey[22].

Germander

In 1986, germander (*Teucrium chamaedrys*) was issued a marketing agreement in France and was frequently used for the supportive treatment of obesity and mild diarrhoea[53]. Germander, a member of the *Labiatae* family, had been known for more than 2000 years as a herbal remedy and was applied for its assumed choleretic and antiseptic properties. It was considered to be absolutely safe but the active ingredients were then unknown. The usual methods of ingestion were capsules and tea bags but germander was also added to liquors and vermouths. Large-scale use resulted in a number of reports in 1992 to the French Regional Centers of Pharmacovigilance about numerous cases of germander-associated acute, chronic and even fulminant hepatitis[54,55]. Most affected individuals were women attempting to lose weight, which most probably reflected the high rate of women taking germander rather than gender-specific susceptibility. The daily dosage averaged approximately 600–1600 mg day^{-1} and hepatitis mostly developed after 2 months of permanent medication[56]. The clinical picture resembled acute hepatitis with markedly elevated transaminases, serum bilirubin levels and impairment of hepatic synthetic function. Histologically, acute cytolytic hepatitis without characteristic features was detected and some patients with a more benign course of liver disease revealed patterns of chronic hepatitis with fibrosis and even cirrhosis[54,57]. However, all patients recovered after the

discontinuation of treatment except for those with cirrhosis, but relapsed under accidental re-exposure which took place due to the fact that germander had not yet been identified as the aetiological toxin[57,58].

The above-mentioned similarities between germander-associated hepatitis and more frequent viral causes might be one reason for the failure to identify this herbal drug as potentially hepatotoxic, and initially it was believed that other contents in the preparation might have caused the liver abnormalities. But investigations could not detect any other source of toxicity (e.g. heavy metals, insecticides or fungal remnants, or manufacturing faults) that proved to be responsible. Eventually, *T. chamaedrys* was thoroughly analysed for its composition and chemical constituents. These comprise saponins, glycosides, flavonoids and a number of furan-containing neoclerodane diterpenoids[59–61]. While saponins are supposed to be hepatoprotective[62], furans are well known to be powerful carcinogens to cholangiocellular epithelium as shown in animal models[63,64]. In addition, several other furano compounds, e.g. furosemide (frusemide), psoralens and aflatoxins, are well known hepatotoxins after metabolization into reactive epoxides and unsaturated aldehydes by cytochrome P450s, in particular by cytochrome P450 3A[65–67]. Recently, germander hepatotoxicity has been elucidated in animal studies *in vivo* and *in vitro*. In a study by Loeper *et al.*[68] the authors showed that germander is toxic to the liver and that the toxicity is mediated via its furano neoclerodane diterpenoids. The animal experiments, which were performed in mice, proved the formation of toxic metabolites by cytochrome P450 3A and also showed that toxicity is enhanced by induction of cytochrome P450 3A and glutathione depletion[68,69]. Two other cell culture studies raised the hypothesis that germander exerts its detrimental effects to liver cells by inducing apoptosis after the formation of large amounts of reactive metabolites[70,71].

Lately, the hepatotoxic properties of *Teucrium polium* have been described. This plant, of the same genus as germander, has been used as an anti-inflammatory and antimicrobial drug as well as for the treatment of scars. It was found that the use of *T. polium* resulted in fulminant hepatic failure[72].

While the biochemical mechanisms through which other herbal compounds convey damage to the liver remain partly obscure, germander toxicity is doubtless and well understood and has already led to logical consequences, namely its withdrawal from the drug market in 1992. Hence, the likelihood of being confronted with a patient suffering from germander-associated liver disease has become rather small.

Chaparral

Chaparral (*Larrea tridentata*) is a desert plant and served as a botanical source for herbal remedies used formerly by native Americans in southwestern USA and Mexico. After grinding the leaves, chaparral – commonly referred to as 'creosote bush' or 'greasewood' – was ingested as tea. A variety of anecdotal reports, a variety of ailments such as the common cold, bone and muscle pain, and snake bites were treated[73]. At present, the plant extracts are manufactured in tablets, capsules and salves for its alleged anti-inflammatory and 'blood purifying' potentials, as a liver tonic and as a treatment for skin disorders. In addition, assumed weight-reducing and antioxidant properties have led to the perception that chaparral may retard the process of ageing. Apart from the above, chaparral is applied in alternative medicine regimens in the treatment of acquired immune deficiency syndrome (AIDS)[74].

Since 1990, publications about chaparral toxicity have mounted up and have led to several reports in the literature and by the Food and Drug Administration (FDA) in Washington[7,73,75]. Recently, all cases were carefully reviewed, delineating a clearer picture about the clinical characteristics. Sheikh *et al.* described 18 patients with reported chaparral-associated toxicity of which 13 revealed liver damage ranging from mild hepatitis to cirrhosis and even fulminant liver failure[73]. Nevertheless, the predominant pattern of liver damage was that of cholestatic hepatitis with high serum transaminases and elevation of bilirubin and alkaline phosphatase[76]. A minority developed cirrhosis and two patients required OLT for fulminant hepatic failure. In these patients, histology showed massive hepatocellular necrosis. Initially, most patients complained about fatigue, abdominal right upper quadrant discomfort and discoloration of stools and urine. Some individuals were administered single-component chaparral, while others took multi-ingredient combinations with other herbal substances. However, all preparations contained *L. tridentata* in significant amounts as proven by chromatography; biochemical and microbial contamination was excluded. A causal relationship was postulated because of a temporal correlation between the intake of chaparral and the onset of liver disease; pattern consistency of the hepatic reactions; and finally through the observation that re-exposure to chaparral or an increase of the dosage led to relapse or aggravation of symptoms and signs.

The pathophysiology of chaparral toxicity is yet unknown. Several possibilities are currently discussed: the active ingredient of chaparral, nordihydroguaiaretic acid (NDGA), can inhibit arachidonic acid transformation by interference with cyclo-oxygenase. In addition, cytochrome P450 inhibition has been described[77,78]. Both inhibitory effects can be responsible for hepatocyte damage. Furthermore, chaparral metabolites reveal oestrogen activity and oestrogens can be hepatotoxic[79]. Eventually, immune-mediated mechanisms have to be taken into consideration as well as interindividual determinants, e.g. age, gender, co-medication, hepatic function and idiosyncratic drug

reactions[80]. A specific therapy has yet to establish whether the most important preventive measure is avoiding intake.

Atractylis gummifera and *Callilepsis laureola*

Toxic hepatitis from *Atractylis gummifera* has been known for quite some time from around the Mediterranean sea. It is used as an antipyretic, emetic and diuretic, and a whitish fluid secreted from the plant is enjoyed by children as chewing gum[44]. Most of the more than two dozen plant species grow around the Mediterranean and the African continent.

The onset of hepatitis induced by this plant variety is usually acute and commences a few hours after ingestion following unspecific symptoms such as nausea, abdominal pain and headache. A clinical picture characterized by neurovegetative symptoms, hepatorenal failure and pronounced hypoglycaemia rapidly ensues, the latter caused by the inhibition of gluconeogenesis. Many patients may die. Consumption of *A. gummifera* is particularly dangerous in spring when toxins are concentrated in the roots or when confused with wild artichoke[56]. Toxicity has been ascribed to atractylosides and gummiferin which have been shown to inhibit mitochondrial functions, e.g. Krebs cycle. Furthermore, tissue culture studies indicate that atractylosides exert both hepatotoxicity and nephrotoxicity through selective toxicity at the liver and the kidneys, probably due to specific uptake mechanisms. In both organ tissues evidence for marked oxidative stress, expressed as glutathione depletion and increase of lipid peroxidation, were observed[81].

Another plant species containing atractylosides is *Callilepsis laureola* which has been associated with several cases of fulminant hepatitis and renal tubular necrosis among Zulus in South Africa[82]. Therapeutically, supplementation of antioxidants may be beneficial, but data about treatment with antioxidants or methyl group donors, e.g. *S*-adenosyl-L-methionine or betaine, are not available.

Miscellaneous plants

Various other botanicals have been linked to toxic liver damage, some of which are extensively used for mild ailments. Among these plants is senna (*Cassia angustifolia*), which was identified as a cause of a relatively benign hepatitis in a young woman taking approximately 10 times the recommended dose. The causal relationship between the preparation and hepatitis was supported by a positive rechallenge[83]. The transformation of senna via intestinal bacteria renders rhein anthron, which shows structural similarities to the well known liver toxic laxative anthron. Similarly, anthraquinones – including rhein anthron – contained in rhubarb have been suspected to cause liver injury[84].

Controversy exists about whether mistletoe (*Viscum album*) possesses hepatotoxic properties. Some discussion was provoked by a report from 1981 but the composition of the suspected preparation was not properly analysed and retrospection showed that the investigated medication actually contained *Scutellaria* (skullcap) and may have not even contained mistletoe[85]. Hence, toxicity of mistletoe remains uncertain, while *Scutellaria*-associated liver damage was already assumed in a case report involving a Chinese herbal remedy[24]. Mistletoe and scullcap once again came under suspect in a combination with valerian (*Valeriana officinalis*) administered for stress relief; this preparation comprises chemical constituents with powerful alkylating agruts and therefore potentially harmful properties[86]. Recently, Mullins and Horowitz described three young men who had injected themselves with an intravenous dose of extract of lettuce and valerian hoping to experience the alleged opioid side effects of these plants. All of them became rather sick and revealed mild to moderate changes of liver enzyme concentrations and liver function but recovered eventually[87].

Another combination of herbal ingredients, known as prostata, has lately led to a case report about a man using this medication for the treatment of benign prostatic hyperplasia. The assumed active ingredient in this drug seems to be *Serrenoa serrulata* which exerts oestrogenic and antiandrogenic effects. Either may be liver toxic under certain circumstances[88]. These hepatotoxic effects have not been reproduced in experimental or human studies in any of the herbal compounds mentioned in this chapter. However, careful surveillance should be instigated when using these ingredients, especially when other liver disease already exists and alcohol consumption is admitted.

In contrast to the above-mentioned herbal compounds, toxicity from pennyroyal occurs rather frequently. This plant, also referred to as squawmint oil, is a herb called *Mentha pulegium*, or its close relation *Hedeoma pulegoides*. It continues to be a source of intoxication and its use is widespread. It was used for centuries as an abortifacient and as a pesticide against fleas although efficacy has never been proven. On the other hand, fulminant hepatic necrosis in connection with its use has been repeatedly reported and the outcome has been lethal on several occasions. The primary constituent is pulegone besides various other monoterpenes characteristically encountered in mint species[89] but found in greater concentrations in pennyroyal. Hepatotoxic effects seem to be exerted by both pulegone producing oxidative stress and via pulegone's primary metabolite menthofuran, the latter being transformed to a hepatotoxin through cytochrome P450[90–92]. Direct depletion of glutathione by the formation of electrophilic metabolites seems to be the crucial step in pulegone toxicity, whereas menthofuran appears to act in a different manner[92]. Thus, replacement of sulphydryl groups by administering *N*-acetylcysteine, similar to treating paracetamol overdose, has recently been advocated as a rescue therapy in pennyroyal poisoning after immediate stomach cleansing[89]. The

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dosing, however, still remains empirical and recommendations are based on experimental data; an initial loading dose of 140 mg kg^{-1} body weight should be followed by a maintenance dose of 70 mg kg^{-1} every 4 hours. Treatment must be started promptly since otherwise oxidative damage cannot be prevented, and it should be given over a period of 24 hours. Severe toxic effects appear to arise after the ingestion of at least 10 ml and fatal hepatotoxicity may be observed after an intake of 15 ml of pennyroyal. Since pennyroyal is still widely available and its reputation remains intact this herbal drug will continue to be a public health concern.

The hepatotoxic effects of margosa oil (*Azadirachza indica*) resemble Reye's syndrome which is histologically characterized by fatty liver degeneration, structural changes of mitochondria and reduction of glycogen in hepatocytes[43,44].

Tea made of coltsfoot and *Sassafras albidum* (sassafras), the latter containing safrole, which is known to be hepatocarcinogenic in rodents, may be another source of chronic liver injury rather than a cause for an acute intoxication[7].

In overview, the frequency with which herbal drugs or supplements cause hepatic damage is not yet clear since their use is entirely uncontrolled and difficult to assess. Controlled treatment trials in diseases for which plant components claim to be effective are still lacking and the few studies so far published do not clarify the incidence of adverse effects of some plants such as Sho-seiko-to. The fact that many of the Chinese preparations have been used for centuries without revealing obvious toxicity does not free these products from being a general health problem. In this context, one should be reminded of the long-term use of tobacco products before their potential of causing cancer was detected.

Beyond that, many plant products do not seem to lead to toxic effects in everybody who takes them. They seem to be rather unpredictable and do not reveal a strict dose–effect relationship. The lack of dose dependency, which is frequently observed in most of the above-mentioned herbal compounds, does not account for mushroom poisoning – the aetiology, clinical picture and treatment of which will be described below.

Mushroom poisoning

With little variation the intake of poisonous mushrooms will inevitably lead to toxic reactions and, if taken in a particular dose, to death. Of the 5000 species of mushrooms, fewer than 100 are poisonous to humans, and less than 10 of these are deadly. The gathering and consumption of wild mushrooms, a traditional social practice in Western Europe, has become increasingly popular in the USA[93]. Although the number of fatal cases per year reported in the USA does not approach the 50–100 annual deaths occurring in Western Europe, fatal mushroom poisoning remains a serious public health concern. The American Association of Poison Control Centers registered 7976 mushroom exposures in the USA in 1993, accounting for 0.5% of all poisonings[94]. Poisonings often occur in amateur mushroom hunters who fail to distinguish edible and non-edible varieties of mushrooms. In addition, immigrants may come from areas where only edible look-alikes exist. Unsupervised children and those looking for hallucinogenic substances may be poisoned as well. Many mushroom poisonings involve young children left unattended outdoors who are later found with mushrooms in their mouths. These exposures are rarely serious, because most lawn mushrooms are innocuous, medical evaluation is quickly sought, and fresh specimens of the mushroom are usually available for analysis. Adult exposures tend to be more serious because mushrooms usually have been eaten in large quantities and were collected in the forest where poisonous species are more likely to exist. Adults often present a longer time after ingestion and may eat more than one species of mushroom, which may lead to confusing clinical presentation[93,95].

Amanita phalloides

Most severe mushroom poisonings are caused by the *Amanita* species, which contain amatoxin, one of the most potent toxins known. Two distinct groups of toxins can be isolated from *Amanita*. Phalloidin, first identified by Wieland[96] in 1937, is a cyclic heptapeptide with a molecular weight of 900. The toxicity of phalloidin has been shown to reside in the thiomide bond of the sulphur atom on the indole ring[97]. The actin polymerization–depolymerization cycle is interrupted, thus impairing cell membrane function[98]. Clinically, this compound induces the initial symptoms of gastroenteritis, which will be discussed subsequently.

Amanitins (primarily α-amanitin) constitute a second group of *Amanita* toxins. α-amanitin is a thermostable, easily dialysable octapeptide, that also has a molecular weight in the range of 900. It is the compound responsible for the severe liver, kidney and brain damage that often leads to a patients's death. Considerable work has been done to elucidate the mechanism of α-amanitin toxicity. Approximately 0.2–0.4 mg of the compound can be recovered from 1 g of fresh *A. phalloides*[99]. α-amanitin is readily absorbed through the intestinal epithelium and despite initial evidence to the contrary, binds very weakly to serum proteins[99]. It penetrates cells very rapidly and, in the case of hepatocytes, is transported across the cell membrane by the same system that mediates the flux of bile salts under physiological conditions[99]. The cytotoxic effect of α-amanitin is due to an inhibition of RNA polymerase II[98]. The amatoxin binds 1 : 1 with the 140 000 molecular weight subunit of RNA polymerase II. Subsequent interference with messenger RNA synthesis and ultimately the production of vital structural proteins results

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in cell necrosis. Tissues that characteristically maintain high rates of protein synthesis incorporate the toxin and manifest its effects early. As mentioned previously, the liver and kidney are primary targets for the toxin. In the case of the liver, hepatocytes are damaged early, while the hepatic sinusoids are spared[97]. When the hepatic parenchyma is examined microscopically, one notes fatty degeneration, as well as an abnormal concentration of lipids and carbohydrates in the cell nuclei[97]. A pattern of centrilobular necrosis with haemorrhage is typical in these cases. Approximately 60% of the absorbed α-amanitin is excreted into the bile and subsequently returns to the liver via the enterohepatic circulation[99]. In humans (unlike mice and rats that do not absorb these toxins from the gastrointestinal tract), this is a significant route of continued toxin exposure that must be considered in the treatment of poisoning. Aside from the liver and the kidneys, other organs affected by α-amanitin include the pancreas, testes and the haematopoietic system.

Clinical presentation

Poisoning with non-lethal poisonous mushrooms produces crampy abdominal pain, nausea, emesis and watery diarrhoea soon after ingestion. With *Amanita* poisoning, patients exhibit signs and symptoms that typically occur in stages. The lethal dose is about 50 g, which corresponds to three medium-sized mushrooms. There is an initial latent asymptomatic period of 6–24 hours; 12–24 hours of severe gastrointestinal symptoms ensue with the patients often being misdiagnosed with viral gastroenteritis. A second latent phase follows with improvement of gastrointestinal symptoms, but the development of abnormal liver chemistry tests. A hepatic phase occurs 48–96 hours after ingestion with precipitous elevation of serum aminotransferases into the thousands, coagulopathy and jaundice. Fulminant hepatic failure (FHF) develops rapidly, occurring 6–16 days after ingestion[93,101]. Renal failure secondary to FHF or to direct nephrotoxicity of amatoxin also develops. Half of the patients with *Amanita* poisoning have clinical or biochemical evidence of pancreatitis[93,101].

Treatment

Establishing a rational protocol for the treatment of patients with documented *Amanita* poisoning has been hampered by the paucity of controlled clinical trials comparing the various therapeutic modalities. Although specific modalities are debated, one can summarize the therapeutic goals as follows: (i) evacuation of *Amanita* from the gastrointestinal tract before toxins are absorbed into the blood stream; (ii) fluid and electrolyte resuscitation; (iii) elimination of *Amanita* toxins from blood and tissues; (iv) prevention of enterohepatic recirculation; (v) protection of the liver and other organs from the toxic effects of the amanitins and their metabolites; and (vi) treatment of coagulopathy and encephalopathy secondary to liver failure.

The induction of emesis following the ingestion of poisonous mushrooms will significantly reduce the toxin load of the patient. Unfortunately, in the case of *Amanita* most patients present 6–8 hours after the meal, and such methods are of limited usefulness. None the less, the insertion of a large-bore nasogastric tube and aspiration of the remaining mushroom fragments immediately upon presentation is recommended[102–106].

The cholera-type diarrhoea seen most commonly as an effect of phalloidin during the first 24 hours of illness produces a profound metabolic alkalosis, requiring vigorous fluid replacement and electrolyte substitution. The magnitude of the metabolic imbalance has no prognostic value. The most reliable indicator is the prothrombin time[106]. The toxins are easily dialysable and, thus, early charcoal haemoperfusion or haemodialysis might be expected to remove the toxin. Wauters *et al.* described seven patients who ingested a supposedly lethal dose of *A. phalloides*[107]. They were treated with charcoal haemoperfusion and survived, but other studies have not supported the effectiveness of this therapy, and there is little evidence that significant quantities of the toxin are actually removed by this therapeutical approach. In the later stages of the intoxication process, when hepatic failure and encephalopathy are present, the fluid shifts that often accompany such treatment may be harmful or even lethal. After evacuation of the stomach, however, the administration of charcoal via a nasogastric tube is recommended.

Apart from the above, a number of pharmaceuticals have been tested both clinically and under laboratory conditions, and many have a role to play.

1. *Cytochrome C.* A study by Floersheim indicated a protective effect of cytochrome C in mice given intravenous α-amanitin[108]. Clinical trials of cytochrome C alone or in combination with steroids have shown no beneficial effects.

2. *Penicillin.* Penicillin has perhaps the most broadly based support amongst laboratory investigators. Scientific evidence exists to support the fact that penicillin: (i) displaces amanitin from plasma protein-binding sites and thus allows for increased renal excretion; (ii) does not displace amanitin from plasma proteins but may bind to acid amanitin and phallotoxins; (iii) works primarily at an intracellular level rather than affecting the binding or uptake of amanitin[95]; (iv) inhibits the penetration of amanitin into hepatocytes; and (v) kills certain enteric bacteria that produce γ-aminobutyric acid, an inhibitory neurotransmitter poorly metabolized in liver failure and implicated in portosystemic encephalopathy. The clinical evidence supporting penicillin's efficiency is encouraging, especially when therapy combines penicillin with silymarin[109,110].

3. *Silymarin.* This may exert its hepatoprotective effects at several levels as it has been shown to: (i) interrupt

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enterohepatic recirculation of amanitin; (ii) inhibit the binding of both phalloidin and α-amanitin to hepatocyte membranes; (iii) compete with amatoxins for the transmembranous transport systems; and (vi) inhibit the inoculation of amatoxins into liver cells[99,109]. Silibinin is a water-soluble preparation of silymarin. One clinical study reports 205 patients with *Amanita* poisoning, 46 of whom died. Among the 16 subjects who received silibinin in doses of 20–50 mg kg^{-1} day^{-1}, there were no fatalities[106].

4. *Thioctic acid*. This compound was isolated in 1951 as a cofactor for oxidation–decarboxylation reactions. It has been shown to stimulate prostaglandin-producing cyclooxygenase; furthermore is a cofactor in the citric acid cycle and probably acts as an anti-inflammatory agent[111]. Several European studies have reported exceptionally high survival rates in *Amanita* poisoning victims treated with thioctic acid.

5. *Orthotopic liver transplantation*. As recently as 1989, it was suggested that 'the role of liver transplantation in amatoxin-poisoned patients, once they are obviously in fulminant liver failure remains to be established'[105]. This statement was based largely on the 1983 National Institute of Health consensus study indicating that fulminant hepatitis and multiorgan system failure preclude OLT. *Amanita* intoxication differs from infectious hepatitis and most other aetiologies of liver failure, at least as far as the significance of hepatic encephalopathy is concerned. Once hepatic coma develops in a patient who ingested *Amanita* mushrooms, the chances of survival with medical therapy alone are practically nil[105]. In this sense, such individuals resemble those who take a paracetamol overdose with suicidal intentions. Individuals who experience progression to stage II encephalopathy or beyond in the setting of *Amanita* poisoning should be considered candidates for OLT as well as patients with a realistic recovery potential. It is a frequent observation that other organ dysfunctions such as kidney failure due to hepatorenal syndrome will also improve along with the transplanted liver. Indicators for irreversible liver failure are the prolongation of prothrombin time greater than two times the normal, despite vigorous replacement with fresh-frozen plasma, hypoglycaemia requiring parenteral glucose support, and serum bilirubin levels greater than 25 mg dl^{-1}. Following these guidelines, long-term survival is excellent when compared to other causes of liver disease treated with OLT[112].

As a conclusion, patients who require therapy for *Amanita* intoxication have a realistic chance of survival if medical treatment is commenced early and if they are referred to a specialized centre with linkage to a liver transplant unit as soon as possible.

Conclusions

Liver abnormalities due to conventional medication is widely acknowledged, whereas toxicity from botanical components has been underestimated due to the perception that drugs made from plants are absolutely safe. However, severe liver injury has been described after the ingestion of a large array of different herbal preparations and other botanical ingredients such as mushrooms. These include acute and chronic hepatic abnormalities and even cirrhotic transformation and liver failure mimicking other causes of liver damage.

Chinese herbal medicines have been shown to contain hepatotoxic ingredients but pathomechanisms and crucial ingredients are still unclear since the drug preparations reveal striking inconsistencies with regard to composition, dosage and contamination by other chemicals. On the other hand, hepatoprotective properties of some compounds have also been detected that render the picture even more confusing. Pyrrolizidine alkaloids including comfrey have long been known to cause VOD. *Teucrium chamaedrys*, commonly named germander, was withdrawn from the health market after large-scale intake for the treatment of obesity had led to numerous cases of hepatitis and even cirrhosis. Massive hepatocellular necrosis and a less fulminant picture of liver damage were observed in connection with chaparral. Other potentially hepatotoxic plants include *Atractylis gummifera*, *Callilepsis laureola*, *Scutellaria* species, senna and even such frequently used plants as valerian and mistletoe.

Mushroom poisoning is mostly due to the accidental consumption of *Amanita* species which leads to a characteristic clinical picture and for which active treatment exists. Application of silymarin, thioctic acid, penicillin and liver transplantation have been shown to be effective but require early diagnosis.

The aim of this review is to summarize the current knowledge about liver damage associated with the intake of botanical ingredients and to increase the awareness that chemicals contained in plants – generally believed to be harmless – may certainly be harmful under certain conditions just as conventional drugs are.

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