The efficacy and safety of comfrey

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Abstract
Herbal medication has gathered increasing recognition in recent years with regard to both treatment options and health hazards. Pyrrolizidine alkaloids have been associated with substantial toxicity after their ingestion as tea and in the setting of contaminated cereals have led to endemic outbreaks in Jamaica, India and Afghanistan. In Western Europe, comfrey has been applied for inflammatory disorders such as arthritis, thrombophlebitis and gout and as a treatment for diarrhoea. Only recently was the use of comfrey leaves recognized as a substantial health hazard with hepatic toxicity in humans and carcinogenic potential in rodents. These effects are most likely due to various hepatotoxic pyrrolizidine alkaloids such as lasiocarpine and symphytine, and their related N-oxides. The mechanisms by which toxicity and mutagenicity are conveyed are still not fully understood, but seem to be mediated through a toxic mechanism related to the biotransformation of alkaloids by hepatic microsomal enzymes. This produces highly reactive pyrroles which act as powerful alkylating agents. The main liver injury caused by comfrey (Symphytum officinale) is veno-occlusive disease, a non-thrombotic obliteration of small hepatic veins leading to cirrhosis and eventually liver failure. Patients may present with either acute or chronic clinical signs with portal hypertension, hepatomegaly and abdominal pain as the main features. Therapeutic approaches include avoiding intake and, if hepatic failure is imminent, liver transplantation. In view of the known serious hazards and the ban on distributing comfrey in Germany and Canada, it is difficult to understand why comfrey is still freely available in the United States.

Keywords
Comfrey
Veno-occlusive disease
Herbal medicine
Pyrrolizidine alkaloids

Over thousands of years, physicians and health practitioners have treated patients with innumerable different medicinal preparations with substantially different outcomes. In the last 250 years, efforts towards a scientific treatment approach have increased our understanding of diseases and their possible cures. Many diseases have remained incurable and even relief is often unsatisfactory. In particular, chronically ill individuals, such as those suffering from cancer, AIDS and chronic inflammatory disorders, seek ‘a mental comfort from taking action’ which often seems not provided by conventional medicine1.

Recently, alternative medicine has gained increasing attention with regard to possible curative effects as well as potential health hazards. Alternative medicine comprises a wide array of approaches, of which herbal preparations are only one component aiming to give cure or improvement. The reasons for taking herbal drugs, apart from disappointment with conventional medicine, are variable and the majority of patients use herbs in a complementary fashion2. Often, patients with minor ailments, such as cold or headache, rely on herbal self-medication because professional treatment is not available or is inconvenient. Natural preparations are believed to be less toxic and may be conceived to be ‘the less aggressive way’ to handle uncomfortable but largely harmless complaints. In addition, cultural trends have made natural medicine highly fashionable, along with natural foods, physical exercise and other non-manufactured products. In medieval times, support for the use of herbs as medicines came from the Doctrine of Signatures, which proposed that God would not have created ills without plants to cure them3. More recently, the serious side effects of some conventional drugs have boosted a desire for treatments that complement nature rather than fight against it.

Herbal medicines represent a $1.8 billion market in the United States, with annual increase rates of around 20%, and studies show a use prevalence between 3% and 93% depending on the criteria applied3,4. Around 80% of the
world’s population rely primarily on herbal medicine, mainly because conventional medicine is so costly. This finding led to a recommendation for developing countries issued by the World Health Organization (WHO) to promote herbal medicine in order to ‘fulfil a need unmet by modern systems’. However, medicinal plants do contain powerful compounds, which may explain both their curative properties as well as their toxicity.

Over the last few decades, reports about severe health impairments have mounted and substances associated with various forms of toxicity have been found in herbs used in traditional Chinese medicine, germander (Teucrium chamaedrys), chaparral (Larrea tridentata), atractyllosides (Atractylis gummifera) and various other plant species such as greater celandine (Chelidonium majus), scullcap (Scutellaria spp.) and plants containing pyrrolizidine alkaloids.

The aim of the present review is to summarize the most important facts to date about the efficacy and safety of the pyrrolizidine alkaloid containing herb Symphytum officinale, commonly named comfrey.

History

Human exposure to pyrrolizidines is worldwide since these alkaloids are contained in more than 300 different plant species. Not all of these are used as herbal preparations and not all are toxic. Nevertheless, the toxicity of certain pyrrolizidine alkaloids has been recognized since 1920 after Wilmot and Robertson reported cases of ‘Senecio disease’ in South Africa, showing the development of liver cirrhosis after the ingestion of Senecio longilobus. Subsequently, other investigators showed that the liver disease observed in Senecio poisoning is characterized by an occlusion of hepatic veins resembling Budd-Chiari syndrome. Another pyrrolizidine alkaloid (Crotalaria) ingested as ‘bush tea’ led to numerous cases of veno-occlusive disease in Jamaica. In the seventies, endemic outbreaks of veno-occlusive liver disease were observed in Afghanistan and India related to the intake of Heliotropium, another plant containing pyrrolizidine alkaloids. In the latter epidemic a cereal disease were observed in Afghanistan and India related to Heliotropium. In the seventies, endemic outbreaks of veno-occlusive liver disease in Jamaica was reported. In addition, pyrrolizidine alkaloids have been recognized since 1920 after Wilmot and Robertson reported cases of Senecio disease in South Africa, showing the development of liver cirrhosis after the ingestion of Senecio longilobus. Subsequently, other investigators showed that the liver disease observed in Senecio poisoning is characterized by an occlusion of hepatic veins resembling Budd-Chiari syndrome. Another pyrrolizidine alkaloid (Crotalaria) ingested as ‘bush tea’ led to numerous cases of veno-occlusive disease in Jamaica. In the seventies, endemic outbreaks of veno-occlusive liver disease were observed in Afghanistan and India related to the intake of Heliotropium, another plant containing pyrrolizidine alkaloids.

Pyrrolizidines are the leading plant toxins associated with herb-related diseases and present a serious health hazard to humans through contamination of foodstuffs or when ingested as herbal medicines. In more recent years, toxicity of Symphytum officinale (comfrey) has been recognized. It is currently acknowledged that this particular pyrrolizidine-containing agent acts primarily as a hepatotoxin but can also be mutagenic, carcinogenic and a cause of pulmonary hypertension.

Therapeutic use

While the toxicity of Heliotropium, Senecio and Crotalaria became known as a result of accidental exposure of humans by contamination of foodstuffs or by ingestion as teas, comfrey has been applied as a therapeutic product. Symphytum spp. can be found all over Europe, Siberia (Symphytum uplandicum), North America and Asia. Comfrey belongs to the family Boraginaceae and is an evergreen perennial. It can grow to a height of 50–150 cm, has long, hairy leaves with narrowing ends, and yellowish to red-violet flowers. The term Radix consolidae is applied synonymously and it is known as comfrey root or Symphytum root. Its German and French names are Beinwellwurzel and Racine de consoude, respectively. It grows as a weed, but other Symphytum species may be cultivated as feed for animals or fertilizers (Symphytum asperum, S. uplandicum). In addition, Symphytum pergerinum is grown as a vegetable.

Symphytum officinale has a long tradition as an external treatment for inflammatory disorders of joints, wounds, gout, bone fractures, distorsions, haematomas and thrombophlebitis. It is also applied as a decoction for oral and pharyngeal gargle. For internal application, comfrey is claimed to benefit gastritis and gastroduodenal ulcers, though its effects have never been demonstrated in controlled investigations. In addition, herb practitioners recommend comfrey capsules for the treatment of rheumatoid arthritis, bronchitis, various allergies and for diarrhoea, regardless of the pathogenic cause.

The wide variability of pyrrolizidine content in various comfrey preparations makes it difficult to judge their toxic potential and most physicians, health practitioners and patients are unaware of the total amount ingested, especially when consumed on a regular basis over a long period of time. Ridker and co-workers reported the case of a woman suffering from hepatic veno-occlusive disease, who had drunk ground comfrey tea in addition to taking six comfrey–pepsin capsules daily over a 6 month period. Each comfrey pill contained 400 mg of a white powder which had a pyrrolizidine alkaloid content of 107 nmol g\(^{-1}\) and 757 nmol g\(^{-1}\) pyrrolizidine N-oxides. According to the patient’s history, she drank 480 g of ‘MU-16 herbal tea’, subsequently found to have a pyrrolizidine concentration of 23.9 nmol g\(^{-1}\) tea. Taking all preparations together, she probably consumed a daily amount of 700–740 μg (15 μg kg\(^{-1}\) body weight) of pyrrolizidine alkaloids over a period of several months. By comparison, severe liver disease from Heliotropium alkaloids has been observed after a daily dose of 30–40 μg kg\(^{-1}\) (Ref. 11). Another report from Bach et al. estimated the amount of comfrey alkaloids ingested as tea in a 47-year-old female social worker as high as 26 mg per cup based on a pharmaceutical monograph, whereas other reports show only up to 8.5 mg alkaloids per cup. The lady had consumed 10 cups a day over a period of 1 year following the
recommendations of a homeopathic doctor in order to treat vague symptoms of fatigue and allergies\textsuperscript{17}. Apparently, other preparations contain even higher concentrations\textsuperscript{21}.

The pharmacological mechanisms are based upon allantoin, which is responsible for the stimulation of connective tissue proliferation and regeneration. Anti-inflammatory properties are probably mediated through rosemarinic acid, which is also likely to account for the analgesic and astringent effects\textsuperscript{22}. These anti-phlogistic properties are not conveyed through inhibition of the arachidonic acid metabolism, but seem to be the result of inhibitory actions of plant extracts upon the classical and alternative pathway of complement activation. High molecular glycoproteins so far uncharacterized have been isolated which seem to interact with the complement factors C\textsubscript{3} and C\textsubscript{4} in a dose-dependent fashion but do not affect factors C\textsubscript{1} and C\textsubscript{2}. Other constituents of \textit{Symphytum officinale}, such as triterpenoid saponins, have antibacterial properties\textsuperscript{23} and the bidesmosidic triterpene glycoside Symphytoxide A was shown to lower blood pressure in rats through anti-cholinergic effects\textsuperscript{24}.

According to the above reference, indications for external use are traumatic and inflammatory lesions of bones, muscles and joints as well as infected skin lesions such as furunculosis, mastitis and phlebitis. The recommended mode of application is as a paste under a bandage. In this context, comfrey has anti-inflammatory and slight analgesic properties. Owing to side effects, its external use is restricted in Germany and the daily dose is limited to a maximum of 100 \(\mu\)g per day, since a considerable fraction of externally applied pyrrolizidine alkaloids is absorbed through the skin and between 0.1 and 0.4\% can be detected in urine\textsuperscript{35}.

There are no justified indications for internal use and the German Federal Institute for Drugs and Medicinal Products (BfArM) has banned the use of comfrey alkaloids for the treatment of gastritis, gastroduodenal ulcers and diarrhoea and there are no tea brands available containing comfrey. Nevertheless, sometimes the leaves are harvested and ingested as tea, albeit to a much lesser extent in Germany than in North America.

In summary, the therapeutic effects of \textit{Symphytum officinale} are exerted through plant components other than pyrrolizidine alkaloids, whereas the latter are responsible for the sometimes fatal side effects.

### Biochemistry and metabolism

More than 350 different pyrrolizidine alkaloids have been identified so far in over 6000 different plants of the Boraginaceae, Compositeae and Leguminosae families\textsuperscript{25}. Pyrrolizidine-containing plants are distributed worldwide and about half of the identified pyrrolizidines are toxic. \textit{Symphytum officinale} contains a number of chemically heterogeneous compounds (Table 1). Pyrrolizidine alkaloids and their corresponding N-oxides are of particular interest since these compounds are associated with toxicity. The parent molecule of pyrrolizidine alkaloids is shown in Fig. 1.

Even within comfrey alone, the pyrrolizidine content of this particular species may vary throughout the year and according to the age of the plant. In comfrey, there are also considerable differences in alkaloid content between the roots and aerial parts with higher contents in the former\textsuperscript{26}. Reports show a range between 0.003 and 0.115\% (dry weight) while other \textit{Symphytum} species, such as \textit{S. asperum}, contain concentrations up to 0.4\%\textsuperscript{27}.

After ingestion and uptake in the gastrointestinal tract, pyrrolizidine alkaloids undergo metabolic transformation in the liver via the action of microsomal enzymes. The main enzymatic system responsible for the detoxification of

<table>
<thead>
<tr>
<th>Table 1 Chemical constituents of \textit{Symphytum officinale}</th>
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<tr>
<td><strong>Compound</strong></td>
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<tr>
<td>Allantoin</td>
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<tr>
<td>Pyrrolizidine alkaloids (and N-oxides)</td>
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<tr>
<td>Intermedine</td>
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<td>Acetylintermedine</td>
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<td>Lycopsamine</td>
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<td>Acetylycopsamine</td>
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<td>Symphytine</td>
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<td>Echimidine</td>
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<tr>
<td>Symviridine</td>
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<td>Tannins</td>
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<tr>
<td>Fructanes (mucopolysaccharides)</td>
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<tr>
<td>Starch</td>
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<tr>
<td>Triterpenes (isobauerenole)</td>
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<tr>
<td>Triterpenoid saponins (monodesmosidic and bidesmosidic)</td>
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<tr>
<td>Hederagenin hexasaccharide</td>
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<td>Oleanolic acid</td>
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<td>Sitosterole</td>
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<tr>
<td>Lithospermic acid</td>
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<tr>
<td>Asparagine</td>
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<td>Amino acids</td>
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foreign compounds is the cytochrome P450 enzyme family, which may also form toxic compounds from previously innocuous substances. Pyrrolizidine alkaloids are metabolized by cytochrome P450 enzymes to either dehydroretronecine, a highly toxic pyrrole metabolite with alkylating properties that damages the endothelium of the liver and other organs, or into alkaloid-N-oxides (Fig. 2). The enzymatic formation of toxic necines from alkaloid-N-oxides is also possible. Enzymatically converted alkaloid metabolites may be highly reactive electrophilic compounds capable of reacting with cellular structures, forming adducts which may cause acute or chronic toxicity. Some of these adducts may be persistent in tissues and may re-induce damage long after the initial time point of ingestion. Support for the cytochrome P450-mediated activation of pyrrolizidines into their corresponding toxins comes from the observation that potent microsomal enzyme inducers, such as the anticonvulsant phenobarbital, can enhance the toxicity of pyrrolizidines. There are three essential conditions that can be held responsible for the hepatotoxicity of the pyrrolizidine alkaloid molecule: the double bond of the 1,2-unsaturated necine base, esterification of the hydroxy group in positions 9 and 7 and a branched carbon chain in at least one of the ester side chains.

Until recently, there were considerable problems in detecting pyrrolizidine alkaloids in human blood or tissue samples, whereas a method for the identification of alkaloids in plants and herbal products was developed several years ago. As early as the 1960s, pyrrolizidines were identified using spectrophotometry and subsequent improvements were possible through thin-layer chromatography and gas chromatography–mass spectrometry. Betz et al. reported the development of a capillary gas chromatography technique and subsequent identification of different alkaloids via thin-layer chromatography. More recently, a simple bioassay using a human cell line was developed to enable investigators to evaluate the mutagenic potential of various alkaloids. Lin et al. have established the first analytical method to detect pyrrolizidine alkaloids in blood samples using high performance liquid chromatography (HPLC) which now provides the first tool for a definite diagnosis of pyrrolizidine alkaloid poisoning and for the identification of alkaloids in plants or herbal products.
Toxicity

Pyrrolizidine alkaloid related toxicity may be directed against different target organs. The most frequently observed toxicity is against the liver. The main liver injury caused by comfrey and related pyrrolizidines is that of veno-occlusive disease (VOD) also termed ‘Stuart-Bras syndrome’. Pyrrolizidine-related VOD in Western countries has been recognized primarily in infants, who seem to be particularly susceptible. Other known aetiologies for VOD are cytostatic drugs, bone marrow transplantation, oral contraceptives, systemic lupus erythematosus and alcoholic hepatitis. The histologic picture is essential for the diagnosis although false negative results may occur due to sample errors. Pathologically, a thrombotic form can be distinguished from a non-thrombotic variety and both entities can be observed in pyrrolizidine-induced VOD. The toxic effects of enzymatically generated pyrolyses lead to defects of sinusoidal endothelia with increased permeability and red blood cell extravasation into the space of Disse. Subsequently, reticulin fibres are generated within the lumen of central and sublobular veins eventually followed by the obstruction of the vessels. Eventually the thickening of the venous vessel walls leads to a functional outflow obstruction and to a massive organ congestion (Fig. 3). As a result, necrosis of hepatocytes and mesenchymal cells follows. Functional cells are replaced by fibrotic tissue which shows the pattern of ‘reversed lobulation’ (fibrotic septa extending from perivenular areas rather than from the portal tracts). Signs of inflammation are usually lacking. Ultrastructural investigations revealed the occurrence of hepatocyte blebs in sinusoidal borders leading to an obstruction of sinusoids. The storage of hepatocyte blebs together with cellular debris in the perisinusoidal areas may serve as an explanation for the fact that portal hypertension becomes evident long before venous outflow obstruction has developed. The detection of hepatocyte blebs can be seen in other liver pathologies such as cholestasis, alcoholic hepatitis, transplant rejections as well as in acute Amanita phalloides intoxication. The phenomenon is commonly referred to as clasmatosis and may indicate imminent cell death as a result of either lipid peroxidation or disturbances of the extramitochondrial calcium homeostasis. In acute VOD, light-microscopical lobular architecture may be preserved but cellular plates are severely distorted by massive haemorrhagic congestion affecting predominantly zones II and III. However, reticulin accumulation or even fibrosis is not detectable in these cases and a clear-cut vascular obstruction cannot be shown.

In addition to hepatotoxicity, pyrrolizidine alkaloids have also been shown to damage the lungs. As with VOD, endothelial defects are the cause of blood cell extravasation, venous vascular occlusion and the subsequent development of pulmonary hypertension. Lung toxicity of pyrrolizidine alkaloids has only been described in experimental rodents exposed to monocrotaline, a pyrrolizidine related to comfrey. In fact, monocrotaline is used in an experimental animal model of cor pulmonale. Other potential organ toxicities include lesions to the glomeruli of the kidneys, the pancreas and the gastrointestinal tract, although all of these pathologies have so far only been seen in experimental animals.

Apart from acute and chronic organ damage, pyrrolizidine alkaloids can induce tumorigenesis, particularly in the liver. Symphytine, a major constituent of comfrey, has been associated with hepatocellular carcinoma in rats. The assumption is that the alkylating effects of the highly reactive pyrolyses metabolites lead to the cancerous transformation of hepatocytes. Metabolites of several pyrrolizidine alkaloids are mutagenic in the Salmonella typhimurium/mammalian microsome system and alkaloid extracts of Symphytum officinale induce sister chromatid exchanges as well as chromosome aberrations. This effect was even more pronounced when microsomes were induced prior to pyrrolizidine dosing. Other investigators have recently shown that pyrrolizidines enhance the proliferation of neoplastic cells while an anti-mitotic effect was observed in human T lymphocytes.

However, an association between pyrrolizidine alkaloids and cancer in humans has so far not been found. Considering the possible exposure of humans to pyrrolizidines due to their worldwide occurrence, which is comparable to what experimental animals have been dosed with, it seems unlikely that humans face a relevant threat from these chemical compounds with regard to carcinogenesis. The long-term observation of individuals who have been chronically exposed to pyrrolizidines will clarify this uncertainty.

Clinical presentation

The clinical picture of VOD is often difficult to distinguish from other liver pathologies and sometimes remains unrecognized. The first reports describe Jamaican children with ‘bush tea disease’ due to Senecio longilobus complaining about sudden abdominal right upper quadrant pain, hepatosplenomegaly and a rapid occurrence of ascites. From these observations, a classification has been established separating acute and subacute from chronic signs, the latter being characterized by a subclinical appearance. In general, the symptoms resemble those of Budd-Chiari syndrome but 10% may be asymptomatic. In acute forms, a rapid progression to cirrhosis, complicated by portal hypertension, and finally death from liver failure results in 20% of patients due to extensive hepatocyte necrosis. Chronic cases develop slowly and may only present with asthenia, fatigue, mild diarrhoea and signs of portal hypertension. In advanced liver disease, ascites, bleeding from oesophageal varices, portosystemic encephalopathy
and signs of impaired hepatic synthetic function may become intractable.

Laboratory findings show variable elevation of serum levels of transferases, alkaline phosphatase and γ-glutamyltranspeptidase. Jaundice is usually mild and shows raised indirect bilirubine levels. Thrombocytopenia develops due to splenomegaly and anaemia occurs because of intrahepatic haemolysis. Progression of fibrosis may be monitored by serum levels of procollagen-III-N-propeptide, a surrogate marker of fibrogenesis61. Hepatic vein wedge pressure is moderately to highly elevated according to a post-sinusoidal block15. Ultrasound, computer tomograms and magnetic resonance scans are not particularly helpful since the vascular lesions are sized below the discriminatory level, although changes in portal blood flow can be detected and guide diagnosis62. However, histology is mandatory for a diagnosis.

The natural course of pyrrolizidine poisoning varies as mentioned above. Spontaneous remissions have been reported but, nevertheless, mortality is approximately 50%38,63.

Table 2 Management of veno-occlusive disease

<table>
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<th>Management of hepatic veno-occlusive disease</th>
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<tr>
<td><strong>Conservative</strong></td>
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<tr>
<td>Avoiding further exposure to toxin</td>
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<tr>
<td>Sodium restriction</td>
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<tr>
<td>Fluid restriction</td>
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<tr>
<td>Aldosterone-antagonists (Spironolactone)</td>
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<tr>
<td>Reduction of portal pressure with Nitrates, Molsidomine, Propranolol, Nadolol, Losartan (?)</td>
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<tr>
<td>Avoidance of prostaglandin inhibitors (Diclofenac, Ibuprofen)</td>
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<tr>
<td>Avoidance of sedatives (especially benzodiazepines)</td>
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<tr>
<td>Nutritional support (sufficient protein supply and carbohydrates)</td>
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<tr>
<td><strong>Interventional</strong></td>
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<tr>
<td>Removal of ascites via paracentesis (effective and safe)</td>
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<tr>
<td>Endoscopic treatment of bleeding complications</td>
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<tr>
<td>Transjugular intrahepatic portosystemic shunt (TIPS)</td>
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<td>Surgical shunts (Denver shunt)</td>
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<td>Orthotopic liver transplantation</td>
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Conclusion

Hepatotoxicity following the intake of pyrrolizidine alkaloids including comfrey is established. However, the dose–effect relationship remains unclear and differences in inter-individual susceptibility are high. The frequency with which comfrey alkaloids and other plant medicines cause organ damage still remains unclear. Hepatotoxicity in particular may easily be misinterpreted as the result of other aetiologic factors, e.g. alcoholic liver disease, a tendency frequently noticed in physicians when standard causes of liver disease cannot be identified. However, controlled trials addressing diseases for which herbal drugs are acclaimed to be effective are mostly lacking and dose-finding studies are not available. To date, the effectiveness of comfrey has not been studied but the proven hazardous effects are far more numerous than those showing a benefit.

Hepatotoxic effects of conventional drugs are widely acknowledged and most physicians are well aware of them, but the side effects of herbal preparations have not always reached public awareness. As with conventional drugs, interactions with other prescribed medication cannot be ruled out. Lack of awareness is even more
profound in patients who take herbs mostly for self-medication, with obvious dangers. First, the assumed diagnosis, for which the patient takes herbs, might be wrong. Second, the chosen medication might not be optimal, possibly delaying appropriate treatment. Toxicity symptoms and side effects may occur, but some people even increase the dose of the herbal product as a response to the onset of symptoms.

These concerns may not hold for many herbal products that are distributed on the market but comfrey definitely belongs to a potentially dangerous kind. One should follow the simple but effective rules offered by Ryan Huxtable: do not use herbal drugs in infants and children; avoid medication with herbs during pregnancy and while nursing; do not take herbs on a regular basis and in large quantities; and lastly, beware of taking comfrey.

Acknowledgements

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References

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