# Comfrey toxicity revisited

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**Comfrey is a herbal medicine with a history of efficacious use in humans. However, owing to the presence in comfrey of pyrrolizidine alkaloids (PAs), which are compounds known to be hepatotoxic, many countries have restricted its availability. This review emphasizes crucial aspects of PA toxicity, and suggests that comfrey might not be as dangerous to humans as current restrictions indicate.**

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Comfrey is a common garden plant that has been used as a herbal medicine for >2000 years. Comfrey leaf and root are used by the lay public, herbalists and some physicians for the treatment of broken bones, tendon damage, ulcerations in the gastrointestinal tract, and lung congestion. Typical daily doses of the leaf range from 5 to 30 g, but daily doses of the root are generally lower (0.5–10.0 g). In addition, comfrey can be applied externally to promote wound healing and/or reduce joint inflammation. Comfrey is also rich in many crucial nutrients, such as protein, antioxidant vitamins and vitamin B12, and is a common component in the diet of certain ethnic groups [1].

## Comfrey use restricted

In addition to essential nutrients, comfrey also contains pyrrolizidine alkaloids (PAs). A recent review emphasized the health risks associated with oral consumption of the PAs found in comfrey [2]. The distribution of comfrey in Canada has been restricted, and its use in Germany is limited to external products, provided that normal use results in a daily dose of <100 μg PAs. In the USA, the Food and Drug Administration has requested voluntary compliance for removal of products containing comfrey. Moreover, in the UK, the Medicine Control Agency recently included comfrey in a list of herbs under consideration for restriction to physician prescription only.

One might expect that new toxicity research or an unacceptable number of adverse reactions prompted these recent actions, but neither is the case. The most recent original research regarding comfrey toxicity was published in the early 1990s [2]. More recent research has been designed to examine the therapeutic actions of comfrey. Indeed, there is limited evidence to support anti-inflammatory [3–6], wound healing [7–8], and immune-modulating [9–11] effects.

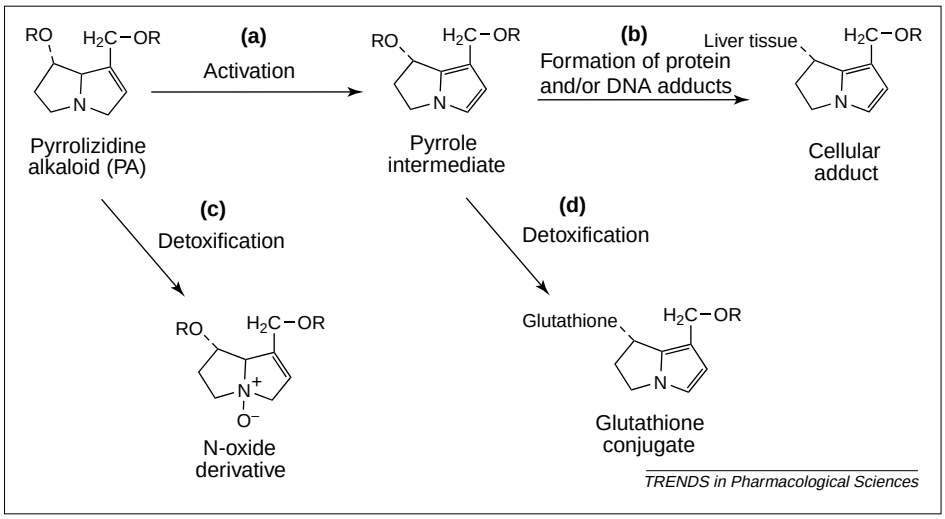


Fig. 1. Activation and detoxification of pyrrolizidine alkaloids (PAs). Pyrrolizidine alkaloids are (a) dehydrogenated to produce a pyrrole intermediate, which then (b) reacts with protein or DNA to form a cellular adduct. Alternatively, detoxification occurs when the PA undergoes (c) N-oxidation or (d) the pyrrole is conjugated with glutathione.

## Human toxicity reports

Although there have been no recent reports of adverse reaction to comfrey, over a decade ago, several cases of veno-occlusive disease (VOD) associated with comfrey ingestion were reported [2]. These case studies support that underlying illness, nutritional status and the concurrent use of hepatotoxic drugs increase the likelihood of VOD development when using PA-containing drugs.

In the clinical setting, hepatic function is commonly assessed by monitoring the serum concentrations of proteins of hepatic origin. For example, elevations in aspartate aminotransferase (AST) might reflect liver pathology, γ-glutamyltransferase (GGT) and bilirubin are elevated with choleostasis, and α-fetoprotein (AFP) is a specific marker for liver cancer. Although these markers are not necessarily elevated in every case of VOD, Anderson and colleagues determined the serum concentration of AST, GGT and bilirubin in 29 long-term comfrey users, and AFP in a subgroup of seven comfrey users. Although this cohort is too small to ascertain risk, it is interesting that AST, GGT, bilirubin and AFP were considered normal, even after prolonged consumption of comfrey leaf (0.5–25 g $day^{-1}$ for 1–30 years) [12].

## Limitations of toxicity research

The conclusion that comfrey is not safe for internal use in humans is primarily based on studies in which high levels of purified PAs were administered to rodents. Systematic toxicity testing or clinical trials have not been performed. Although PA poisoning in humans can occur, this is most commonly a consequence of consumption of plants other than comfrey [13]. Heavy reliance on data obtained from experiments conducted using rodents or from human poisonings by other plants, is probably not an accurate reflection of the risk and/or therapeutic benefit of comfrey in humans.

### *Not all PAs have similar toxicity*

In the liver, PAs are transformed to pyrroles by mixed-function oxidases. Pyrroles exert their toxic effect by reacting with and binding to cellular macromolecules, including proteins and DNA [14] (Fig. 1). These cellular adducts might be acutely toxic, causing VOD, or perivenular fibrosis (with symptoms that would be

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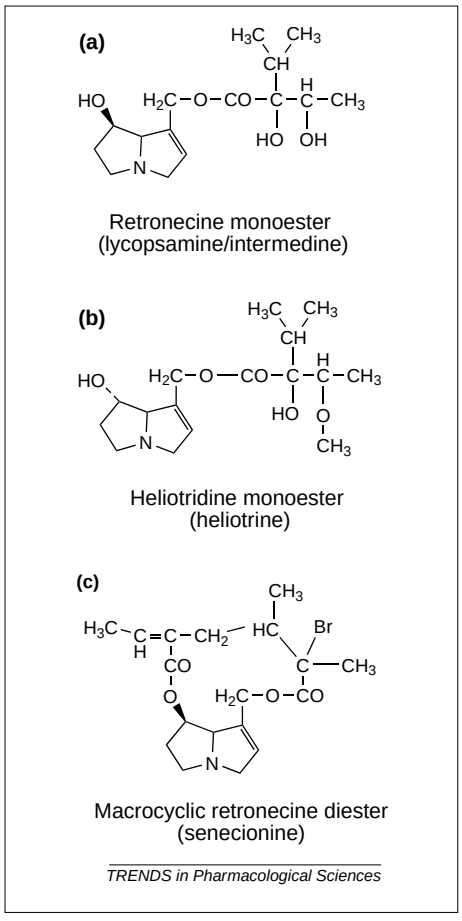


Fig. 2. Representative pyrrolizidine alkaloid (PA) structures and their relative toxicity. (a) Retronecine monoesters display the lowest toxicity to 14-day-old rats. (b) Heliotridine monoesters 2–4 times as toxic as the retronecine monoesters, and diesters of both retronecine and heliotridine are 4 times as toxic as corresponding monoesters. (c) The most toxic PAs are the macrocyclic diesters.

indistinguishable from cirrhosis) [14]. Alternatively, the PA, or its active metabolite, could be processed into soluble metabolites and excreted in urine [14] (Fig. 1).

The structure of PAs defines the stability of the resulting pyrrole and the extent of damage it could induce. The relationship between structure and toxicity has been elucidated (Fig. 2). The most hepatotoxic alkaloids are macrocyclic diesters [13]. Additionally, Culvenor *et al.* [15] report that diesters of heliotridine and retronecine are four times as toxic as the respective monoesters, and heliotridine esters are 2–4 times as toxic as retronecine esters. These structure–toxicity relationships place comfrey PAs (retronecine mono and diesters) in a class of lower toxicity compared with the PAs implicated in human poisonings that have occurred worldwide owing to *Senecio*, *Heliotropium* and *Crotolaria* (heliotridine diesters and macrocyclic diesters of retronecine) [13].

### *Not all animal models are susceptible to PA toxicity*

The response of different animal species to PAs varies tremendously. Pigs, chickens and rats are highly sensitive to poisoning by *Senecio*, whereas mice and sheep are resistant (Table 1). Moreover, the response of a species to *Senecio* might not reflect its susceptibility to other PAs. For example, guinea-pigs are susceptible to *Senecio*, but resistant to monocrotaline [13]. Additionally, the route of administration can dramatically affect the toxic response. For example, rabbits are relatively resistant to chronic feeding of *Senecio*, but are killed by a single injection of the purified alkaloids [16].

Despite their sensitivity to PAs, pigs readily accept comfrey and show no adverse effects, even when comfrey represents 40% of their diet [1]. Chickens, another sensitive species, also show no ill effects when fed comfrey [1]. By contrast, rats appear to be sensitive to the PAs in comfrey. Indeed, when rats consume high levels of comfrey or are injected with purified comfrey PAs, they develop liver tumors and hepatic lesions indicative of PA poisoning [2]. However, rats might not be an appropriate human model because their hepatic response to PAs seems to differ from the human response [17].

### *Comfrey species vary in their content of PAs*

Comfrey (*Symphytum* spp.) contains seven PAs: intermedine, lycopsamine, acetyl intermedine, acetyl lycopsamine, symlandine, symphytine and echimidine. However, nearly all (85–97%) of the PAs in the comfrey commonly grown in US gardens (*Symphytum officinale* L.) are retronecine monoesters or are readily hydrolyzed to monoesters [18]. The remaining constituents are retronecine diesters. By contrast, Russian comfrey (*Symphytum x uplanidicum* Nym.) contains a high proportion of the slightly more toxic retronecine diester form of PA [18]. Owing to the established differences in toxicity of different members of the PA family, and the heterogeneous distribution of PAs among comfrey species, research regarding one comfrey species might not accurately reflect the results that would be obtained using an alternate species. In addition, misidentification could occur unless rigorous standards of botanical classification are followed.

**Table 1. Comparative ranking of animals based on susceptibility to poisoning by *Senecio jacobaea***

| Animal | Chronic lethal dose (% of body weight) | Refs |
|---|---|---|
| Pig | 1[a] | [20] |
| Cow | 4 | [13] |
| Chicken | 5 | [20] |
| Horse | 7 | [13] |
| Rat | 21 | [13] |
| Rabbit | 115 | [13] |
| Guinea-pig | 119 | [13] |
| Mouse | 150 | [20] |
| Goat | 205 | [13] |
| Sheep | 302 | [13] |
| Hamster | 338 | [13] |
| Gerbils | >3640 | [13] |

[a]Pig susceptibility is based on Crotalaria retusa poisoning.

### *Isolated PA might not be representative of whole plant use*

The formation of PA toxic metabolites is attenuated by concurrent administration of sulfur-containing amino acids such as methionine or cysteine [13]. Indeed, diets low in protein enhance the toxic effects of PAs [19]. Fortunately, dry comfrey leaf is rich in protein (35%) and sulfur-containing amino acids [1]. Most toxicity studies have examined the response to administration of purified PAs. Given the protective effect of the sulfur-containing amino acids, studies using purified PAs probably overstate the health risk associated with administration of crude comfrey extracts or ingestion of the whole plant.

## Concluding remarks

Comfrey is an herbal medicine with a history of effective therapeutic use in humans. It has documented anti-inflammatory and wound-healing properties and many holistic healthcare providers view comfrey as a crucial element in their repertoire of herbal therapies for treating injury and disease in humans. However, because PAs are an intrinsic component of comfrey, its therapeutic use might increase the risk of liver toxicity. Clearly, the risk of hepatic damage during treatment with comfrey will be influenced by its source, the amount consumed, the duration of treatment, and the health and nutritional status of the patient. However, the information currently available is not sufficient to permit an accurate assessment of the

risks or potential therapeutic benefits of comfrey. A more precise and credible measure of health benefits would ensure appropriate use by herbalists and medical practitioners.

Research to date has often been flawed by the use of inappropriate animal models and faulty experimental design. Correct botanical identification and analysis of the plant material for PA content and profile is essential. In addition, animal species vary widely in their susceptibility to PA toxicity, and the toxic response is dependent on the specific PA. Therefore, it seems imperative that toxicity testing be conducted in several animal species.

Perhaps the most direct approach to assessing the benefits and attendant risks of the therapeutic use of comfrey would be to screen the current population of comfrey users. A direct determination of risk would offer the greatest protection to individuals currently consuming comfrey, and provide the information required for placebo-controlled prospective clinical studies designed to determine efficacy and define safe use.

**References**


1 Hills, L.D. (1976) *Comfrey*, Faber and Faber, London
2 Stickel, F. and Seitz, H.K. (2000) The efficacy and safety of comfrey. *Public Health Nutrition* 3, 501–508
3 Lohmann, K. *et al.* (2000) Screening of European anti-inflammatory herbal drugs for inhibition of cyclooxygenase-1 and -2. *Phytomedicine* 7 (Suppl. 2), 99
4 Hiermann, A. and Writzel, M. (1998) Antiphlogistic glycopeptide from the roots of *Symphytum officinale*. *Pharm. and Pharmacol. Lett.* 8, 154–157
5 Tunon, H. *et al.* (1995) Evaluation of anti-inflammatory activity of some Swedish medicinal plants. Inhibition of prostaglandin biosynthesis and PAF-induced exocytosis. *J. Ethnopharmacol.* 48, 61–76
6 Andres, R. *et al.* (1990) The antiphlogistic efficacy of dermatics containing pyrrolizidine alkaloid-free extracts of *Symphytum officinale*. *Planta. Med.* 56, 664
7 Goldman, R.S. *et al.* (1986) Wound healing and analgesic effect of crude extracts of *Symphytum officinale* in rats. *Fitoterapia* 56, 323–330
8 Gafar, M. *et al.* (1989) Apiphytotherapeutic original preparations in the treatment of chronic marginal parodontopathies. A clinical and microbiological study. *Stomatologie* 36, 91–98
9 Van den Dungen, F. *et al.* (1991) High molecular weight complement inhibitors of *Symphytum officinale*. *Clin. Exp. Immunol.* 86 (Suppl. 1), 3
10 Makhatadze, M. *et al.* (1993) Immunopharmacologic study of glucofructan from *Symphytum asperum* roots. *Ann. New York Acad. Sci.* 685, 383–385
11 Lenghel, V. *et al.* (1995) The influence of some vegetable extracts on the *in vitro* adherence of mouse and human lymphocytes to nylon fibers. *Roum. Arch. Microbiol. Immunol.* 54, 15–30
12 Anderson, P. and McLean, A.E.M. (1989) Comfrey and liver damage. *Hum. Toxicol.* 8, 68–69
13 Cheeke, P.R. (1998) Pyrrolizidine alkaloids. In *Natural Toxicants in Feeds, Forages, and Poisonous Plants* (2nd ed.), pp. 338–352, Interstate Publishers, Danville, IL, USA
14 Stegelmeier, B.L. *et al.* (1999) Pyrrolizidine alkaloid plants, metabolism and toxicity. *J. Nat. Tox.* 8, 95–116
15 Culvenor, C.C. *et al.* (1976) Hepato- and pneumotoxicity of pyrrolizidine alkaloids and derivatives in relation to molecular structure. *Chem. Biol. Interact.* 12, 299–324
16 Pierson, M.L. *et al.* (1977) Resistance of the rabbit to dietary pyrrolizidine (Senecio) alkaloid. *Res. Commun. Chem. Pathol. Pharmacol.* 16, 561–564
17 Prakash, A.S. *et al.* (1999) Pyrrolizidine alkaloids in human diet. *Mutat. Res.* 443, 53–67
18 Muetterlein, R. and Arnold, C-G. (1993) Investigations concerning the content and the pattern of pyrrolizidine alkaloids in *Symphytum officalene* L. (comfrey). *Pharmazeutische Zeitung* 138, 119–125
19 Schoental, R. (1968) Toxicology and carcinogenic action of pyrrolizidine alkaloids. *Cancer Res.* 28, 2237–2246
20 Hooper, P.T. (1977) Pyrrolizidine alkaloid poisoning – pathology with particular reference to differences in animal and plant species. In *Effects of Poisonous Plants on Livestock* (Keeler, R.F. *et al.*, eds), pp. 161–176, Academic Press



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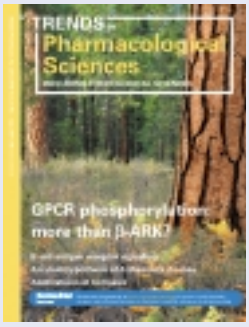



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