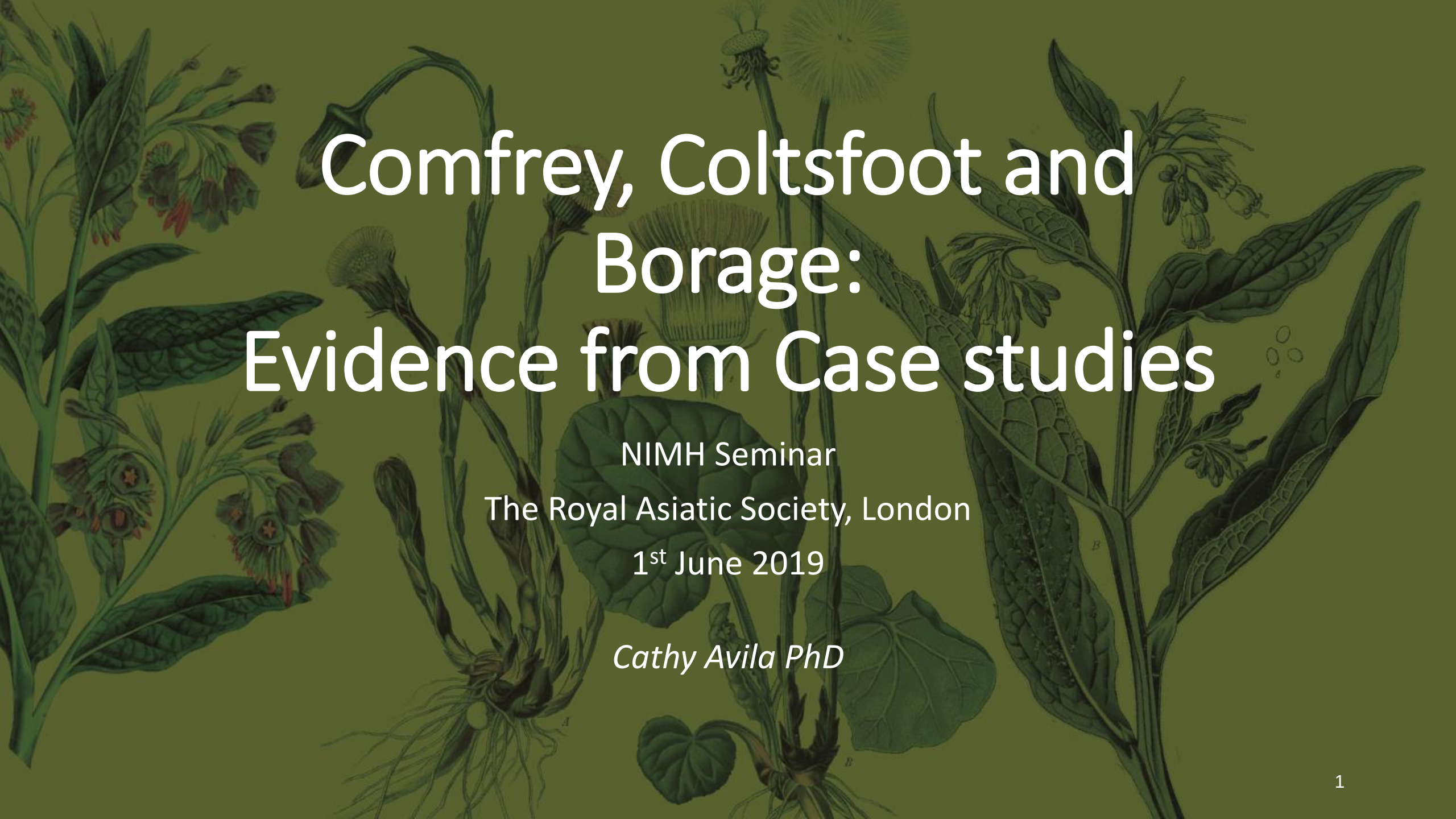


Comfrey, Coltsfoot and Borage: Evidence from Case studies

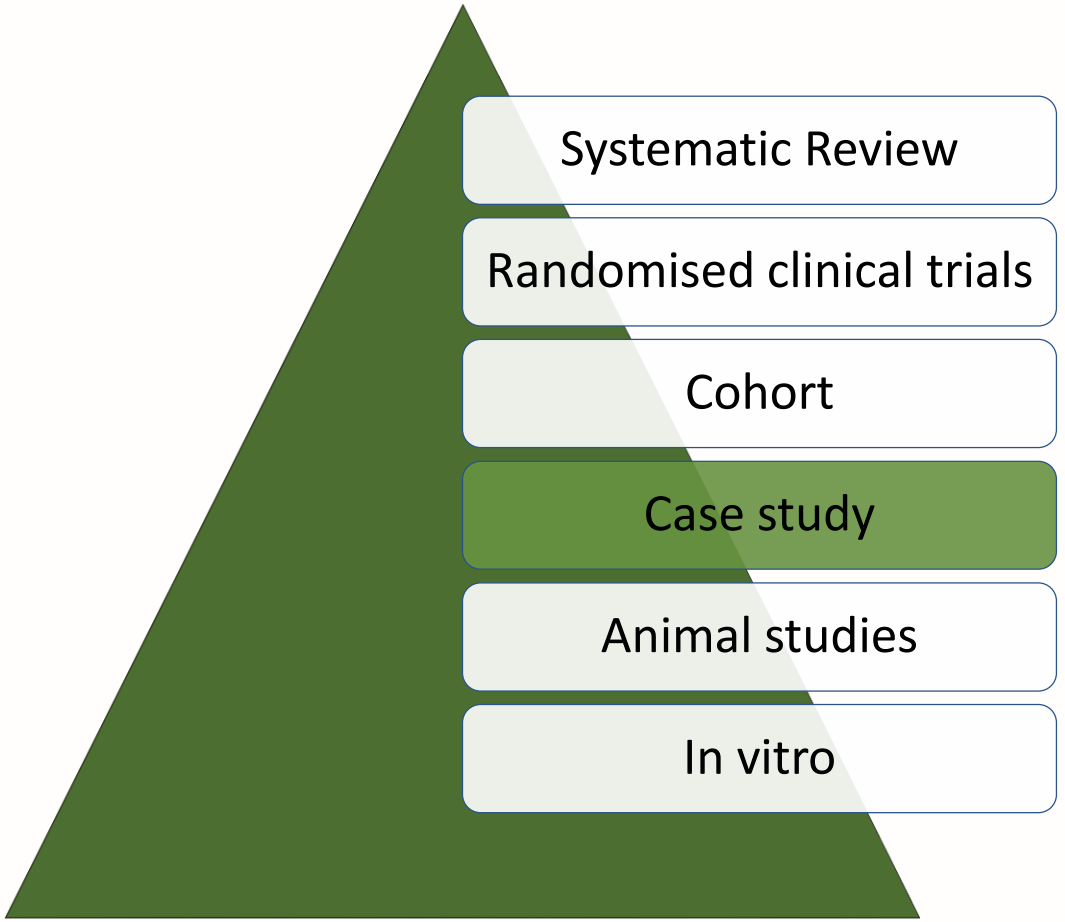
NIMH Seminar

The Royal Asiatic Society, London

1st June 2019

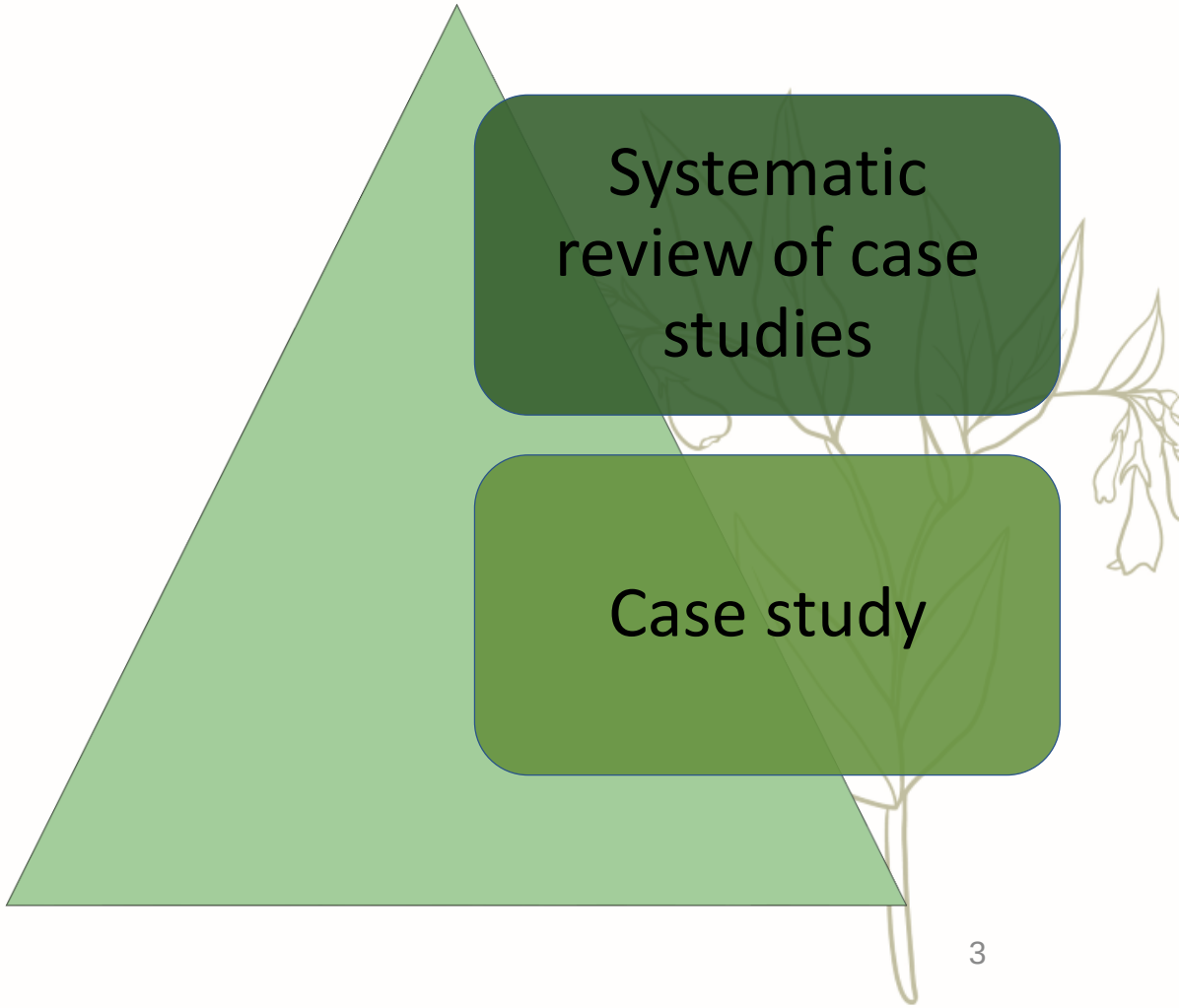
Cathy Avila PhD

Where is the evidence about the safety of consumption by humans?



Systematic Review of Case studies

- **Systematic and replicable**
  - Extensive search
  - Extraction of data
  - Validated instruments
    - Quality of reporting
    - Estimated strength of association
  - Independent assessment



The cases

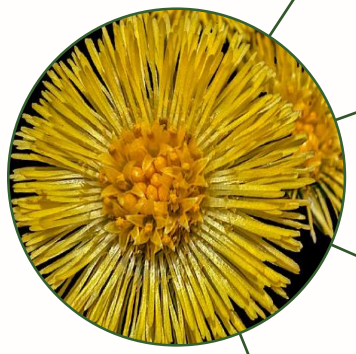
Eleven cases published between 1985-2013

Gender
- 4 female
- 3 male

Age range
- 5 days
- 77 years

Organ
- 6 hepatic
- 1 pulmonary

Sequel
- 4 recovered
- 1 partial
- 2 deaths



Gender
- 1 female
- I male

Age range
- 27 week foetus
- 63 years

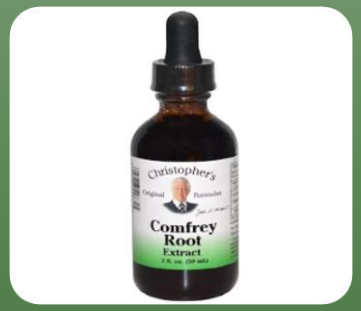
Organ
- 2 hepatic

Sequel
- 1 recovered
- 1 partial
- 1 death

Credible evidence: a quality case

Who?

- Health at time of initiation
- Medical history
- Pre-existing condition, lifestyle



What?

- Identification of plant material, dose, duration
- Concomitant medications

What happened?

- Signs and symptoms
- Pathology results
- Dechallenge, rechallenge

Quality Assessment of Case Reports of Adverse Events Instrument (QCRAEI) Agbabiaka et al., 2008

Category	Question	Rating (please tick one box) Yes	Unclear	No	Item Score
I Information about the medicinal product and treatment	***A – Drug information***				
	Are the following details reported?				
	1. Drug name (i.e. International Nonproprietary Name INN or generic name)				
	2. Brand name and/or manufacturer				
	B – Therapeutic regimen				
	Are the following details reported?				
	3. Daily dose and dosing regimen				
	4. Route of administration *(i.e. oral, subcutaneous)*				
	5. Length of treatment period *(dates and duration of treatment)*				
II Patient history, diagnosis, medical condition(s) and medications	***B – Concurrent diseases and/or medical conditions:***				
	8. Are concurrent diseases and/or medical conditions reported (including and allergies)? *(If explicitly stated that there were none, give 2 points)*				
	C – Quality Assessment of Case Reports of Adverse Events Instrument				
	9. Are concurrent diseases analysed/considered with regards to their relevance to the AE?				

Roussel Uclaf Causality Assess-ment Method (**RUCAM**) in Drug Induced Liver Injury

Worksheet available from https://livertox.nih.gov/rucam.html

RUCAM Causality Assessment

Drug: _____ Initial ALT: _____ Initial Alk P: _____ R ratio = [ALT/ULN] ÷ [Alk P/ULN] = _____ ÷ _____ = _____

The R ratio determines whether the injury is hepatocellular (R > 5.0), cholestatic (R < 2.0), or mixed (R = 2.0 – 5.0)

	Hepatocellular Type		Cholestatic or Mixed Type		Assessment
1. Time to onset					
	Initial Treatment	**Subsequent Treatment**	**Initial Treatment**	**Subsequent Treatment**	**Score (check one only)**
○ From the beginning of the drug:					
• Suggestive	5 – 90 days	1 – 15 days	5 – 90 days	1 – 90 days	☐ +2
• Compatible	< 5 or > 90 days	> 15 days	< 5 or > 90 days	> 90 days	☐ +1
○ From cessation of the drug:					
• Compatible	≤ 15 days	≤ 15 days	≤ 30 days	≤ 30 days	☐ +1
Note: If reaction begins before starting the medication or >15 days after stopping (hepatocellular), or >30 days after stopping (cholestatic), the injury should be considered unrelated and the RUCAM cannot be calculated.					
2. Course	**Change in ALT between peak value and ULN**		**Change in Alk P (or total bilirubin) between peak value and ULN**		**Score (check one only)**
After stopping the drug:					
• Highly suggestive	Decrease ≥ 50% within 8 days		Not applicable		☐ +3
• Suggestive	Decrease ≥ 50% within 30 days		Decrease ≥ 50% within 180 days		☐ +2
• Compatible	Not applicable		Decrease < 50% within 180 days		☐ +1
• Inconclusive	No information or decrease ≥ 50% after 30 days		Persistence or increase or no information		☐ 0
• Against the role of the drug	Decrease < 50% after 30 days OR Recurrent increase		Not applicable		☐ -2
○ If the drug is continued:					
• Inconclusive	All situations		All situations		☐ 0
3. Risk Factors:	**Ethanol**		**Ethanol or Pregnancy (either)**		**Score (check one for each)**
○ Alcohol or Pregnancy	Presence		Presence		☐ +1
	Absence		Absence		☐ 0
○ Age	Age of the patient ≥ 55 years		Age of the patient ≥ 55 years		☐ +1
	Age of the patient < 55 years		Age of the patient < 55 years		☐ 0

WHO-UMC system for standardised case causality assessment

Case		
Causality term	**Assessment Criteria**	
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenolgically (ie an objective and specific medical disorder or a recognised pharmacological phenomenon Rechallenge satisfactory, if necessary	
Probable/Likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required	
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drub withdrawal may be lacking or unclear	
Unlikely	Event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations	
Conditional/Unclassified	Event or laboratory test abnormality More data for proper assessment needed, or Additional data under examination	
Unassessable/Unclassifiable	Report suggesting an adverse reaction Cannot be judged because information is insufficient of contradictory Data cannot be supplemented or verified	

http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf

Estimate of the risk of ingesting comfrey or coltsfoot from the case studies

- Qualitative assessment of causation
  - WHO-UMC: likelihood of the ingested plants having a causative role in the adverse reaction
    - **3 'Probable'**
    - **6 'Possible'**
    - 1 'Unassessable' in one case

- Quantitative assessment of causation of liver injury
  - RUCAM (8 cases with hepatic involvement)
    - **2 'Possible'** cause of liver injury
    - 5 'Unlikely'
    - 1 'Unassessable'

The critical question

Ranked Upper Medium quality reporting.
WHO-UMC: Probable RUCAM: Unlikely

Death of a newborn

	Roulet 1988
Patient	Female newborn
Herb	1 cup expectorant tea including *Tussilago farfara* daily for 9 months 9 other herbs listed in the tea; details not reported
History and Adverse event	Mother developed pruritus at 4 months gestation Caesarean delivery at 36 weeks Rapid development, jaundice, hepatomegaly and ascites Died when 28 days old Autopsy revealed hepatic veno-occlusive disease
Analysis	Toxic metabolite of Senecionine identified in a sample of the tea

1st

The avoidance of sources of unsaturated PAs including comfrey, coltsfoot and borage is strongly recommended in pregnancy and lactation.

Conclusion:

Prolonged daily exposure to Tussilago farfara – led to cumulative toxicity causing veno-occlusive disease.

Roulet 1988

Senecionine is found in *Adenostyles alliariae*, *A. glabra*, *Petasites hybridus, Senecio* spp. as well as *Tussilago farfara.*

Further analysis of samples of the tea found it ‘contained not only leaves and flowers of *Tussilago farfara* but also roots of *Petasites officinalis.*

Sprang 1989

Misidentification

Tussilago farfara

Petasites (here *P. hybridus*

Photos: Steven Foster

Ranked low medium quality reporting.
WHO-UMC: Possible RUCAM: Unlikely

Acute poisoning

	Schroff 2013
Patient	Female 63 years old
Herb	Collected leaves growing by a stream that resembled plant grown in homeland in Asia and cooked into a regional dish. Plant identification details not reported.
History and Adverse event	Acute onset nausea and vomiting 3 hours after consumption. Hospitalised. Liver biopsy at 14 days revealed hepatic veno-occlusive disease. Repeat at 3 months showed slight progression. Partial recovery reported over time.
Analysis	Material examined and found to include both *Petasites* and *Tussilago.*

Conclusion:

'Veno-occlusive liver-disease caused by pyrrolizidine alkaloid containing herbs may account for significant morbidity.'

Schroff 2013

Unpublished details:

Analysis conducted on the samples of the uneaten portion of the meal taken from the patient's kitchen. Toxicologist attributed the toxicity in this case to the Petasites rather then the Tussilago.

Helmut Wiedenfeld Toxicologist

Case notes further revealed concomitant medications including psychoactive medications for long standing depression, potentially exacerbating patients vulnerability.

Florian Eyer Personal communication

Ranked Medium Low quality reporting
WHO-UMC: Possible RUCAM: Unlikely

Insidious onset

	Bach 1989
Patient	Female 49 years old
Herb	Comfrey tea (up to 10 cups a day) plus comfrey-pepsin capsule (by the handful) for 12 months – 24 months. Identification not reported.
History and Adverse event	*3 years after stopping herbs* investigated for hepatomegaly and palmar erythema. Liver biopsies twenty months apart revealed progressing hepatic veno-occlusive disease.
Analysis	No analysis, given time lag

Conclusion:

'Habitual use of comfrey, as occurred in our patient, has caused veno-occlusive disease.' Bach 1989

Considerations:

Exposure to PAs, probably at high dose for extended period.

Timeline allowed no analysis of the tea or capsules.

Relevant history not reported.

Earlier case study involves a comfrey-pepsin capsules. The capsules were analysed and contained unspecified PAs and the content described as a white powder. Ridker 1985

Ridker 1985 Analysis of comfrey-pepsin tablet

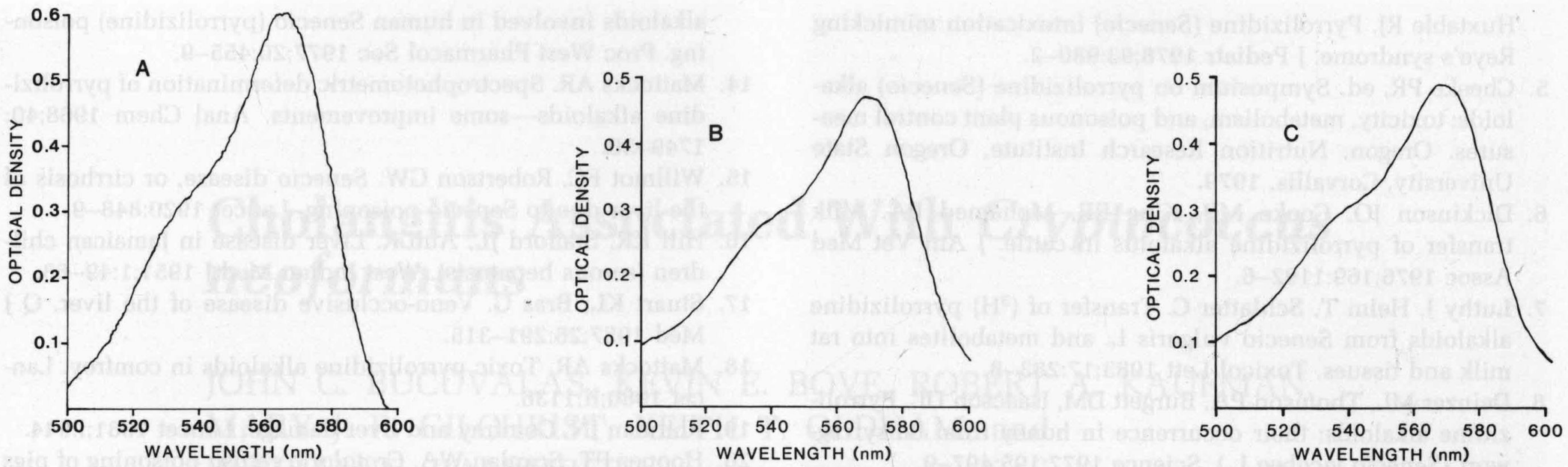


Figure 3. *A.* Spectrum of reaction product of authentic monocrotaline with Ehrlich reagent (5 μg monocrotaline in a final volume of 1.1 ml). *B.* Spectrum of Ehrlich reaction product of alkaloidal extract equivalent to 125 mg of comfrey-pepsin powder. *C.* Spectrum of Ehrlich reaction product of N-oxide fraction equivalent to 20 mg of comfrey-pepsin powder.

2nd

Accurate and complete botanical and phytochemical identification of ingested plant material is vital to inform decisions about the safety of herbal medicines.

Vulnerable patients

	Gyorick 2009	Weston 1987	Yeong 1990
Patient	Female 66 years	Male 13 years	Male 23 years
History	Chronic disease: T2DM, moderate adiposity, arterial hypertension, mild renal insufficiency	Crohn's disease Prior treatment: Prednisolone and sulphsalazine Concurrent episodic Prednisolone	Long term inadequate diet Emaciated with oedema and 'flu like symptoms prior to consumption of comfrey
Herb	Herbal tea blend daily including comfrey – months **Identification not reported**	Comfrey 3 years **Identification not reported**	Comfrey - 5 stemmed leaves of comfrey for 14 days **Identification not reported**
Adverse event	Pulmonary hypertension	Hepatic VOD	Hepatic VOD
Follow up	Recovered	Recovered	Fatal

3rd

Identification of vulnerable patients will help to mitigate risk.

Consideration of a patients history, nutritional status and concomitant CM and pharmaceutical use is recommended.

Discussion and Conclusions

- Confirm exposure to pyrrolizidine alkaloids can cause serious toxicity – therefore emphasise the importance of **complete botanical and phytochemical identification** if accurate causal attribution is to result from the investigation of an adverse event.
- Note the majority of these cases involved **self-prescription** and suggest the need to distinguish assumptions about popular use medicinal plants and professional prescriptions.
- Identification of **vulnerable patients** will help to mitigate risk.
- **Sources of pyrrolizidine alkaloids, including comfrey, borage and coltsfoot, should be avoided during pregnancy and lactation**.

Thank you to NIHM for the opportunity to research these plants. It has been a privilege. Thank you for your attention.

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Image

- https://s3.images-iherb.com/cro/cro49831/u/1.jpg (Christopher's comfrey)