Liver Let Die: Hepatotoxicity from Herbal Remedies

Ram Subramanian M.D.
Emory University School of Medicine
Atlanta

Disclosures: None

OUTLINE

• Review Herb Induced Liver Injury (HILI) in the context of Drug Induced Liver Injury (DILI).

• Review the etiological agents of HILI, with particular attention to the proposed active ingredient, mechanism and pattern of injury.

• Review toxicity related to interactions between herbs and medications.

Diagnostic Challenges

• Definition of Herb Induced Liver Injury (HILI): Liver injury induced by a herbal medicine leading to liver test abnormalities or liver dysfunction with reasonable exclusion of other competing etiologies.

• HILI diagnosis subject to underreporting and underrecognition

• Most of the current information comes from individual case reports or case series.

• HILI implicated as a cause of hepatotoxicity in 9% of patients with drug induced liver injury (DILI)¹

¹Chalasani et al. Gastro 2008; 135; 1904
### Herb Preparations

- Multiple ingredients/presence of contaminants further complicate the identification of a specific hepatotoxic product.
- Herbal products come in 2 forms: the crude form and the commercial form.
- The crude form - herbs that are used directly as seeds or leaves
  - Common in the less developed countries.
  - Formulated as a mixture of compounds – the exact composition unknown
  - Sometimes contain harmful contaminants such as heavy metals.
- The commercial form is used in the West
  - Prepared as tablets or capsules.
  - Often vary in content and concentration of the chemical constituents among different manufacturers, which results in variations in bioavailability and pharmacological activity.

### Regulation

- The Dietary Supplement Health and Education Act (DSHEA) was implemented in 1994 for the regulation of dietary supplements including herbal products.
- According to DSHEA, United States Pharmacopeia (USP) is the official reference for herbal preparations; however, conformity to the USP standards is voluntary.
- Under the DSHEA, the FDA is responsible for proving any safety concerns and taking action against unsafe products only after they reach the market.
- It is not mandatory for manufacturers to report any adverse affects to the FDA.
The Herbs (1)

- Extensive list of herbs that have been implicated in hepatotoxicity.
- Evidence on each ranges from comprehensive review of case reports and animal models, to a single case report of the suspected toxicity.
- From a hepatic perspective, a useful way to categorize HILI is by the histologic pattern of liver injury, as this may also have treatment implications.
  - Hepatocellular
  - Cholestatic
  - Veno-occlusive pattern
  - Steatotic
  - Autoimmune type

The Herbs (2)

- Although most herbs reviewed here can present with overlapping patterns of injury, they have been classified based on the predominant presentation.
- Also, almost all herbs can eventually lead to progressive hepatic failure, in the form of decompensated cirrhosis or acute (fulminant) hepatic failure.
- Each herb is covered under the following heads:
  - Uses
  - Proposed active ingredients and mechanism of action
  - Clinical presentation
  - Type of liver injury and histology

The Normal Liver

Portal tract and Hepatic Vein Relationship along with liver zones
The Hepatocellular Class

1. Germander (Teucrium chamaedrys)
2. Black Cohosh (Actaea racemosa)
3. Green Tea (Camellia sinensis)
4. Pennyroyal (Mentha pulegium)
5. Kava-kava (Piper methysticum)

Hepatocellular Injury

- Elevated ALT, AST, INR
- May or may not have elevated bilirubin
- Near normal ALP

Herb: Germander (Teucrium chamaedrys)

An ornamental plant native to Europe and the Middle East
Germander

- **Uses:** Weight loss, dyspepsia, hypertension, gout, diabetes.
- **Proposed active ingredients and mechanism of action:** Furan containing diterpenoids. In rat studies, these are oxidised by cytochrome P450 3A4 to reactive metabolites that bind to proteins, deplete cellular glutathione, induce membrane disruption and hepatocyte apoptosis.<sup>1</sup>
- **Clinical presentation:** Include acute liver failure, acute hepatitis, and chronic hepatitis.<sup>2</sup>
- **Type of liver injury and histology:** Hepatocyte necrosis, chronic hepatitis, fibrosis.<sup>2</sup>


---

**Herb: Black Cohosh (Actaea racemosa)**

A plant native to North America

---

Black Cohosh

- **Uses:** Treatment of menopausal symptoms.
- **Proposed active ingredients and mechanism of action:** Chemicals such as triterpene glycosides, phenolic acids and flavonoids have been isolated from the plant but mechanism of liver injury is not known.
- **Clinical presentation:** Acute hepatitis, and autoimmune hepatitis.<sup>1</sup>
- **Type of liver injury and histology:** Acute hepatocellular pattern.<sup>1</sup>
- **However, studies of causality assessment,** including randomized controlled clinical trials to assess hepatotoxicity of black cohosh, have concluded that the toxic nature of Black Cohosh is uncertain.<sup>1</sup>

**Herb: Green Tea (Camellia sinensis)**

A plant traditionally from China, but available across the world.

**Green Tea**

- **Uses:** general “health drink” and weight loss.
- **Proposed active ingredients and mechanism of action:** Probably catechins and their gallic acid esters, particularly epigallocatechin-3-gallate. Under conditions such as fasting, these induce reactive oxygen species formation, that affect mitochondrial membrane potential.
- **Clinical presentation:** Acute hepatitis, and autoimmune hepatitis.
- **Type of liver injury and histology:** Hepatocellular in most cases, but cholestasis and a mixed pattern also observed.
- **Causality assessment studies categorized the hepatotoxicity of green tea extracts as “possible” and “probable.”


**Herb: Pennyroyal (Mentha pulegium)**

A European herb
Pennroyal

- **Uses:** It is used as mint teas and as an abortifacient.

- **Proposed active ingredients and mechanism of action:** Considered to be menthofuran: oxidised by cytochrome P450, which depletes glutathione\(^1\).

- **Clinical presentation:** Severe GI and CNS effects within 1–2 h following ingestion of the oil. Severe fatal hepatic necrosis and multi-organ failure reported when more than 15 mL is ingested\(^1\).

- **Type of liver injury and histology:** Severe centrilobular necrosis\(^1\).

- **Possible reversal of toxicity by repletion of glutathione with N-Acetylcysteine\(^2\).**


**Herb: Kava-kava (Piper methysticum)**

A crop of the Western Pacific

Kava-kava

- **Uses:** Treatment of Stress, anxiety, insomnia and menopausal symptoms.

- **Proposed active ingredients and mechanism of action:** Several potential hepatotoxic constituents such as pipermethystine and flavokavain B have been reviewed, though the mechanism of toxicity unclear.

- **Type of liver injury and histology:** Both hepatocellular and cholestatic patterns have been observed. (Personal experience with a case of acute liver failure requiring LT)
Case of Kava kava induced ALF:
26 y/o F, Grade 4 encephalopathy, ALT 15,000 U/L, INR 7

Centrilobular necrosis

Kava-kava hepatotoxicity treatment:
• Patient listed for liver transplant (LT), NAC initiated
• Molecular Adsorbent Recirculating System (MARS) used to stabilize patient prior to LT. (MARS currently FDA approved for treatment of ALF due to drugs or toxins)
• Successfully underwent LT without complications

Principles of MARS® Therapy

Other herbs in the hepatocellular category
• Atractylis gummifera:
  • antipyretic, antiemetic and abortifacient
  • causes hepatocellular pattern of liver injury due to inhibition of mitochondrial oxidative phosphorylation.
  • Current immunotherapy research using polyclonal Fab fragments against toxic components.

• Impila (Callilepis laureola):
  • Traditional remedy of the Zulu Tribe can cause acute hepatocellular injury by depleting cellular glutathione.

• Chinese herb Ma huang:
  • Used as a nasal decongestant and bronchodilator
  • Can cause acute, and sometimes severe, hepatocellular injury.
The Cholestatic Class

- Elevated ALP and bilirubin
- Elevated serum bile acids
- Normal transaminases

Herb: Chaparral (Larrea tridentate)

A desert shrub, known as the creosote bush, found in South-western United States and Mexico

Chaparral

- Uses: A variety of conditions such as pains, bronchitis, skin conditions, cancer, and also as an alternative medicine for AIDS.

- Proposed active ingredients and mechanism of action: Nordihydroguaretic acid. potent inhibitor of lipoxgenase and cyclooxygenase pathways.

- Clinical presentation: Jaundice, acute hepatitis, sub-acute hepatitis, cirrhosis.

- Type of liver injury and histology: Cholestasis, and hepatic necrosis, particularly in zone 3.

The Mixed Picture

- Hepatocyte necrosis
- Cholestasis

Examples: Kava kava, chaparral

The Veno-occlusive Class (Hepatic Outflow Obstruction)

Pyrrolizidine alkaloids from
1. Heliotropium sp.
2. Senecio sp.
3. Crotalaria sp.
4. Symphytum sp.

Veno-occlusive disease

Reticulin shows central vein occlusion

VOD by special stain
Herb: Pyrrolizidine alkaloids from Heliotropium, Senecio, Crotalaria and Symphytum

- **Heliotropium**
- **Senecio**
- **Crotalaria**
- **Symphytum**

**Uses:**
- South-western United States: as Comfrey, derived from the roots of Symphytum officinale, as natural home remedy for wound/bone healing.
- South Africa: bread contaminated with Senecio.
- India: cereal contaminated with Crotalaria.
- Afghanistan: wheat contaminated with Heliotropium

**Proposed active ingredients and mechanism of action:**
Pyrrolizidine alkaloids undergo biotransformation by cytochrome P450 3A4 into unstable toxic metabolites (pyrrole derivatives) that may act as alkylating agents\(^2\). (similar VOD injury in oncology related chemotherapy agents)

**Clinical presentation:** The cases typically present with ascites, edema and hepatomegaly.

**Pyrrolizidine alkaloids : Clinical Presentation (cont.)**

- **Acute form:** sudden abdominal pain, jaundice, severe transaminitis, ALF.
- **Chronic form:** Progressive perivenular and bridging fibrosis, with progression to cirrhosis and portal hypertension\(^1\).
- **Type of liver injury and histology:** The key pattern is Veno-occlusive disease (VOD), newly termed Sinusoidal obstruction syndrome (SOS), characterised by nonthrombotic occlusion of small terminal hepatic venules, leading to sinusoidal dilatation and, eventually, hemorrhagic centrilobular necrosis\(^1\).
- **No role for anticoagulation:** poor prognosis

Hepatic vein occluded by macrophages & fibrous tissue

- Elevated bilirubin
- Elevated liver enzymes
- Usually diagnosed by liver biopsy, with Doppler Ultrasound typically normal

The Steatotic Class

Chinese herbs such as
1. Jin Bu Huan
2. Sho-saiko-to

Steatosis

Microvesicular steatosis
**Herb: Jin Bu Huan (Lycopodium serratum)**

- **Uses**: sedative and analgesic.
- **Proposed active ingredients and mechanism of action**: Unclear active ingredient and mechanism of action, but an immune-mediated process might play a role.
- **Clinical presentation**: Acute hepatitis, usually within 20 weeks of ingestion, with some cases also developing a typical drug reaction such as fever, rash and eosinophilia.\(^1\)\(^2\)
- **Type of liver injury and histology**: micro-vesicular steatosis, with or without eosinophilic infiltrates\(^1\)\(^2\), and hepatitis


---

**Herb: Sho-saiko-to/Dai-saiko-to**

A Chinese herb
Sho-saiko-to

- **Uses:** Used widely in Japan for the treatment of liver diseases, in preventing hepatic inflammation, fibrosis, and hepatocellular carcinoma.

- **Proposed active ingredients and mechanism of action:** The agents involved in the liver protective or the liver toxic action of the herb has yet to be described.

- **Clinical presentation:** Acute hepatitis following an average latency period of 1.5–3 months.

- **Type of liver injury and histology:** micro-vesicular fatty change, centrilobular confluent necrosis.

---

The Autoimmune Class

**Greater celandine (Chelidonium majus)**

Apart from Greater Celandine, some of the drugs from the previous sets have also been implicated in the development of an autoimmune hepatitis like picture, including:

- Black Cohosh
- Green Tea
- Sho-saiko-to

---

Autoimmune Hepatitis

Portal and lobular lymphoplasmacytic inflammation seen in AIH
Herb: Greater celandine (Chelidonium majus)

A herbaceous perennial plant, native to Europe and western Asia and introduced widely in North America.

Greater celandine

- **Uses:** Gastrointestinal complaints, dyspepsia and gallbladder disease.

- **Proposed active ingredients and mechanism of action:** Isoquinoline alkaloids, but the mechanism of their hepatotoxicity is unknown.

- **Clinical presentation:** Hepatitis with moderate elevations of ALT and ALP with low titre of antinuclear and smooth muscle autoantibodies.

- **Type of liver injury and histology:** Portal inflammation and eosinophilic infiltrates, cholestasis.

- **Potential role for steroid therapy (as used in non DILI AIH)**


Hepatic fibrosis

Any of the listed herbs can eventually lead to chronic inflammation, fibrosis and cirrhosis, eventually requiring liver transplantation.

Bridging fibrosis
**HERB – MEDICATION INTERACTIONS**

**Herb – Drug Interactions**

- The concomitant use of conventional drugs and herbs can increase toxicity of the conventional drug or the herb.
- The mechanism of interaction is based on the property of some herbs/drugs to function as substrate/inducers/inhibitors of the Cytochrome P450 enzymes.
- Unexplained conventional drug toxicity or deficiency should raise the concern for unreported herbal coingestion.

<table>
<thead>
<tr>
<th>Herb</th>
<th>Conventional Drug</th>
<th>Interaction</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrrolizidines</td>
<td>Anticonvulsants, Phenobarbital, Rifampin</td>
<td>CYP3A4 induction by the conventional drugs – ↑ toxic metabolites of pyrrolizidine alkaloids</td>
<td>Increased hepatotoxicity of pyrrolizidine alkaloids</td>
</tr>
<tr>
<td>Germander</td>
<td>Anticonvulsants, Phenobarbital, Rifampin</td>
<td>CYP3A4 induction by the conventional drugs – ↑ toxic metabolites of Germander</td>
<td>Increased hepatotoxicity of Germander</td>
</tr>
<tr>
<td>St. John’s wort (Anti-depressant)</td>
<td>Cyclosporine</td>
<td>St. John’s wort is a CYP3A4 inducer – ↓ levels of Cyclosporine</td>
<td>Risk of rejection</td>
</tr>
<tr>
<td>Grapefruit juice (Anti-hyperlipidemic)</td>
<td>Cyclosporine</td>
<td>Grapefruit juice is a CYP3A4 inducer – ↓ levels of Cyclosporine</td>
<td>Risk of rejection</td>
</tr>
<tr>
<td>St. John’s wort (Anti-depressant)</td>
<td>Warfarin</td>
<td>St. John’s wort is a CYP3A4 inducer – ↓ levels of Warfarin</td>
<td>Non-therapeutic INR</td>
</tr>
</tbody>
</table>
Summary

- Herb Induced Liver Injury (HILI) is a growing concern within the field of DILI
- Underreporting, under-diagnosis, lack of regulation and paucity of evidence based data limit the study of HILI
- Histologic analysis of HILI may provide insight into mechanisms of injury, and potential therapies