Drug-Induced Liver Injury (DILI) Caused by Dietary and Herbal Supplements

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History of Traditional Herbal Medicine

Medieval Herbs

Traditional African Herbals

Japanese Kampo Medicine

Traditional Chinese Medicine
Complementary Alternative Medicine (CAM) Nowadays

Accupuncture

Moxibustion
Drugs derived from plants

- **Digoxin** – *Digitalis*
  (Foxglove)

- **Quinine** – *Cinchona*
  (China Bark)

- **Salicylic acid** – willow tree

- **Paclitaxel** – *Taxus*
  (Pacific Yew)

- **Vincristin** – *Catharante*
  (Pink periwinkle)

- **Camptothecin** – *Camptotheca*
  (Happy/Cancer Tree)
CAM is trendy...

- 15 Mio. Americans use CAM methods and products (including herbals)
- 20% of liver-diseased patients take phytopharmaceuticals (mostly silymarin, glycyrrhizin)
- Typical patient: Female, higher education, higher income

Out-of-pocket expenditure for herbal supplements (USA)

Seeff L, Stickel F, Navarro VJ. 2013
Why do patients turn to CAM?

- Confirmed or presumed efficacy
- Belief in preventive potential
- Diappointment about conventional drug/medicine in general
- Avoidance of side effects from conventional drugs
- Reputation of „tender medicine“
- No prescription required
- Relatively cheap
Expectations towards CAM

- Influence natural history of disease
- Promote well-being
- Lower side effects
- Take control of one’s health
- Relieve symptoms
- Boost the immune system
- Provide emotional support
- Improve quality of life
- Cope better with illness
- Support natural healing

*Ernst E, Hung SK. Patient 2011*
National Policy on Traditional Medicine and Herbal Drugs

http://apps.who.int/medicinedocs/en/d/Js7916e/9.4.html
Case report I

- 39-year old female teacher
- AST 827, ALT 912, Bili 11,2, GGT 116, AP 368, INR 1.7
- Sulfametoxazole (5 days)
- 4 weeks later AST/ALT > 800
- Intake of penicilline for dental infection (10 days)
- All other causes excluded
- Remission after 7 weeks
- Intake of Greater Celandine product

Stickel et al., Scand J Gastroenterol 2003
Greater Celandine (*Chelidonium majus*)

- Used as „choleretic“, non-ulcer-dyspepsia
- Contains chelidonine, berberine, coptisine, chelerythrine
- No clinical evidence of efficacy
- Products marketed (84):
  - Cholarist®, Neurochol C®, Panchelidon N®, Siosol®, Spasmo gallo sanol®
Hepatotoxicity from Greater celandine (*Chelidonium majus*)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of intake (months)</th>
<th>GOT/GPT/AP/GGT/Bili</th>
<th>Auto-AB</th>
<th>Histology</th>
<th>Remission (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (67)</td>
<td>9</td>
<td>350/460/282/286/2.0</td>
<td>ANA 1:160</td>
<td>Hepatitis</td>
<td>6</td>
</tr>
<tr>
<td>2 (46)</td>
<td>4</td>
<td>77/123/65/48/2.3</td>
<td>None</td>
<td>Septal fibrosis</td>
<td>None</td>
</tr>
<tr>
<td>3 (54)</td>
<td>1</td>
<td>571/870/226/96/20.5</td>
<td>SMA 1:40</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>4 (46)</td>
<td>6</td>
<td>425/873/451/421/6.9</td>
<td>None</td>
<td>Severe hepatitis</td>
<td>None</td>
</tr>
<tr>
<td>5 (37)</td>
<td>3</td>
<td>89/152/451/179/1.0</td>
<td>None</td>
<td>Septal fibrosis</td>
<td>None</td>
</tr>
<tr>
<td>6 (65)</td>
<td>3</td>
<td>353/480/192/30/2.4</td>
<td>SMA 1:40</td>
<td>Severe hepatitis, necrosis, septal fibrosis</td>
<td>3</td>
</tr>
<tr>
<td>7 (40)</td>
<td>2</td>
<td>320/540/370/230/2.4</td>
<td>ANA 1:160</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>8 (66)</td>
<td>4</td>
<td>192/328/140/118/0.9</td>
<td>ANA 1:160</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>9 (40)</td>
<td>2</td>
<td>577/734/431/275/11</td>
<td>ANA 1:160</td>
<td>moderate hepatitis, marked fibrosis</td>
<td>None</td>
</tr>
<tr>
<td>10 (41)</td>
<td>3</td>
<td>688/1338/368/133/38</td>
<td>ANA 1:40</td>
<td>Severe hepatitis</td>
<td>None</td>
</tr>
</tbody>
</table>

*April 9th, 2008 (Germany)*

Revocation of approval of all products containing >2.5mg Chelidonine

*Benninger et al., Gastroenterology 1999*
Case report IV

- 46-year old female bank clerk
- Sudden onset of fatigue and jaundice
- No history of LDs
- No alcohol
- Partnership crisis leading to sleeping disorder and anxiety
- Intake of a herbal anxiolytic of unknown kind

transplantation

Days
0 12 24 36 48

ALT

Fatigue

Bili

INR

0 100 200 300 400 500

0 1000 2000 3000
Case report II - histology

Massive parenchymal necrosis
Unclear pathophysiology

Possible explanations:
- Immunoallergic reaction?
- Individual idiosyncrasy?
- CYP 2D6 polymorphism?
- CYP induction via comedication or concomitant alcohol consumption?

Unlikely:
- Dose-dependent toxicity
- Contamination
Liver injury from Kava-Kava

• **1990-2002** Reporting of 39 cases of liver injury associated with the intake of commecrical Kava products to pharmacovigilance authorities (BfArM, Bonn).

• **Causality** In 29 of cases causality with Kava intake „confirmed“ oder „probable“.
   (CIOMS Score, *Benichou et al.*, J. Hepatology 1990)

• **Results** 6 case of fulminant liver failure
   5 cases requiring liver transplantation
   2 lethal cases

• **Status quo** revocation of all Kava containing products in EU, Canada, USA

*Stickel et al, J Hepatol 2003*
Case report V

- 2-year old infant with abdominal pain, weight loss, vomiting
- Liver enzyme elevation, painful hepatomegaly, ascites
- No infectious, metabolic, autoimmune diseases
- No drug intake (aspirin)
- Self-made tea from common heliotrope

*Sperl et al., Europ J Pediatr 1995*
Sinusoidal obstruction syndrome (SOS) after intake of heliotrope

Occluded central vein
Pyrrolizidine alkaloids

Heliotropium (heliotrope)
India, Afghanistan

Senecio (ragwort)
South Africa

Crotalaria (desert senna)
„Bush tea disease“ in Jamaica

Symphytum (comfrey)
USA, Europe
Sinusoidal obstructive syndrome (SOS)

Toxic damage of sinusoidal endothelium

Platelet activation, plasmatic coagulation

Thrombotic and non-thrombotic vascular obstruction

Liver congestion

Parenchymal necrosis

Acute hepatocellular injury, fibrosis and cirrhosis

Liver failure
SOS after intake of common heliotrope (Heliotropium peruvianum) contaminating cereal
The obesity pandemic
Icons have changed....

2000 B.C.

EVOLUTION...

2000 A.D.

[Image of a statue; one of evolution's stances]

[Image of a modern statue; one of modern stances]
Case report VI

- 63-yr woman with nausea, vomiting, jaundice, urticaria
- Obesity (BMI 31.4), voluntary weight loss of 14kg/3months
- Ultrasound inapparent
- Drugs: amiloride (2 yrs)
- Hepatitis serology Hep. A, B, C, EBV, CMV negative
- AMA 1:80, ANA 1:40
- LBX: compatible with DILI (eosinophilia!)
- Remission within 8 weeks
- Recurrence of symptoms...

Hoffmann et al., Schweiz Med Forum 2005;5:147-8
Only identifiable cause.....

- Consumption of Herbalife® since 5 months (*Shape Works, Green and Beige Capsules, Thermojetics Tea*)

- Weight reduction remedy

- *Petroselini radix, Solidaginis gigantea, Mate folium, Foeniculi fructus, Matricariae chamomillae, Garcinia cambogia*, etc.....
Acute hepatitis of unknown origin...

## Herbalife and liver injury – bacterial contamination?

<table>
<thead>
<tr>
<th>Product</th>
<th>Bacterial Culture</th>
<th>gyrB gene sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herbalife - Shape Works Shake Formula 1 (Strawberry)</td>
<td><em>Bacillus subtilis</em></td>
<td><em>Bacillus subtilis</em></td>
</tr>
<tr>
<td>Herbalife - Shape Works Shake Formula 1 (Cappuccino)</td>
<td><em>Brevibacillus parabrevis</em></td>
<td>Not assayed</td>
</tr>
<tr>
<td>Herbalife - Shape Works Shake Formula 1 (Cappuccino)</td>
<td>No growth</td>
<td>-</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herbalife - Personalized Protein Powder Formula 3</td>
<td><em>Bacillus subtilis</em></td>
<td><em>Bacillus subtilis</em></td>
</tr>
<tr>
<td></td>
<td><em>Paenibacillus polymyxa</em></td>
<td><em>Paenibacillus polymyxa</em></td>
</tr>
<tr>
<td>Vitamin C tablets</td>
<td><em>Bacillus subtilis</em></td>
<td><em>Bacillus subtilis</em></td>
</tr>
<tr>
<td></td>
<td><em>Bacillus cereus</em></td>
<td>Not assayed</td>
</tr>
<tr>
<td>Tang Kuei Plus tablets</td>
<td>No growth</td>
<td></td>
</tr>
<tr>
<td>RoseOx tablets</td>
<td>No growth</td>
<td></td>
</tr>
<tr>
<td>Multivitamin tablets</td>
<td>No growth</td>
<td></td>
</tr>
<tr>
<td>Thermojetics granules</td>
<td>No growth</td>
<td></td>
</tr>
<tr>
<td>Herbalifeline omega 3 fatty acids caps.</td>
<td>No growth</td>
<td></td>
</tr>
</tbody>
</table>

*Stickel et al. J Hepatol 2009;50:111-7*
Herbalife and liver injury – bacterial contamination?

Fig. 4. LDH leakage from HepG2 after incubation of 24 h with serial dilution of bacterial supernatant from *Bacillus subtilis* cultures.

*Stickel et al. J Hepatol 2009;50:111-7*
# Case reports on liver injury after Herbalife products

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Type and number of products</th>
<th>Duration of intake (months)</th>
<th>Type of injury</th>
<th>Outcome</th>
<th>Causality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elinav et al. (20)</td>
<td>12 (11F)</td>
<td>Variable; between 6 and 17 different products</td>
<td>2–28</td>
<td>Hepatocellular (n = 11), mixed (n = 1)</td>
<td>Recovery (n = 11), death (n = 1)</td>
<td>WHO score; certain (n = 3; positive rechallenge); probable (n = 6); possible (n = 3)</td>
</tr>
<tr>
<td>Schoepfer et al. (21)*</td>
<td>10 (7F)</td>
<td>Variable; between 3 and 13 different products</td>
<td>2–26</td>
<td>Hepatocellular (n = 9), mixed (n = 1)</td>
<td>Recovery (n = 8), liver transplantation (n = 1), cirrhosis (n = 1)</td>
<td>WHO score; certain (n = 2; positive rechallenge); probable (n = 7); possible (n = 1)</td>
</tr>
<tr>
<td>Duque et al. (22)</td>
<td>4 (4F)</td>
<td>Nine different products</td>
<td>1–26</td>
<td>Hepatocellular (n = 2); mixed (n = 2)</td>
<td>Recovery of all four</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Chao et al. (23)</td>
<td>1 (F)</td>
<td>Three different products</td>
<td>2.5</td>
<td>Mixed (n = 1)</td>
<td>Recovery</td>
<td>WHO score; probable</td>
</tr>
<tr>
<td>Stickel et al. (24)</td>
<td>2 (1F)</td>
<td>Variable; between six and eight different products</td>
<td>12–36</td>
<td>Mixed (n = 1), cholestatic (n = 1)</td>
<td>Recovery (n = 1), cirrhosis (n = 1)</td>
<td>CIOMS; probable (n = 2)</td>
</tr>
<tr>
<td>Johannsson et al. (25)</td>
<td>5 (4F)</td>
<td>Variable; between two and five different products</td>
<td>1–7</td>
<td>Hepatocellular (n = 3), cholestatic (n = 2)</td>
<td>Recovery (n = 5)</td>
<td>RUCAM; probable (n = 3), possible (n = 2); WHO; certain (n = 1), probable (n = 2), possible (n = 2)</td>
</tr>
</tbody>
</table>

Total = 34
<table>
<thead>
<tr>
<th>Dietary supplement</th>
<th>Indication for use</th>
<th>Liver lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbalife®</td>
<td>Various (weight loss, nutritional support,</td>
<td>Variable (acute and chronic hepatitis, cholestasis, cirrhosis, hepatic failure)</td>
</tr>
<tr>
<td></td>
<td>‘well-being’)</td>
<td></td>
</tr>
<tr>
<td>Camellia sinensis (green</td>
<td>Weight loss</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>tea)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LipoKinetix®</td>
<td>Weight loss</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Hydroxycut</td>
<td>Weight loss</td>
<td>Acute and/or cholestatic hepatitis, liver failure</td>
</tr>
<tr>
<td>Senna (Cassia angustifolia)</td>
<td>Constipation</td>
<td>Variable (acute hepatitis, granulomatous hepatitis, cirrhosis)</td>
</tr>
<tr>
<td>Noni juice (Morinda</td>
<td>‘Immunostimulation’, health tonic</td>
<td>Acute hepatitis, hepatic failure</td>
</tr>
<tr>
<td>citrifolia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ma huang (Ephedra sinica)</td>
<td>Weight loss</td>
<td>Acute hepatitis, hepatic failure</td>
</tr>
<tr>
<td>Germander (Teucrium</td>
<td>Weight loss</td>
<td>Acute, and fulminant hepatitis, chronic hepatitis with fibrosis/cirrhosis</td>
</tr>
<tr>
<td>chamaedrys)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Onshidou-Genbi-Kounou’,</td>
<td>Weight loss</td>
<td>Acute hepatitis, hepatic failure</td>
</tr>
<tr>
<td>‘Chaso’ (Japanese herbals)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Disease prevention, immune function</td>
<td>Chronic hepatitis, cholestasis, cirrhosis</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Muscle build-up</td>
<td>Cholestasis, benign/malignant liver tumours</td>
</tr>
</tbody>
</table>

HSC, hepatic stellate cells; MFB, portal myofibroblasts.
<table>
<thead>
<tr>
<th>Herbal</th>
<th>Application</th>
<th>Toxin</th>
<th>Mechanism</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atractylis gummifera &amp; Callilepsis laureola</td>
<td>Antiemetic, chewing gum, health tonic</td>
<td>Atractylosides</td>
<td>Inhibition of gluconeogenesis</td>
<td>Acute hepatitis, hepatic failure</td>
</tr>
<tr>
<td>Cascara sagrada</td>
<td>Laxative</td>
<td>Anthracene glycoside</td>
<td>unknown</td>
<td>Cholestatic hepatitis</td>
</tr>
<tr>
<td>Chaparral (larrea tridentata)</td>
<td>Antioxidant, snake bites, health tonic</td>
<td>Nordihydroguaiaretic acid</td>
<td>CYP inhibition</td>
<td>Cholestasis, chronic hepatitis, cirrhosis</td>
</tr>
<tr>
<td>Chinese herbs (paeonia, dictamnus), Jin Bu Huan, Ma Huang</td>
<td>Miscellaneous</td>
<td>unknown</td>
<td>unknown</td>
<td>Acute and chronic hepatitis, liver failure, fibrosis</td>
</tr>
<tr>
<td>Pennyroyal</td>
<td>Pesticide, Abortifacient</td>
<td>Menthofurane</td>
<td>Glutathione depletion</td>
<td>Fulminant hepatic failure</td>
</tr>
<tr>
<td>Sassafras</td>
<td>Herbal tea</td>
<td>S. albidum</td>
<td>unknown</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Saw palmetto</td>
<td>Prostatism</td>
<td>unknown</td>
<td>unknown</td>
<td>Mild hepatitis</td>
</tr>
<tr>
<td>Valerian</td>
<td>Sedative</td>
<td>unknown</td>
<td>unknown</td>
<td>Mild hepatitis</td>
</tr>
<tr>
<td>Black cohosh</td>
<td>Arthromyalgia, postmenopausal complaints</td>
<td>unknown</td>
<td>Mitochondrial damage?</td>
<td>Acute hepatitis, liver failure</td>
</tr>
<tr>
<td>Senna (Cassia angustofolia)</td>
<td>Laxative</td>
<td>unknown</td>
<td>unknown</td>
<td>Mild hepatitis</td>
</tr>
</tbody>
</table>
Vitamin A-associated liver injury

- Retinoids often contained in multivitamin supplements (usually <50,000 IU/day)
- Longterm vitamin A supplementation may cause chronic cholestatic hepatitis, fibrosis (and possibly cirrhosis) in susceptible individuals
- Coexisting liver disease may enhance vitamin A toxicity (steatosis, alcohol consumption)
- With alcohol consumption, tolerance towards vitamin A may be lower
Vitamin A hepatotoxicity - mechanism

Dan et al. FASEB J 2005;19:845
Anabolic steroids
Anabolic steroids – liver lesions

Methasteron, Oxymetholone, Methenolone, Drostanolone and others

Intrahepatic/canalicular cholestasis

Peliosis hepatis
Toxicant-associated fatty liver disease (TAFLD)

• Case-control study from Brazil on anabolic androgenic steroids (AAS)

• 180 recreational body builders taking AAS (n=95) or controls (n=85)

• 12.6% of cases had TAFLD; 2.4% of controls had NAFLD

• Intake of AAS increased the risk of TAFLD 6-fold

*Schwingel et al, Liver Int 2011;31:348-53*
Summary and Conclusion

• Consumption of herbal drugs/dietary supplements is widespread, rising and largely uncontrolled

• Multiple herbal and dietary supplements may cause liver injury

• Pattern, natural course, diagnostics and mechanisms of hepatotoxicity indistinguishable from DILI from synthetic drugs

• Particular problems: poor regulations (no "drug status"), ill-defined contents, contamination, no safety data/control, unsupervised consumption (self-medication), no disclosure of intake

• Consider herbal and/or dietary supplements as a potential cause of liver injury when all other etiologies are excluded

• Report known or unknown adverse hepatic reaction to herbals/dietary supplements to pharmacovigilance authorities!