Herbal and Dietary Supplement (HDS) Hepatotoxicity

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Scope of My Talk

- Overview of HDS from around the world
- Epidemiology of HDS hepatotoxicity
- Diagnosis and causality assessment of HDS hepatotoxicity
- Clinical features of each particular HDS hepatotoxicity (both from the Western and Eastern Countries)
- Herb-drug interactions
Acknowledgement

Professor Rajender K. Reddy, MD.
- Professor of Medicine
- Professor of Medicine in Surgery
- Director of Hepatology
- Director, Center for Viral Hepatitis
- University of Pennsylvania, Philadelphia, USA

รศ.ดร. ถนอมศักดิ์ สนธิทรัพย์
- ผู้เชี่ยวชาญด้านสมุนไพร
- ภาควิชาเภสัชวินิจฉัย
- คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล
Types of Herbal and Dietary Supplements

Herbs

Vitamins, minerals, antioxidants, nutrients, immune modulators

Single ingredient
Examples
- Silymarin
- Senna

Mixtures
Examples
- Chinese herbal medicine
- Indian ayurvedic medicine
- Thai herbal medicine
- Herbalife®

- Crude (e.g. roots, leaves, seeds, tea, ยาหมี่, น้ำหมัก)
- Extracts/commercial products (e.g. tablets, capsules, defined formulations)
Use of HDS in the USA

- ~19% of US adults used HDS during previous 12 months (NHIS CAM survey in 2002)
- Represent a $180 billion market in US
- Americans spend more than $6 billion annually on nutritional supplements, and $1 billion on herbs and teas
- Increasing use by US public has been documented by many surveys
- 20-40% did not disclose the use of HDS to their Physicians

Use of Complementary and Alternative Medicine (CAM) in Patients with Liver Disease

989 patients from 6 geographically diverse Liver Clinics in the US

- 39% used CAM in the preceding month (26% did not inform their physician)
- 21% used herbal preparations (milk thistle = most common 12%)
- 13% used herbs to treat their liver disease

Why Patients Use HDS?

- Limitation of conventional therapies
- Paradigm shift to natural products
- Perception that HDS is safer and cheaper form of therapy
- Embracing a more holistic and spiritual orientation to life
- Had transformation experience
- False/overstate advertising claims
- Marketing (online, direct selling)

Astin JA. JAMA 1998;279:1548-53
Verma S, Thuluvath PJ. Clin Gastroenterol Hepatol 2007;5:408-16
หลังมีข้อราชการ

โรคหัวใจ โรคสมอง (เส้นเลือดสมองดีบ, อัลไซเมอร์) โรคตับ โรคไต โรคภูมิแพ้ แพ้อากาศ ไซนัส หัวเด็กและผู้ใหญ่ ไตรอยด์เป็นพิษ คนที่มีวง ไม่มีเรียกแรง ใจค่อนเหลือเยียว โรคซิมเบร้า โรคที่รักษาไม่หาย แต่ให้ความแข็งแรงขึ้น ซ่วยเหลือตัวเองได้ โรคมะเร็ง โรคเอดส์ อัมพฤกษ์ อัมพาต ทุกโรคทานได้

ทานได้ด้วยแค่เด็กทหารถึงผู้สูงอายุ ให้ธาตุติน-น้ำ-ลม-ไฟ (พลังงานชีวิต)

4 ขวด (ราคาสามชิ้น) ราคา 9,100 บาท หรือ 200 CC

http://morsengrich.blogspot.com
Health Risks of Herbal Remedies

• Self treatment and diagnosis
• Hepatotoxicity and/or toxicity to other organ systems
  – Dose-dependent, idiosyncrasy, immunoallergic
• Herb-drug interactions
• Contaminations: preparation, storage
  – Infectious agents: e.g. bacteria, fungus
  – Toxins: e.g. aflatoxin
  – Heavy metals: e.g. arsenic, mercury, lead
  – Synthetic drugs: steroids, NSAIDs, antivirals
Epidemiology: HDS Hepatotoxicity

• The true prevalence is unknown
  – No strict regulations and surveillance
  – Data taken from anecdotal case reports, case series, and prospective DILI registries
  – Seems to be high, but is underreported

• The incidence is variable
  – Overall seems to be low
  – Few RCT and prospective studies
  – Chinese traditional medicine
    • Prospective study of 1,507 patients*: ~1% developed
      ↑ALT >2×ULN; only 2 patients were symptomatic

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
# Prevalence of HDS Hepatotoxicity in DILI Registry

<table>
<thead>
<tr>
<th>Reports</th>
<th>Country / Patient characteristics</th>
<th>Prevalence</th>
<th>Features and prognosis of HDS Hepatotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibunez et al.</td>
<td>Spain (1993–1998) N = 103; DILI</td>
<td>11%</td>
<td>64% hepatocellular injury 18% mixed injury 18% cholestasis injury</td>
</tr>
<tr>
<td></td>
<td>Population-based, prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andrade et al.</td>
<td>Spain (1994–2004) N = 446; DILI</td>
<td>2%</td>
<td>89% hepatocellular 11% cholestasis 56% hospitalized; 11% death</td>
</tr>
<tr>
<td></td>
<td>Multi-centre, prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chalasani et al.</td>
<td>USA (2003–2008) N = 300; DILI</td>
<td>9%</td>
<td>63% hepatocellular 17% cholestasis; 21% mixed 41% hospitalized 6% ALF; 9% chronic DILI</td>
</tr>
<tr>
<td></td>
<td>Multi-centre, prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suk et al.</td>
<td>Korea (2005–2007) N = 371; DILI</td>
<td>73%</td>
<td>78% hepatocellular 10% cholestasis; 12% mixed 1.5% death or LT</td>
</tr>
<tr>
<td></td>
<td>Multi-centre, prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wai et al.</td>
<td>Singapore (2004–2006) N = 31; DILI</td>
<td>71%</td>
<td>74% hepatocellular 19% cholestasis 7% mixed injury</td>
</tr>
<tr>
<td></td>
<td>Multi-centre, prospective</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Bunchothavakul C. Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
## Prevalence of HDS Hepatotoxicity in ALF Registry

<table>
<thead>
<tr>
<th>Reports</th>
<th>Countries / pt characteristics</th>
<th>Prevalence of HDS hepatotoxicity</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russo et al.</td>
<td>USA (1990–2002) N = 270; ALF from drug Retrospective, UNOS data</td>
<td>5.1%</td>
<td>All underwent LT</td>
</tr>
<tr>
<td>Reuben et al.</td>
<td>USA (1998–2007) N = 133; ALF from drug Multi-centre, prospective</td>
<td>10%</td>
<td>21% spontaneous recovery 50% underwent LT 29% death</td>
</tr>
<tr>
<td>Estes et al.</td>
<td>USA (2001-2002) N=20, ALF Single-center, retrospective</td>
<td>50%</td>
<td>60% underwent LT</td>
</tr>
</tbody>
</table>
Difficulties in the Diagnosis and Causality Assessment of HDS Hepatotoxicity

- Lack of scientific testing and data
- Numerous combinations
- Unknown active ingredient(s) and other non-standardized ingredient(s)
- Production/manufacturing variability
- Contaminations
- Mislabeling
- Unqualified practitioners
- Concomitant medications and liver disease
Diagnosis and Causality Assessment of HDS Hepatotoxicity

- High index of suspicion
- Detailed history on all HDS used and timing
- Examination of HDS and its label
- Prompt recognition of known common culprit HDS and their hepatotoxicity patterns
- Liver biopsy – not specific
- Exclusion of other cause(s) of liver disease
- DILI scoring system: CIOMS/RUCAM, Maria & Victorino, HDS-CAT (HDS-specific)*

Bunchorntavakul C. Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
* Proposed by Navarro VJ, et al. in the EASL Meeting 2012
Pyrrolizidine Alkaloids (PA)

- One of the most important and common plant toxin associated with liver injury
- Found in >350 plant species worldwide
  - Jamaica bush tea, robage, coltsfoot, Senecio, Comfrey, *Crotalaria spp.* Heliotrope and some Chinese herbs
- Used: various conditions
- Metabolized by CYP450, forming pyrrole derivatives (dose-dependent hepatotoxin)
- Types of liver injury
  - Veno-occlusive disease (VOD)
  - Carcinogenesis – HCC?

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
PA-Containing Plants in Thailand

หญ้าวงช้าง (Heliotropium indicum)

ต้นหึงหา (Crotalaria verrucosa)

ปอเทือง (Crotalaria juncea)
Clinical Features of PA-related VOD

- Clinical onset (acute, subacute or chronic) and severity are variable
- Ascites, hepatomegaly, edema, liver dysfunction
- Liver histology: non-thrombotic occlusion of small terminal hepatic venules, leading to sinusoidal dilatation and centrilobular necrosis

Bunchorntavakul C. Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Enzymatic transformation of pyrrolizidine alkaloids into nontoxic alkaloid N-oxides

Comedication with microsomal enzyme inducers (e.g. phenobarbital) favors the formation of toxic pyrroles by several microsomal CYP450 enzymes
Prognosis and Rx of PA-related VOD

• Acute form
  – 20-40% Death
  – 50% Complete recovery
  – 15-20% Protracted disease – progressive perivenular and bridging fibrosis, and some may die from ESLD several years later

• Subacute or chronic onset: smaller proportion

• Management
  – Mainly supportive; consider OLT for ALF or ESLD
  – ? Defibrotide – no data in PA-related VOD

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Germander (*Teucrium chamaedrys*)

- Europe and Middle East
- Used: fever, dyspepsia, etc.
- Furan-containing diterpenoids
  - cytotoxic and carcinogenic
- Types of liver injury
  - Acute hepatitis
    (occur few months after use)
  - Massive centrilobular necrosis – ALF
  - Cirrhosis

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Germander: Mechanism of Hepatotoxicity

- CYP450 3A activates furane neo-clerodane diterpenoids contained in germander into toxic epoxides, which may be neutralized by conjugation with glutathione.
- In conditions of glutathione deficiency (as in starvation), epoxides may react with hepatic proteins and lead to liver cell death through the induction of apoptosis.
Greater Celandine
 (*Chelidonium majus*)

- Found mainly in Europe
- Used: biliary disease, IBS
- Contains several alkaloids
- Types of liver injury
  - Acute hepatitis (within 3 mo)
    - Immune-mediated (AIH-like ?)
    - Histology – portal inflammation and eosinophilic infiltrates
  - Chronic hepatitis, cirrhosis
  - Cholestasis

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Chaparral (*Larrea tridentata*)

- Leaves of desert bush: Greasewood (found in California and Mexico)
- Used: various conditions e.g. pain, cancer, wt. reduction
- Types of liver injury
  - Hepatitis (zone 3 necrosis): 3-52 wk after ingestion
  - ALF
  - Cirrhosis

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Black Cohosh

- Actaea racemosa and Cimicifuga racemosa (found in the Eastern US and Canada)
- Used: post-menopausal symptoms
- Contains triterpene glycerides, phenolic acids, flavonoids, volatile oils, and tannins
- Types of liver injury
  - Acute hepatitis and ALF
  - AIH-like hepatitis

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Pennyroyal Oil

- Squawmint or mosquito plant (พืชวงศ์กะเพรา หรือ วงศ์มิ้นต์)
- Used: abortifacient, pesticide
- Centrilobular necrosis
  - CYP450-induced toxic metabolite of menthofuran → induces reactive metabolites and GSH depletion
  - ALF, multiorgan failure can occur
- Theoretically, replacement of GSH by NAC may help

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Chinese Herbal Medicines

- Widely used by Asia and Asian communities throughout the world
- Usually in combination form
  - 3-6 different herbs with a primary active component (King herbs)
- Contaminations with synthetic drugs and heavy metals have been reported

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Jin Bu Huan (*Lycodium serratum*)

- Contains neuroactive substance
- Used: sedative and analgesic
- Types of liver injury
  - Acute hepatitis
    - Duration 7-52 wk (mean 20) after taking
    - Eosinophilia and serum autoantibodies may observe (immune-mediated?)
    - Histology – hepatitis, periportal necrosis and fibrosis, and microvesicular steatosis
  - Chronic hepatitis
  - Cholestasis or cholestatic hepatitis

References:
- Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Ma-Haung (*Ephreda*)

- Sympathomimetic effects
- Used: nasal and sinus congestion, bronchodilator, weight reduction, increased athletic performance
- Types of liver injury
  - Acute hepatitis (3-16 wk)
  - AIH-like hepatitis
  - ALF

Dai-Saiko-To, Sho-Saiko-To or TJ-9

- Consists of 7 herb components: bupleurum root, pinellia tuber, scutellaria root, jujube fruit, ginger rhizome, ginseng root, and glycyrrhiza root
- Used in China and Japan to treat liver disease
- Types of liver injury
  - Acute hepatitis (1.5-3 mo)
  - AIH-like hepatitis

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Lingzhi Mushroom, เห็ดหลินจือ
((Ganoderma lucidum))

- One of the oldest medicinal mushroom
- Used: cytoprotective, anti-tumor, and antioxidant
- Contains triterpenes (ganoderic acids)
- 2 cases of severe hepatotoxicity
  - Both had taken powder form
  - Onset 1-2 mo after use
  - LFT: severe hepatitis ± cholestasis
  - One died / one recovered in 5 mo

Lingzhi Mushroom Hepatotoxicity

- Liver histology: portal and lobular changes including cholestasis [C], macrovesicular fatty change [F], acidphilic bodies [A] and polymorphs [P]

- The presence of eosinophil infiltrations in the portal tracts suggests that the mechanism of the hepatotoxicity is mediated through an immunoallergic reaction

Ayurvedic Herbal Medicine

- Generally consists of numerous plants; may combination with metals, minerals and gems
- Types of liver injury
  - Acute and chronic hepatitis
  - Worsening of cirrhosis (Liv.52)*
- Extrahepatic symptoms are common

Bunchorntavakul C. Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
บอระเพ็ด (Tinospora cordifolia, T. crispa)

- ไม่มีเลื้อยมีรสขม
- Used: various conditions, esp. DM
- Contains alkaloids (berberine)
- Data from RCTs*
  - 10-12% developed hepatitis
  - Often occurs during 3-6 mo
  - Most asymptomatic
  - Severe hepatitis in some cases
- สมุนไพรแฮม/แหม (Coscinium fenestratum) also contains berberine

ต้นซีเมาเล็ก or Cassod tree (Senna siamea)

- **Used:** food or medicinal herb
- ส่วนใบอ่อน ดอก และ ยอด
  - Contain: anhydrobarakol
  - Effect: anxiolytic
  - Acute hepatitis, ALF
- ส่วนใบ
  - Contain: anthraquinones
  - Effect: laxative
  - Acute hepatitis
Herbal Laxatives

• มะขามแขก (Senna alexandrina), คูน (Cassia fistula หรือ Golden shower), ชุมเห็ดเทศ (Senna alata หรือ Ring worm cassia) และ ใบขี้เหล็ก (Senna siamea)

• Anthraquinones: dose-dependent hepatotoxin

• Types of liver injury
  • Acute hepatitis and ALF (esp. with proximal tubular acidosis)
  • Acute PVT

Phytoestrogen

- กวางเครือขาว (Pueraria candollei) และ ว่านชักมดลูกตัวเมีย (Curcuma comosa)
- Used: post-menopausal symptoms, promote women’s health
- Increased risk of breast CA
- ? Increased risk for estrogen-related liver disease e.g. hepatic adenoma, cholestasis, peliosis hepatitis
วานชักมดลูก

ตัวเมีย (Curcuma comosa)
- ก้านช่อดอกสั้น
- Phytoestrogen +

ตัวผู้ (Curcuma zanthorrhiza)
- No phytoestrogen
- Induces platelet dysfunction – causing spontaneous bleeding in animal model
Herbalife® Products

- HDS in the form of drinks, tablets, capsules and energy bars for weight control, nutritional support and improvement in well-being
- Each product often has several ingredients
- Distributed in over 60 countries with the possibility of regional variations in product quality

Navarro VJ. Semin Liver Dis 2009;29:373-82
Herbalife® Hepatotoxicity

• Series of Herbalife-associated hepatotoxicity
  – Major case series: from Israel (14 cases)\textsuperscript{1}, Spain (20 cases)\textsuperscript{2}, and Switzerland (10 cases)\textsuperscript{3}
  – Causality assessment was ‘probable’ in most cases, although ‘certain’ cases were also reported (total of 6)

• Types of liver injury
  – Acute hepatitis in most cases (AIH-like features may be seen), but cholestasis and mixed were also observed
  – ALF requiring OLT

• Contamination with \textit{Bacillus subtilis} (producing dose-dependent hepatotoxins) also reported \textsuperscript{4}

Aflatoxins

- Naturally occurring mycotoxins that are produced by many species of Aspergillus
- Heat resistant (up to 260 °C)
- Chronic exposure – intercalate into DNA causing mutation – increased risk for HCC
Hypervitaminosis A and Liver

- Liver is the major storage site for vitamin A
- In the liver, 90% of vitamin A is stored within the stellate cells (↑↑ amount – stellate cell activation)
- Chronic toxicity dose
  - >100,000 IU/day for 6 mo
  - >25,000 IU/day for 6 yr
  - Lower threshold in children and elderly
- Types of liver injury
  - Non-cirrhotic portal hypertension
  - Chronic hepatitis and cirrhosis

Penniston KL. Tanumihardjo SA. Am J Clin Nutr 2006;83:191-201
Hypervitaminosis A and Liver

- Liver biopsy: Stellate cell hyperplasia (located within sinusoids) and vacuolated Kupffer cells
- Other features: Hair loss, dystrophic nail changes

Glucosamine

- Precursor for glycosaminoglycans (major component of joint cartilage)
- Used: osteoarthritis, joint pain
- Often sold in combination with others e.g. chondroitin sulfate and MSM
- No hepatotoxicity reported in RCTs
- Types of liver injury reported
  - Acute hepatitis, mixed and ALF
  - Causality assessment ~ probable
  - Move Free Advanced® contains Chinese skullcap

Other HDS Associated with Hepatotoxicity

- Green tea (ชาเขียวจีน)
- Kava
- Camphor oil (น้ำมันหอมการบูร)
- Gardenia fruit (พุดซ์ฮัง, จีจีอ้อ)
- *Atractylis gummifera*
- *Callilepsis laureola*
- Paeonia (สมุนไพรตระกูลโบตั๋น)
- Shou-wu-pian
- Aloe vera (ส่วนยาง)
- Saw palmetto (ต้นปาล์มแคระ)
- *Centella asiatica* (ใบบัวบก)
- Noni juice (น้ำลูกยอ)
- *Cascara sagrada*
- Mistletoe
- Skullcap
- Valerian
- Margosa oil
- Pennyroyal oil
- Usnic acid
- Hydroxycut®
- Chaparral
- Psyllium husk

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Management of HDS Hepatotoxicity

- Discontinuation of use
- Supportive treatment
- Consider OLT for ALF
- Potential antidote?
  - Pyrrolizidine alkaloids – defibrotide
  - Germander – NAC
  - Pennyroyal oil – NAC
  - Amanita mushroom – NAC, silibinin, penicillin
  - HDS-induced AIH – corticosteroids
Herb-Drug Interactions

- Some herbs may have interactions with certain prescription medications by various mechanisms leading to adverse events.
- Many herbs have been identified as substrates, inhibitors, and/or inducers of various CYP450, such as St. John’s Wort, garlic, pepper, licorice, flavonoids, triterpenoids and anthraquinones.
St. John’s Wort

- *Hypericum perforatum* extract
- Used: variety of indications especially depressive disorders
- Inhibits synaptosomal uptake of 5-HT, NE, DA, and GABA
- Potent inducer of CYP3A4
  - ↑ Acetaminophen toxicity
  - ↓ Levels of warfarin, cyclosporine and protease inhibitors (HIV, HCV)

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# Herb-drug Interactions: Warfarin and Aspirin

<table>
<thead>
<tr>
<th>Herbs</th>
<th>Interactions and potential consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danshen <em>(S. miltiorrhiza)</em></td>
<td>Increased INR → bleeding risk</td>
</tr>
<tr>
<td>Lingzhi mushroom (เห็ดหลินจือ)</td>
<td>Increased INR → bleeding risk</td>
</tr>
<tr>
<td>Garlic (กระเทียม)</td>
<td>Increased INR → bleeding risk</td>
</tr>
<tr>
<td>Papaya (มะละกอ)</td>
<td>Increased INR → bleeding risk</td>
</tr>
<tr>
<td>Tamarind (มะขาม)</td>
<td>Increased aspirin level → bleeding risk</td>
</tr>
<tr>
<td>Feverfew <em>(T. parthenium)</em></td>
<td>Platelet dysfunction → bleeding risk</td>
</tr>
<tr>
<td>Gingko biloba (แปะก๊วย)</td>
<td>Platelet dysfunction → bleeding risk</td>
</tr>
<tr>
<td>ว่านชําบัดลูกคัตั๋ว (C. zanthorrhiza)</td>
<td>Platelet dysfunction → bleeding risk</td>
</tr>
<tr>
<td>Ginseng (โสม)</td>
<td>Decreased INR → clotting risk</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Decreased INR → clotting risk</td>
</tr>
<tr>
<td>Devil’s claw <em>(H. cumbens)</em></td>
<td>Purpura</td>
</tr>
</tbody>
</table>

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
# Herb-drug Interactions: Other Medications

<table>
<thead>
<tr>
<th>Medications</th>
<th>Herbs</th>
<th>Interactions and potential consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 drugs</td>
<td>Pyrrolizidine alkaloids Germander</td>
<td>CYP3A4 induction → increased hepatotoxicity</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>St. John’s Wort Grape fruit juice</td>
<td>CYP3A4 induction → increased rejection risk</td>
</tr>
<tr>
<td>MTX</td>
<td>St. John’s Wort Echinacea (ดอกโคน)</td>
<td>Increased methotrexate toxicity</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Ginseng (โสม)</td>
<td>Possible additive effect</td>
</tr>
<tr>
<td></td>
<td>Licorice (ชะเอม)</td>
<td>Reduced clearance → hypokalemia</td>
</tr>
<tr>
<td></td>
<td>Sho-saiko-to</td>
<td>Altered clearance → low pred level</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>St. John’s Wort Garlic (กระเทียม)</td>
<td>CYP3A4 induction → suboptimal antiviral activity</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Licorice (ชะเอม)</td>
<td>Mineralocorticoid → Reduced spironolactone effect</td>
</tr>
</tbody>
</table>

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther 2013;37:3-17
Thank You for Your Kind Attention

You’re eating too many herbs!