Traditional Medicine: From Grandma’s Observations to Evidence-based Science

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Appetite For Life
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Traditional Medicine (TM):
Traditional medicine refers to the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, used in the maintenance of health and in the prevention, diagnosis, improvement or treatment of physical and mental illness. (WHO definition)

Traditional Chinese Medicine (TCM):
The traditional medicine indigenous to Chinese culture and history.

Herbal Medicine (HM)
Traditional Medicine that uses herbs for treatment.
Elements of Today’s Presentation

• History of using herbal medicine for disease treatment.

• Efficacy and Toxicity of using herbs.

• Scientific insight of herbal medicine: the natural product basis and the mode of action.
Herbal Medicine: Grandmas’ Observations and Simple Philosophy

Grandmas’ observations

Summaries in documents

Compendiums/Pharmacopoeias

Theory, Principles, philosophy

Traditional Medicine

Five tastes: Acrid, Sweet, Sour, Bitter, Salty

Four properties: Cold, Cool, Warm, Hot
The most important herb compendiums in history:

**Earliest compendium:**
- **Shennong’s herbal classic**
- The EARLIEST herbal compendium
- Include 365 herbs; 2000+ years ago

**The First Pharmacopeia**
- Tang dynasty compendium of herbal medicine
- The first Pharmacopeia in the world; 800+ years ago

**The Most Comprehensive Encyclopedia:**
- Compendium of Materia Medica written by Li Shizhen (1518–1593 AD) during the Ming Dynasty of China.

**Modern Pharmacopeia**
- The first modern Pharmacopeia was published in 1953.
- Updates every 5 years. The current version is 2015.
- ~2500 species are included in the current Pharmacopeia for traditional medicine, including individual herb and herbal formulas.
o Raw herbs processed into ready-to-use herbal slices.

o TCM doctor diagnoses patient and prescribes herbal formula or pharmaceutical product from a formula

o TCM promotes dietary therapy. A lot of TCM herbs can be used as functional food.

o Herbal products are regulated by CFDA as OTC drugs.

Pharmaceutical products from TCM formula
Examples of TCM herbs to Prevent and Manage Diseases

- Obesity, type 2 diabetes (T2D), and the related metabolic symptoms
  - TCM philosophy

  Yang

  Early stage: Yang excessive

  Further stage: Yin and Yang both reduced; Yang > Yin

  Heat clearing herbs
  - Radix Rehmanniae
  - Coptis Root
  - Bitter melon
  - Lycii Cortex
  - Radix Astragal

- Herb cannot replace hypoglycemic medication.
- Please Consult the endocrinologists!
Example of Herbal Medicine to Prevent and Manage Diseases

- Cardiovascular Diseases
  - Salvia miltiorrhiza (Danshen) or Red Sage
    - Coronary heart diseases (Clinical trial phase II approved)
    - Prevention and management of diabetes and its complications (under clinical trial)
    - Acute mountain sickness (under clinical trial)
  - Danshen Dripping Pills

- Cancer
  - Job's tears or Coix lacryma-jobi
    - Pancreas cancer (combined with Gemcitabine)
  - Kanglaite®
    - Advanced non-small cell lung cancer (NSCLC)
    - Under clinical trials

- Alcohol Abuse
  - Kudzu root
    - Inhibit alcohol consumption
  - Kudzu Extract
    - Under clinical trials
Nearly 1 in 5 adults in the U.S. report taking an herbal product.

Thousands of herbal products are available over the counter and commonly used in the U.S.

Herbal products are regulated as dietary supplements. They are produced, sold, and marketed without first demonstrating safety and efficacy, as is required for pharmaceutical drugs.

### Table 1. The Ten Most Commonly Used Herbal Medicines in the United States

<table>
<thead>
<tr>
<th>Herb</th>
<th>Percent use in U.S.*</th>
<th>Common use†</th>
<th>Scientific evidence for efficacy‡</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinacea</td>
<td>7.0</td>
<td>Upper respiratory tract infection</td>
<td>Inconclusive⁹</td>
<td>Side effects similar to placebo⁹</td>
</tr>
<tr>
<td>Ginseng</td>
<td>4.2</td>
<td>Physical and cognitive performance</td>
<td>Inconclusive¹²</td>
<td>Limited data; hyperactivity and restlessness in case reports¹²</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>3.7</td>
<td>Dementia</td>
<td>Likely Effective¹³</td>
<td>Side effects similar to placebo;¹⁶ case reports of bleeding¹⁷</td>
</tr>
<tr>
<td>Garlic</td>
<td>3.4</td>
<td>Claudication, Hypercholesterolemia</td>
<td>Likely Effective¹⁵</td>
<td>Mild gastrointestinal side effects and garlic odor;¹⁶ case reports of bleeding²⁰,²¹</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>2.1</td>
<td>Depression</td>
<td>Likely Effective for mild-moderate depression²²,²³</td>
<td>Numerous reports of drug interactions²⁶</td>
</tr>
<tr>
<td>Peppermint</td>
<td>2.1</td>
<td>Upset stomach / irritable bowel syndrome</td>
<td>Inconclusive²⁷</td>
<td>Limited data, but side effects appear to be mild²⁷</td>
</tr>
<tr>
<td>Ginger</td>
<td>1.8</td>
<td>Nausea</td>
<td>Inconclusive²⁸</td>
<td>No known side effects⁵</td>
</tr>
<tr>
<td>Soy</td>
<td>1.7</td>
<td>Menopausal symptoms</td>
<td>Not effective²⁹</td>
<td>Concerns regarding long-term estrogenic effects²⁹</td>
</tr>
<tr>
<td>Chamomile</td>
<td>1.5</td>
<td>Hypercholesterolemia</td>
<td>Effective³⁰</td>
<td>Rare allergic reactions³¹</td>
</tr>
<tr>
<td>Kava kava</td>
<td>1.2</td>
<td>Insomnia / gastrointestinal problems</td>
<td>Likely Effective³²</td>
<td>Case reports of severe hepatotoxicity³³</td>
</tr>
</tbody>
</table>

*Percent are based on estimates from a 2002 National Health Interview Study, age adjusted to the year 2000 U.S. Standard Population.

†Common use was determined from herbal medicine textbooks.

‡Scientific evidence is based on conclusions from recently published systematic reviews.
The Safety Issue of Herbal Medicine

Nature ≠ Nontoxic

*Aristolochia* plants cause renal failure, cancer, liver damage

Licorice Root and any plants or extracts with Glycyrrhizic acids may cause hypertension and kidney failure.
Why Scientific Research for Herbal Medicine is Important?

**Key Scientific Questions**

- What are the bioactive compounds in herbs?
- What are the mechanisms of the efficacy?
- What are the adverse effects?
- What causes the toxicity? How?
- How to evaluate the quality of herbs?
- How to share the knowledge with the world?

**Understanding scientific insight of Herbal Medicine requires interdisciplinary efforts.**
Two major Mentalities in Herb Research

1) Screen for pure compound leading to chemical drug.

Successful cases:

- The selection of plants was sometimes inspired by traditional medicine
- The relationship between structure and activity is clear
- Efficacy/toxicity evaluated by scientific study design
- The successful rate from screening to drug is low
- The synergistic effects were normally ignored.
- The effect/toxicity of the screened pure compound is not equal to the crude extract

Dr. Mansukh C. Wani

Artemisia annua (Qinghao)
Artemisinin
Galega officinalis (goat's rue)
Metformin
Taxus
Taxil
Two major mentality in Herb Research

- Use herbs as food, nutraceuticals, and botanical drugs with understanding of scientific insights in chemical composition and working mechanism.

Quality Standardization

Chemical Composition

Evaluation of Efficacy/toxicity

Clinical trial

Animal models, cell models

Mode of action

- A translational research based on herbs that used in disease treatment for long history
- Focus on understanding the overall effect of the standard extract from herb instead of one compound
- Efficacy/toxicity evaluated by scientific study design
- Most of them are less potent as the chemical drug but also with less adverse effect
- Challenging to achieve quality consistency for herb
- The working mechanism and synergistic effects are difficult to study
Government Efforts to Improve Quality Standard on Herbal Medicine

- The Hong Kong Chinese Materia Medica Standards Program (HKCMMS)

## Source and Origins

### Quality Control Standards:

1. Morphology
   - Plants, part of plant for medicinal use, harvest time and post-harvest processing
   - Macroscopical and microscopical features
2. Chemistry
   - Featured compound, fingerprint, content limit for bioactive compound
3. Hazardous substance
   - Pesticide, heavy metal, mycotoxins

## Project Priority:

1. Raw Material
2. Ready-to-use herb
3. Formula/pharmaceutical products
Quality Research on Lycii Cortex

What is Lycii Cortex (LyC)?

Lycium chinense
- Leaves

Lycium barbarum
- Fruit
- Root bark

Lycii Folium

Lycii Fructus

Vegetable medicine food homology

Property in cold and function in clearing heat
Prescribed for heat symptoms, like early diabetes, hypertension, fever, and sepsis.

Kukoamine B (KB) is the Major and Unique compound in LyC
KB has been adopted as quality control marker for LyC

Abbreviations: MC, Moutan Cortex; EC, Erythrinae Cortex; PC, Periplocae Cortex; AC, Acanthopanacis Cortex; Mori C, Mori Cortex; and CC, Cinnamoni Cortex.

KB and KA are only existed in LyC but not other cortex herbs.
Research of LyC and KB for intervention of early type 2 diabetes

Research Questions:
1. Is KB the bioactive compound?
2. How does it work?

Study Design

<table>
<thead>
<tr>
<th>Strain</th>
<th>Grouping</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6 mice, male</td>
<td>Wild Type (WT)</td>
<td>WT+ vehicle (saline)</td>
</tr>
<tr>
<td>db/db mice, male</td>
<td>Disease model (Control)</td>
<td>db/db + vehicle</td>
</tr>
<tr>
<td></td>
<td>KB</td>
<td>db/db + KB (50 mg/kg/day)</td>
</tr>
<tr>
<td></td>
<td>LyC</td>
<td>db/db + LyC (5 g/kg/day)</td>
</tr>
<tr>
<td></td>
<td>Metformin (pos 1)</td>
<td>db/db + met (5 mg/kg/day)</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone (pos 2)</td>
<td>db/db + Rosi (5 mg/kg/day)</td>
</tr>
</tbody>
</table>

The treatment lasted for 9 weeks
KB inhibited blood glucose increase without bodyweight gain

Comparison of glucose-lowering effects between KB, LyC, metformin and Rosiglitazone (n=10)

Wild type, C57 mice + vehicle;
Db/db mice, db/db mice based on gene background of C57 + vehicle
KB high, db/db mice + kukoamine B (50 mg/kg)
LyC, db/db mice + LyC extract (5g/Kg)
Metformin, db/db mice + metformine (5 mg/kg)
Rosiglitazone, db/db mice + rosiglitazone (5 mg/Kg)
Significance is compared to db/db mice, *, p<0.05, **, p<0.01

KB down-regulated blood glucose without influencing bodyweight
LyC has no effect on blood glucose
Rosiglitazone showed severe adverse effects
How KB intervenes early type 2 diabetes?
Diabetes is a complicated disease with systemic disorders in metabolism.

- Excessive nutrition > metabolic capability
- Chronic inflammation
- Insulin signaling disorder
- Catabolism > Metabolism
- Dyslipidemia: TG↑, Cholesterol↑, FFA↑
- Disturbing Amino acids metabolism
- Gluconeogenesis
- Glucose ↑

Metabolomics will tell you more than just blood glucose.....
**KB intervened dyslipidemia in diabetic mice**

**Take home message:**

1. KB reduced TG, PE and cholesterol, and increased PC. This may relate to improvement of lipoprotein function in lipid secretion, transpiration, clearance.

2. KB intervened lipids in a similar way as rosiglitazone, but with much less potency than rosiglitazone. Metformin displayed less influence on lipid profile alterations.

**Abbreviations and Symbols**

- TG, Triglyceride
- DG, diacylgycerol
- MG, monoglycerol
- PC, Phosphatidylcholine (Acyl)
- PC, Phosphatidylcholine (Alkyl)
- Lyso-PC, lysophosphatidylcholine
- SM, Sphingomyelin
- PE, phosphatidylethanolamine
- PI, Phosphatidylinositol
- Cer, ceramides
- Cholesterol
KB improves fatty acid metabolism

Take home message:

1. KB accelerates fatty acid oxidation in starvation for energy supply and lipid homeostasis.
2. The way that KB stimulates fatty acid metabolism is similar to Rosiglitazone (Ros), but in much less potency.
3. Metformin works in a different route from KB and Ros. Metformin inhibits gluconeogenesis which can be shown in the reduced short chain acylcarnitines.

<table>
<thead>
<tr>
<th>Acylcarnitines</th>
<th>Range of Value (nM)</th>
<th>KB Vs db/db FC*</th>
<th>Met Vs db/db FC</th>
<th>Ros Vs db/db FC</th>
<th>WT Vs db/db FC</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0</td>
<td>64.95-34.7</td>
<td>-1.25</td>
<td>-1.42</td>
<td>-1.24</td>
<td>-1.16</td>
</tr>
<tr>
<td>C14</td>
<td>0.081-0.427</td>
<td>1.06</td>
<td>0.49</td>
<td>-1.12</td>
<td>0.21</td>
</tr>
<tr>
<td>C14:1</td>
<td>0.058-0.294</td>
<td>1.19</td>
<td>0.03</td>
<td>-1.09</td>
<td>0.29</td>
</tr>
<tr>
<td>C14:1-OH</td>
<td>0.01-0.037</td>
<td>1.20</td>
<td>0.04</td>
<td>-1.01</td>
<td>0.87</td>
</tr>
<tr>
<td>C14:2</td>
<td>0.014-0.044</td>
<td>-1.06</td>
<td>0.57</td>
<td>-1.24</td>
<td>0.06</td>
</tr>
<tr>
<td>C16</td>
<td>0.295-1.01</td>
<td>1.07</td>
<td>0.31</td>
<td>1.09</td>
<td>0.22</td>
</tr>
<tr>
<td>C16-OH</td>
<td>0.009-0.045</td>
<td>1.34</td>
<td>0.02</td>
<td>1.27</td>
<td>0.01</td>
</tr>
<tr>
<td>C16:1</td>
<td>0.064-0.298</td>
<td>1.35</td>
<td>0.01</td>
<td>-1.02</td>
<td>0.84</td>
</tr>
<tr>
<td>C16:1-OH</td>
<td>0.011-0.039</td>
<td>1.16</td>
<td>0.16</td>
<td>1.18</td>
<td>0.05</td>
</tr>
<tr>
<td>C16:2</td>
<td>0.014-0.065</td>
<td>-1.03</td>
<td>0.79</td>
<td>-1.26</td>
<td>0.13</td>
</tr>
<tr>
<td>C18</td>
<td>0.04-0.235</td>
<td>-1.17</td>
<td>0.02</td>
<td>-1.01</td>
<td>0.89</td>
</tr>
<tr>
<td>C18:1</td>
<td>0.209-0.588</td>
<td>1.21</td>
<td>0.02</td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>C18:1-OH</td>
<td>0.013-0.048</td>
<td>1.36</td>
<td>0.01</td>
<td>1.18</td>
<td>0.05</td>
</tr>
<tr>
<td>C18:2</td>
<td>0.037-0.286</td>
<td>-1.06</td>
<td>0.65</td>
<td>-1.25</td>
<td>0.12</td>
</tr>
<tr>
<td>C2</td>
<td>64.95-34.7</td>
<td>-1.25</td>
<td>0.11</td>
<td>-1.42</td>
<td>0.03</td>
</tr>
<tr>
<td>C3</td>
<td>0.119-1.01</td>
<td>1.12</td>
<td>0.44</td>
<td>-1.18</td>
<td>0.28</td>
</tr>
<tr>
<td>C4</td>
<td>0.275-1.35</td>
<td>1.25</td>
<td>0.06</td>
<td>-1.29</td>
<td>0.03</td>
</tr>
<tr>
<td>C3-DC (C4-OH)</td>
<td>0.086-0.441</td>
<td>1.44</td>
<td>0.02</td>
<td>1.11</td>
<td>0.50</td>
</tr>
<tr>
<td>C5</td>
<td>0.082-0.231</td>
<td>-1.07</td>
<td>0.44</td>
<td>-1.30</td>
<td>0.01</td>
</tr>
<tr>
<td>C6 (C4:1-DC)</td>
<td>0.032-0.206</td>
<td>1.00</td>
<td>0.99</td>
<td>-1.41</td>
<td>0.02</td>
</tr>
<tr>
<td>C5-DC (C6-OH)</td>
<td>0.008-0.041</td>
<td>1.22</td>
<td>0.10</td>
<td>-1.07</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Note: Paired t-test was used for calculating the “p value”. Threshold for significance: *FC>1.5, or **p<0.05. Range of value (nM), concentration range of each acylcarnitine across all investigated samples. The unit for acyl carnitine C0 (carnitine) and C2 (acetyl carnitine) are µM.
KB reduced chronic inflammation in db/db mice

The healthy WT mice show lower inflammation level than the diabetic mice.

• KB reduced chronic inflammation (KB Vs db/db)

• Metformin showed less effect in inflammation (Metformin Vs db/db)

• Rosiglitazone severely decreased all inflammatory cytokines (Rosiglitazone Vs db/db); It might cause immune-compromised related side-effects.

### Fold change Vs. db/db + vehicle

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>KB</th>
<th>Met</th>
<th>Rosi</th>
<th>WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP-1delta</td>
<td>-1.51</td>
<td>-1.68</td>
<td>-4.25</td>
<td>-5.51</td>
</tr>
<tr>
<td>MIP-3 alpha</td>
<td>-1.81</td>
<td>-1.96</td>
<td>-7.18</td>
<td>-7.04</td>
</tr>
<tr>
<td>NAP-2</td>
<td>-1.52</td>
<td>-1.46</td>
<td>-6.23</td>
<td>-5.67</td>
</tr>
<tr>
<td>NT-3</td>
<td>1.09</td>
<td>1.09</td>
<td>-3.92</td>
<td>-4.16</td>
</tr>
<tr>
<td>NT-4</td>
<td>-1.60</td>
<td>-1.55</td>
<td>-6.92</td>
<td>-5.64</td>
</tr>
<tr>
<td>Oncostatin M</td>
<td>1.02</td>
<td>1.14</td>
<td>-2.40</td>
<td>-2.87</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>-1.34</td>
<td>-1.23</td>
<td>-4.60</td>
<td>-6.15</td>
</tr>
<tr>
<td>Osteoprotegerin</td>
<td>-1.62</td>
<td>-1.57</td>
<td>-5.78</td>
<td>-6.39</td>
</tr>
</tbody>
</table>

Evaluate 80 cytokines in one assay

Work flow of cytokine array:

- **KB** reduced chronic inflammation in db/db mice
- The healthy WT mice show lower inflammation level than the diabetic mice.
- KB reduced chronic inflammation (KB Vs db/db)
- Metformin showed less effect in inflammation (Metformin Vs db/db)
- Rosiglitazone severely decreased all inflammatory cytokines (Rosiglitazone Vs db/db); It might cause immune-compromised related side-effects.

**Heat map of serum cytokines from different treatment groups**

**Abbreviation:** KB, db/db + KB; Met, db/db + metformin; Ros, db/db + rosiglitazone; db/db, db/db+ vehicle; WT, wild type + vehicle.
What is the effect of Lycii Cortex on early type 2 diabetes?
The highlighted effect of LyC for lowering AGE *in vivo*

“Advanced glycation end-products (AGEs) are reactive metabolites produced as a by-product of sugar metabolism. Failure to remove these highly reactive metabolites can lead to protein damage, aberrant cell signaling, increased stress responses, and decreased genetic fidelity.”

AGE level determined in mice blood by ELISA

- **LyC**
- **KB**
- **Met**
- **Rosi**
- **Control**

- Both LyC and KB lowers AGE *in vivo*
- **LyC > KB**

- Diabetic complications
- Aging
- Alzheimer’s
- Cardiovascular diseases
- Oxidative stress
- Chronic inflammation
- Cell damaged
## Efficacy of Lycii Cortex (LyC): Something out of blood glucose

<table>
<thead>
<tr>
<th>Impact</th>
<th>LyC vs Control</th>
<th>Comparison with other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting blood glucose</strong></td>
<td>Not significant effect</td>
<td>Blood glucose lowering effects: Ros&gt;met&gt;KB</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td>PE↓; Cholesterol↓; PC↓; SM↓</td>
<td>Ros&gt;KB&gt;Met (TG Cholesterol↓; PC, SM, Lyso PC↑) LyC lowers most of lipids</td>
</tr>
<tr>
<td><strong>Acylcarnitines</strong></td>
<td>--</td>
<td>Ros&gt;KB&gt;Met&gt;LyC</td>
</tr>
<tr>
<td><strong>Chronic inflammation</strong></td>
<td>Significantly ↓</td>
<td>Ros&gt;LyC&gt;KB&gt;Met</td>
</tr>
<tr>
<td><strong>Amino acids</strong></td>
<td>Glycogenic amino acids↑</td>
<td>Ros&gt;LyC&gt;Met&gt;KB</td>
</tr>
<tr>
<td><strong>Advanced glycation end products (AGE)</strong></td>
<td>Significantly ↓</td>
<td>LyC&gt;KB; Met and Ros: AGE ↑</td>
</tr>
</tbody>
</table>

- Although showing limit efficacy in fasting blood glucose, LyC significantly reduced chronic inflammation and intervened amino acid metabolism.
- KB and LyC are common in lowering chronic inflammation and AGE levels.
- These activities might be link to the “Heat clearing” function
- The synergetic effects cannot be ignored.
This research was supported by NIH Eastern Regional Comprehensive Metabolomics Resource Core (1U24DK097193) and the Hong Kong Chinese Materia Medica Standards (HKCMMS) (CityU No. 9210029)
Q & A?