

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

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# Traditional Medicine, Traditional Chinese Medicine, Herbal Medicine





# Traditional Medicine

#### **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. Herbal Medicine Traditional Chinese Medicine

- 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



# 

**Yin Yang and Five Elements** 

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

Four properties: Cold, Cool, Warm, Hot

#### Herbal Medicine: The History and Development of the Herb Compendiums

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





Compendium of Materia Medica written by Li Shizhen (1518– 1593 AD) during the Ming Dynasty of China.

The Most Comprehensive Encyclopedia

#### Modern Pharmacopeia



- The first modern Pharmacopeia was published in 1953.
- $\circ~$  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.

# **Use and Regulation of TCM Herbs in China**

- Raw herbs processed into ready-touse herbal slices.
- TCM doctor diagnoses patient and prescribes herbal formula or pharmaceutical product from a formula

Individual herb

#### Herbal formula



- TCM promotes dietary therapy. A lot of TCM herbs can be used as functional food.
- Herbal products are regulated by CFDA as OTC drugs.



Pharmaceutical products from TCM formula

#### **Examples of TCM herbs to Prevent and Manage Diseases**

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



# **Example of Herbal Medicine to Prevent and Manage Diseases**

#### • Cardiovascular Diseases



Salvia miltiorrhiza **Or Danshen Or Red Sage** 

**Danshen Dripping Pills** 

Cancer Ο



Job's tears or Coix lacryma-jobi

The Extract Seed Oil



**Kanglaite**®

#### • Alcohol Abuse



Kudzu root

Kudzu Extract

- 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)

- Pancreas cancer (combined with Gemcitabine)
- Advanced non-small cell lung cancer (NSCLC)
- Under clinical trials

- Inhibit alcohol consumption •
- Under clinical trials •



#### Use and Regulation of herbal products in the U.S.

Herb	Percent use	Common use†	Scientific evidence for	Safety
	III 0.3.		enicacy	
Echinacea	7.0	Upper respiratory tract	Inconclusive <sup>9</sup>	Side effects similar to placebo <sup>9</sup>
Ginseng	4.2	infection Physical and cognitive performance	Inconclusive <sup>12</sup>	Limited data; hyperactivity and restlessness in case reports <sup>12</sup>
Ginkgo biloba	3.7	Dementia	Likely Effective <sup>13</sup>	Side effects similar to placebo; <sup>16</sup> case reports of bleeding <sup>17</sup>
		Claudication	Likely effective <sup>15</sup>	
Garlic	3.4	Hypercholesterolemia	Likely Effective <sup>18</sup>	Mild gastrointestinal side effects and garlic odor; <sup>18</sup> case reports of bleeding <sup>20,21</sup>
St. John's wort	2.1	Depression	Likely Effective for mild- moderate depression <sup>22,23</sup>	Numerous reports of drug interactions <sup>26</sup>
Peppermint	2.1	Upset stomach / irritable bowel syndrome	Inconclusive <sup>27</sup>	Limited data, but side effects appear to be mild <sup>27</sup>
Ginger	1.8	Nausea	Inconclusive <sup>28</sup>	No known side effects <sup>5</sup>
Soy	1.7	Menopausal symptoms	Not effective <sup>29</sup>	Concerns regarding long-term estrogenic effects <sup>29</sup>
		Hypercholesterolemia	Effective <sup>30</sup>	
Chamomile	1.5	Insomnia / gastrointestinal problems	No high-quality data	Rare allergic reactions <sup>31</sup>
Kava kava	1.2	Anxiety	Likely Effective <sup>32</sup>	Case reports of severe hepatotoxicity <sup>33</sup>

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

\*Percents are based on estimates from a 2002 National Health Interview Study, age adjusted to the year 2000 U.S. Standard Population<sup>1</sup> <sup>†</sup>Common use was determined from herbal medicine textbooks.<sup>5,31,57</sup>

<sup>‡</sup>Scientific evidence is based on conclusions from recently published systematic reviews.<sup>36</sup>

# The Safety Issue of Herbal Medicine

# Nature ≠ Nontoxic

Aristolochia plants cause renal failure, cancer, liver damage



Figure 1 | Aristolochia plant from a copy by a Byzantine artist (AD 512) of the treatise on pharmacology of antiquity, *De Materia Medica*, written by the Greek military doctor **Dioscorides Pedanius** (AD 40–90). The copy is currently conserved at the National Library of Austria, Medias Graecas 1, in Vienna. Licorice Root and any plants or extracts with Glycyrrhizic acids may cause hypertension and kidney failure.





#### **Two major Mentalities in Herb Research**

1):Screen for pure compound leading to chemical drug.





- 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

## Two major mentality in Herb Research

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



- 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)



#### Quality Research on Lycii Cortex



#### 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

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



The treatment lasted for 9 weeks

# KB inhibited blood glucose increase without bodyweight gain



# How KB intervenes early type 2 diabetes?

#### Diabetes is a complicated disease with systemic disorders in metabolism



 Excessive nutrition > metabolic capability

 $\,\circ\,$  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 .



#### **KB** improves fatty acid metabolism



- 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.

C3	0.119-1.01	1.12	0.44	-1.18	0.28	1.00	0.99	1.76	0.04
C4	0.275-1.35	1.25	0.06	-1.29	0.03	1.53	0.00	-1.14	0.25
C3-DC (C4-O	<b>H)</b> 0.086-0.441	1.44	0.02	1.11	0.50	1.26	0.12	1.34	0.03
C5	0.082-0.231	-1.07	0.44	-1.30	0.01	-1.05	0.53	1.21	0.16
C6 (C4:1-DC)	0.032-0.206	1.00	0.99	-1.41	0.02	1.21	0.18	2.26	0.00
C5-DC (C6-O	<b>H)</b> 0.008-0.041	1.22	0.10	-1.07	0.57	1.43	0.01	1.94	0.00

Decreased significantly — Increased significantly \_ Not changed

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.  $^{\Delta}$ , the unit for acyl carnitine CO (carnitine) and C2 (acetyl carnitine) are  $\mu$ M.



or v up- and down- regulation of metabolites and FAO level in **diabetic mice vs healthy mice**;

Schooneman M G, et al. Acylcarnitines Reflecting or Inflicting Insulin Resistance? Diabetes, 2013, 62(1): 1-8.

#### KB reduced chronic inflammation in db/db mice



	КВ	iviet	RUSI	VVI	
Angiogenin	-1.15	1.03	-2.72	-3.43	
BDNF	-1.30	-1.03	-1.60	-1.70	
BLC	-1.72	-1.41	-2.88	-4.17	
Ck beta 8-1	-1.89	-1.35	-4.21	-4.54	
EGF	-1.69	-1.79	-0.00	-5.60	
Eotaxin	-1.38	-1.07	-2.71	-2.88	
Eotaxin-2	-1.33	-1.48	-3.37	-3.90	
Eotaxin-3	-1.23	-1.22	-2.23	-2.59	
FGF-4	-1.06	1.15	-2.13	-2.48	
FGF-6	-1.24	1.08	-2.06	-3.00	
FGF-/	-1.20	1.14	-2.24	-2.40	
Flt-3 Ligand	-1.28	1.08	-2.04	-2.37	
Fractalkine	-1.76	-1.82	-6.03	-5.53	
GCP-2	-1.87	-1.66	-3.42	-5.16	
G-CSF	-1.22	1.03	-2.81	-2.09	
GDNF	-2.04	-1.54	-3.21	-5.29	
GRO	-1.25	1.20	-1.18	-1.00	
GRO-alpha	1.01	-1.01	-2.60	-1.67	
HGF	-1.99	-1.62	-4.38	-5.07	
1-309	-1.92	-1.35	-3.59	-4.57	
IFN-gamma	-1.33	-1.10	-3.93	-2.13	
IGFBP-1	-1.85	-1.43	-4.72	-5.31	
IGFBP-2	-1.15	-1.73	-2.08	-2 79	
IGFBP-4	-1.70	-1.60	-6.76	-7.45	
IGF-I	-1.53	-1.20	-3.19	-3.87	
IL-1 alpha	-1.19	-1.05	-2.50	-1.96	
IL-1 beta	-1.81	-1.39	-4.67	-4.61	
IL-10	-1.40	1.29	-2.23	-1.92	
IL-12 p/0	-1.43	-1.03	-1.49	-2.17	
IL-15	-1.45	-1.03	-2.63	-1.93	
IL-16	-1.30	-1.07	-3.37	-4.41	
IL-2	-1.27	1.01	-2.49	-2.10	
IL-3	-1.41	-1.15	-2.09	-2.69	
IL-4	-1.23	1.09	-1.75	-2.02	
IL-5 II -6	-1.35	-1.05	-3.06	-2.16	
IL-7	-1.05	1.13	-2.13	-1.57	
IL-8	-1.29	1.14	-2.35	-1.73	
IP-10	-1.59	-1.26	-3.62	-4.48	
Leptin	-1.67	-1.56	-4.07	-3.97	
LIGHT	-1.25	1.15	-2.02	-2.46	
MCP-1	-1.30	1.06	-3.51	-2.15	
MCP-2	-1.47	-1.65	-4.55	-3.47	
MCP-3	-1.26	-1.09	-2.65	-2.83	
MCP-4	-1.81	-1.83	-5.37	-5.22	
MDC	-1.23	-1.27	-3.73	-3.30	
MIF	-1.00	-1.62	-5.63	-5.12	
MIG	-1.43	1.08	-3.53	-2.41	
MIP 1 beta	1.21	1.01	2.02	2.41	E
MIP-1delta	-1.51	-1.68	-4.25	-5.51	
MIP-3 alpha	-1.81	-1.96	-7.18	-7.04	
NT-3	1.09	1.09	-3.92	-4.16	a
NT-4	-1.60	-1.55	-6.92	-5.54	
Oncostatin M	1.02	1.14	-2.40	-2.87	
Osteopontin	-1.34	-1.23	-4.60	-6.15	
PARC	-1.01	1.16	-3.01	-2 54	
PDGF-BB	-1.41	-1.22	-4.22	-2.54	
PIGF	-1.59	-1.12	-3.55	-4.99	
RANTES	-1.44	-1.25	-3.92	-5.32	
SCF	-1.48	-1.37	-3.09	-3.91	
SDF-1	-1.45	-1.18	-3.32	-3.58	
TGE-beta 1	-1.54	-1.11	-2.77	-2.34	
TGF-beta 2	-1.23	1.14	-2.21	-2.95	
TGF-beta 3	-1.34	-1.00	-2.28	-3.55	1
Thrombopoietin	-1.27	-1.06	-1.75	-1.88	
TIMP-1	-1.26	-1.09	-3.29	-4.06	
TNF-alpha	-1.43	-1.44	-5.57	-5.38	
TNF-beta	-1.37	1.02	-2.63	-2.13	
VEGF	-1.27	-1.23	-2.94	-2.71	

VD NA V DOCI W/T

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

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

-1.5	
-2.0	
-3.0	
-4.0	
-5.0	
-6.0	
-7.0	
-8.0	$\mathbf{\Lambda}$

Abbreviation: KB, db/db + KB; Met, db/db + metformin; Ros, db/db + rosiglitazone; db/db, db/db+ vehicle; WT, wild type + vehicle.

# Heat map of serum cytokines from different treatment groups

# 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

0

2000

# Efficacy of Lycii Cortex (LyC): Something out of blood glucose

Impact	LyC vs Control	Comparison with other treatments		
Fasting blood glucose	Not significant effect	Blood glucose lowering effects: Ros>met>KB		
Lipids	PE↓; Cholesterol↓; PC↓; SM↓	Ros>KB>Met (TG Cholesterol↓; PC, SM, Lyso PC个) LyC lowers most of lipids		
Acylcarnitines		Ros>KB>Met>LyC		
Chronic inflammation	Significantly 🗸	Ros>LyC>KB>Met		
Amino acids	Glycogenic amino acids ↑	Ros>LyC>Met>KB		
Advanced glycation end products (AGE)	Significantly 🗸	LyC>KB; Met and Ros: AGE 个		

- Although showing limit efficacy in fasting blood glucose, LyC significantly reduced chronic inflammation and intervened amino acid metabolism.
- KB and LyC are common is lowering chronic inflammation and AGE levels.
- These activities might be link to the "Heat clearing" function
- The synergetic effects cannot be ignored.

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# Q & A?