

NAS STEP “ The Dragon and the Elepahnt”

Spetmebr24/25, 2007

Traditional Medicine and Modern Medicine

Full speed ahead

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NATIONAL INSTITUTES
OF HEALTH

Bone and Joint Decade, USA ,2002-2011

THEN



"I'll be back!"



NOW



"Oh, my back!"



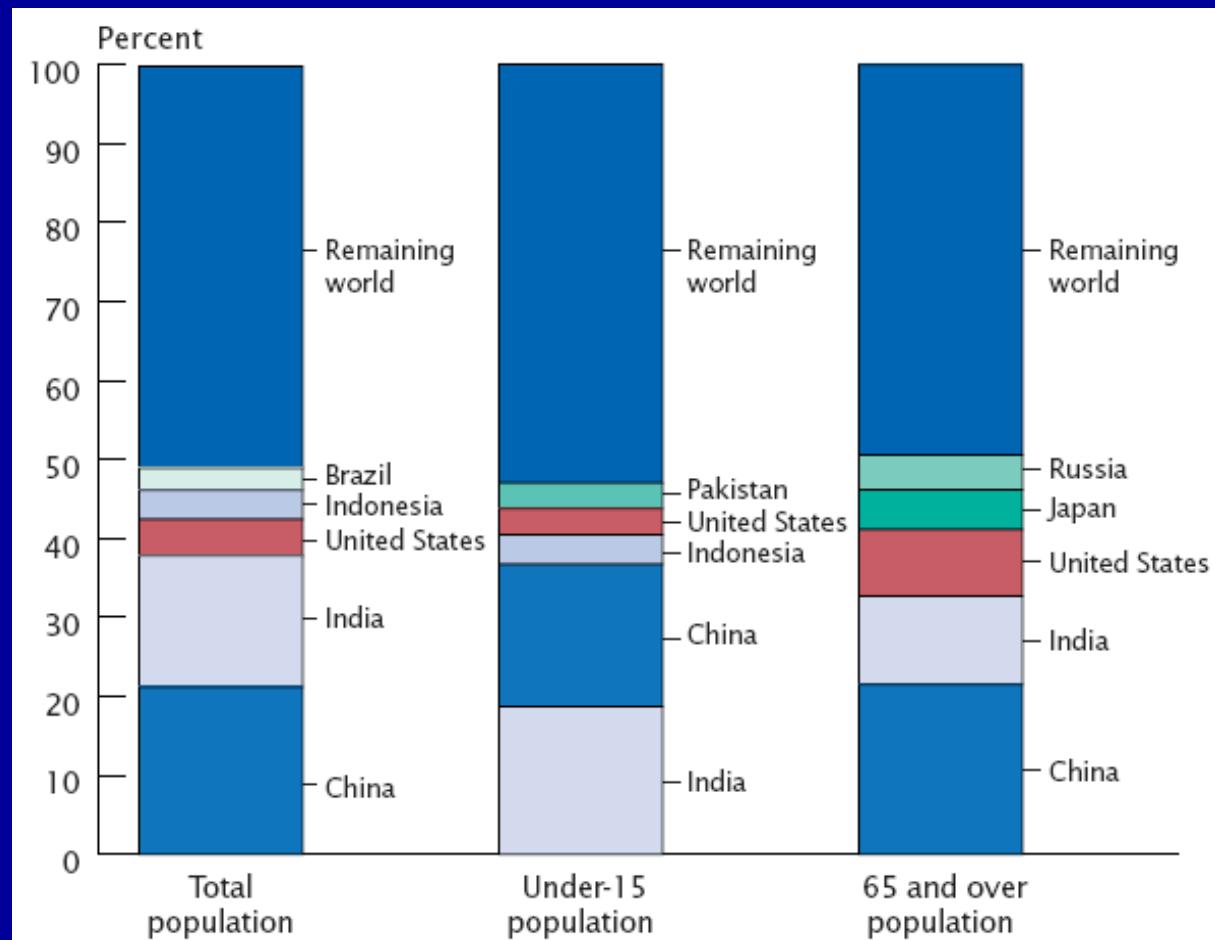
Musculoskeletal impairments : Chronic Diseases

- Musculoskeletal conditions cost US society an estimated \$254 billion every year
- 1 out of every 7 Americans reports a musculoskeletal impairment
- More than 43 million people have some form of arthritis
- Aging population: ~35 million (US), ~110 million (China), ~50 million (India) over 65.

Global Health Grand Challenges

~600 million over 65 at 2025

Traditional medicine : Traditional Chinese Medicine and Indian Ayurveda medicine



WESTERN AND CHINESE MEDICINE

Both have made great contributions to health and treatment of disease. However, each has formed its own fundamental rules, in practice as in theory, making the two quite different, especially in the drugs they design and use.

Western Medicine (Modern Medicine)

- Uses pure compounds
- Either natural or synthetic products originating from Modern new drug discovery approaches
- Aimed to effect a single target as an inhibitor
- Results in side effects

Chinese Medicine (Traditional Chinese Medicine, TCM)

- Uses combinations of compounds based on human experience
- Mainly processed crude natural products
- Formulated to effect multiple targets as regulators or biological response modifiers
- Results in fewer side effects

Drug Discovery: new pipelines

Traditional herb medicine as sources of drug discovery.

Many success stories

- **Dr. H. K. Lee.** The Natural Products Research Laboratories (NPRL). University of North Carolina. ~2000 leads.
 - *GL-331*, an anticancer drug. Phase II trial.
 - *Bevirimat (PA-457, DSB)*, anti-AID drug. Phase II trial.
 - *Novel curcumin analogs*: for treating acne. Phase I trial.
 - *PA-344B*, an inhibitor of HIV reverse transcriptase.
Preclinical studies.
- **Drs. Tao and Lipsky**, NIAMS, NIH :
 - *Tripolide and Celastrol*: Rheumatoid arthritis.

Turmeric / Curcumin

Turmeric in Ayurvedic medicine

- antiseptic for cuts and burns
- fluoride with dental benefits

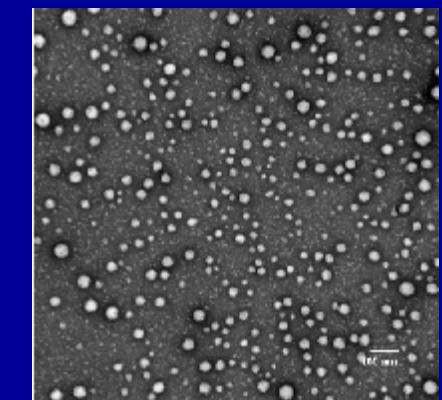
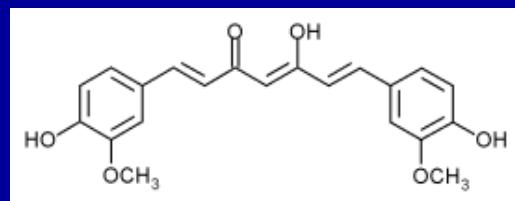
Used for treating depression and stomach ailments



Koehler's Medicinal-Plants 1887

The active substance of turmeric is **curcumin**:

- Natural Yellow 3 (E100 in E.U.)
- (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione.



From cell and animal studies

- Anti-tumoral
- Anti-inflammatory
- anti-nociceptive
- anti-amyloidogenic

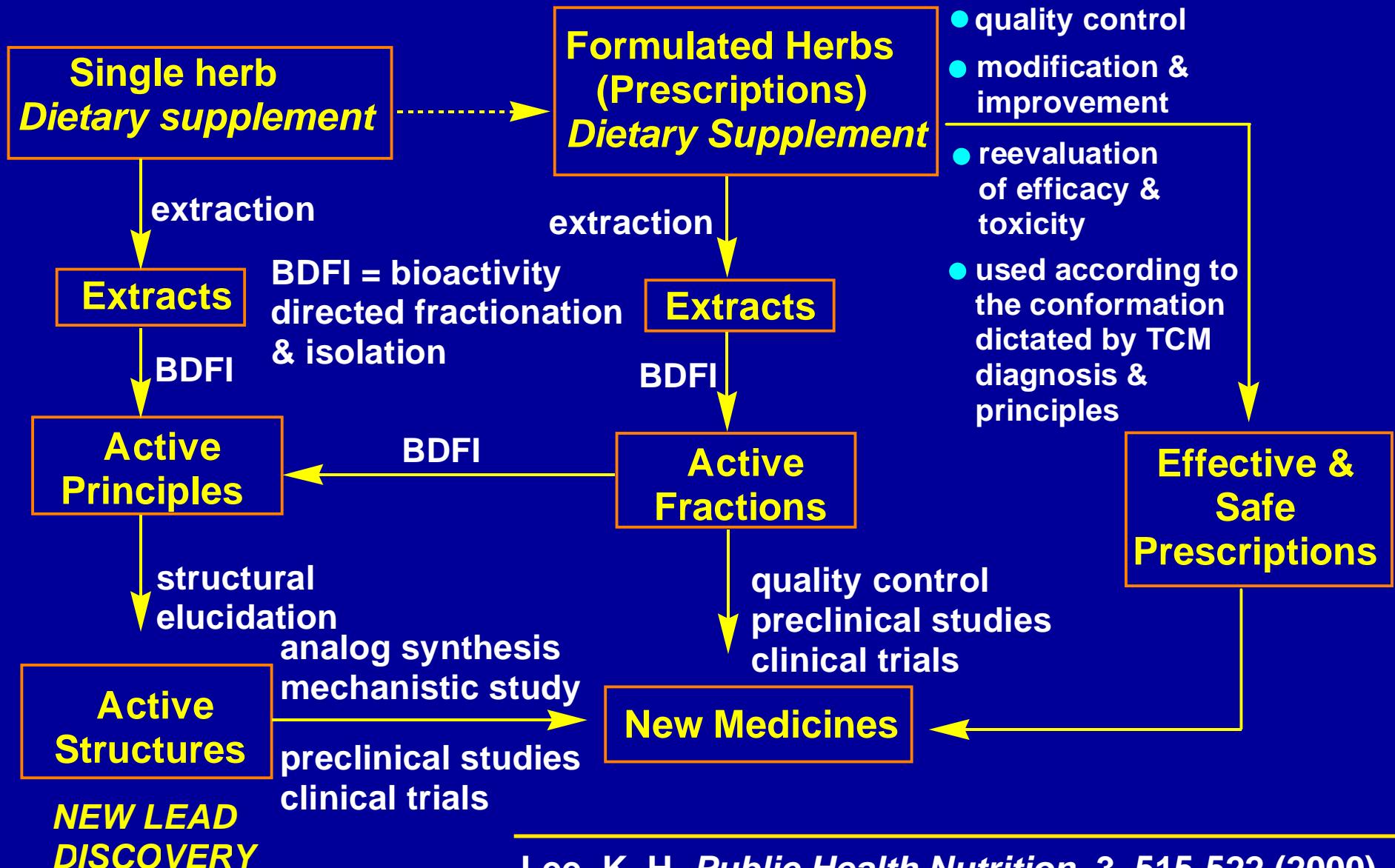
Problem as therapeutic agent:

- Poor aqueous solubility
- Poor bioavailability

Encapsulation in nanoparticles increases bioavailability and inhibits Pancreatic cancer cell lines.

“nanocurcumin”
Bisht, et al., J. Nanobiotech. (2007)

Principal Concepts of Research on New Medicines



What main issues should be addressed in bringing herbal & traditional medicines into the mainstream pharmaceutical market?

- Supply
- Quality Control
- Safety – Including Possible Interactions with Other Drugs
- Proven Efficacy
- Publications in Mainstream Journals
- Publicity in the Media

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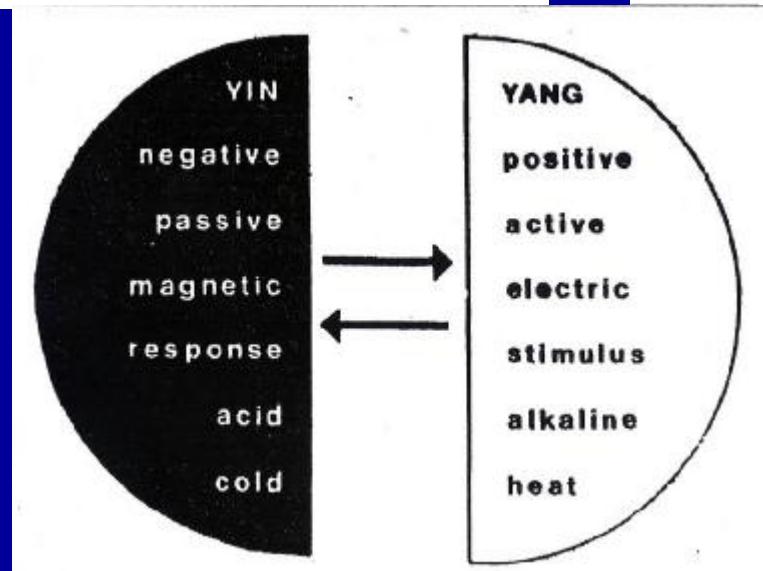
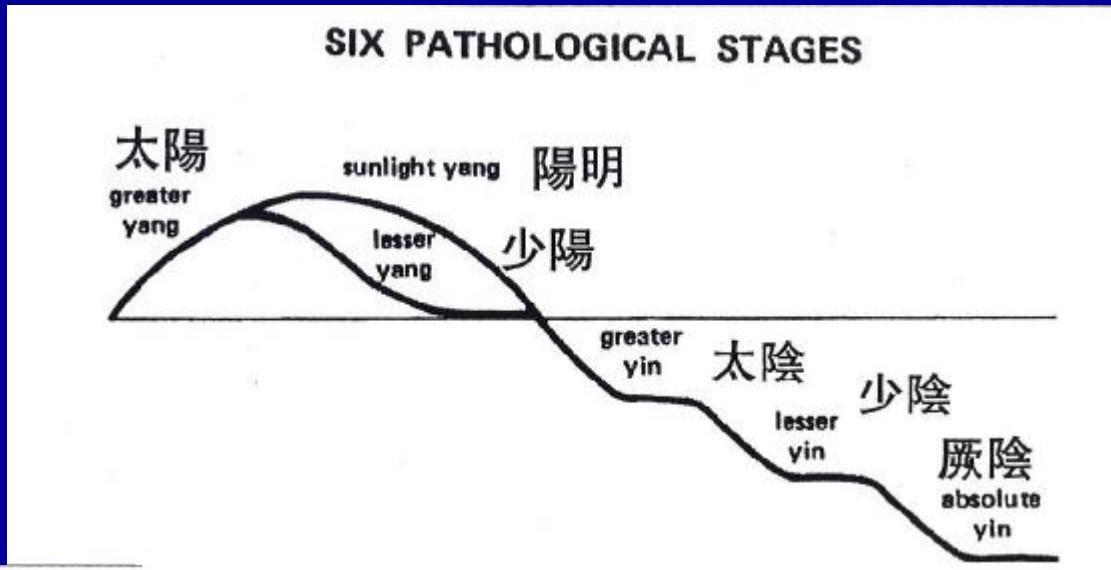
Numbers of CMM Formulas in Use

	Formulas Recorded
Shang Han Lun (Treatise on Febrile Diseases)	113
Chin Kuei Yao Lueh (Summaries of Household Remedies)	110
Tai-Ping Sheng Hui Fang	30,000
Pu Chi Fang	61,739
Pen Tsao Kang Mu	8,000
I Fang Chi Chieh	100,000
Formulas currently used in China	1,200
Formulas currently used in Japan	200
Commonly used contemporary Formula	365

Formula usually contains 4 to 12 individual herbs with different pharmacological actions

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Six Pathological Stages Based on Yin-Yang Theory: System Biology ??



Based on Yin-Yang Theory, Chung-Ching Chang's (張仲景, A.D. 142-220, The Sage Of Chinese Medicine) Shang Han Lun ("Manual of Febrile Diseases", 傷寒論) Divides the progression of disease into six Stages.

HY Hsu, "Chinese Herbal Medicine", OHAI press, Los Angeles, 1982, p. 19

Opportunities and Challenges of Current Biomedical Sciences in China

- **Opportunities:**
- Large and diverse populations (1.3 billion) with wide disease spectrum and relatively good disease registration
- Nationwide public health and medical care systems (life expectancy:from 35yr in 1950 to 71.4yr in 2000)
- Culture of tolerance for new technologies
- Integration of Western and Chinese medicines
- Commitment to the human-centered well-off society
- **Challenges**
- Complex disease profiles of both developed and developing worlds
- Incompleteness of system reform of social insurance
- Unsatisfactory allocation of healthcare resources
- Shortage in talents and insufficient innovation capacity
- Separation of basic research from industrial development

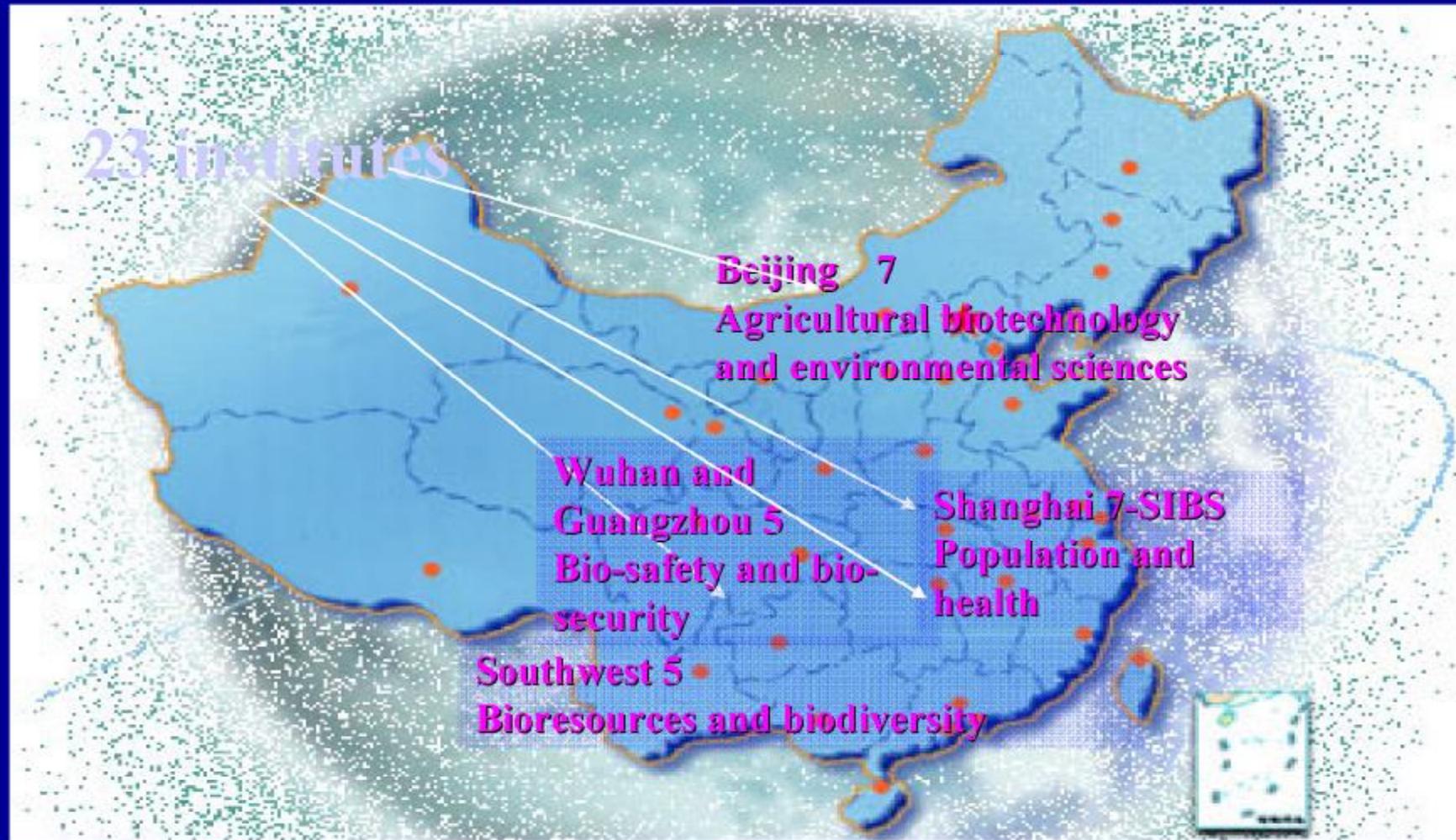
Consortium for Globalization of Chinese Medicine

- Academia Sinica (Taiwan)
- China Academy of Traditional Chinese Medicine
- Chinese Academy of Medical Science & Peking Union Medical College
- The Chinese University of Hong Kong
- Hong Kong Baptist University
- Hong Kong University of Science & Technology
- National Health Research Institutes
- Peking University
- Phyto Ceutica, Inc
- Shanghai Innovative Research Center of Traditional Chinese Medicine
- Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences
- Shanghai Research Center/Standardization of Chinese Medicine
- Shanghai University of Traditional Chinese Medicine
- Tsinghua University
- The University of Hong Kong
- Yale University (*Prof. Yung-chi CHENG*)

Taiwan: 5-Year Master Plan of modernizing TCM. (*K. H. Lee, UNC*)

Hong Kong: 10 year plan to make HK “International Center for Chinese Medicine”

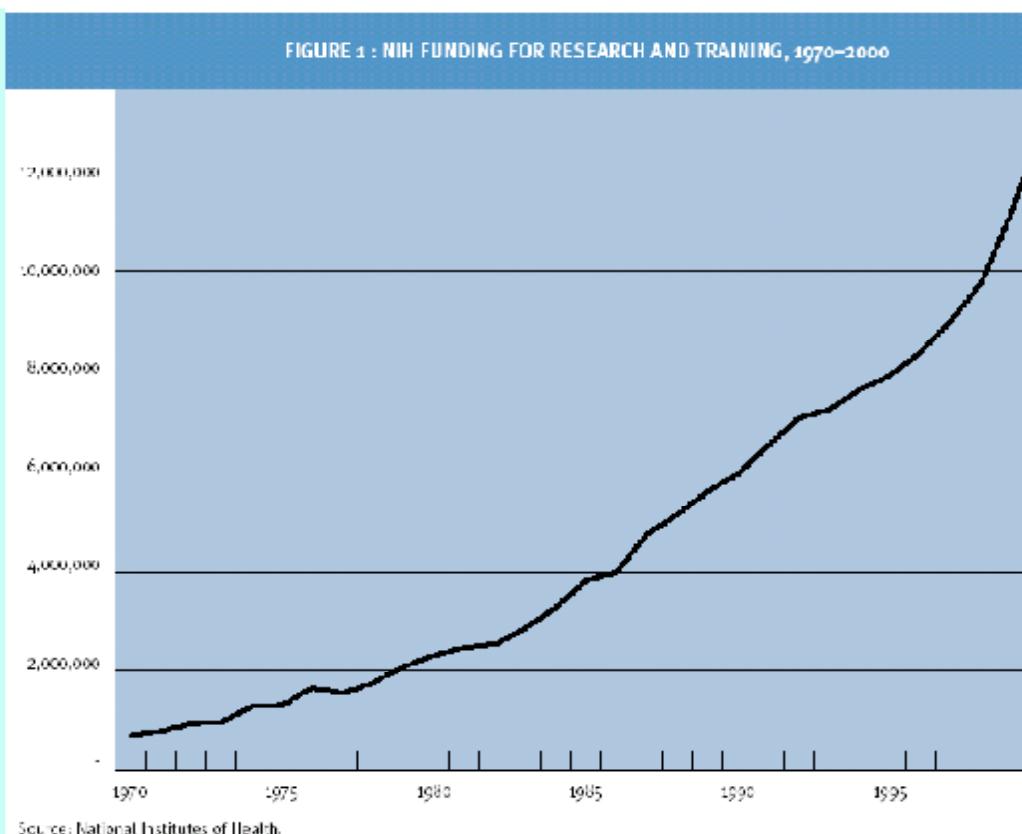
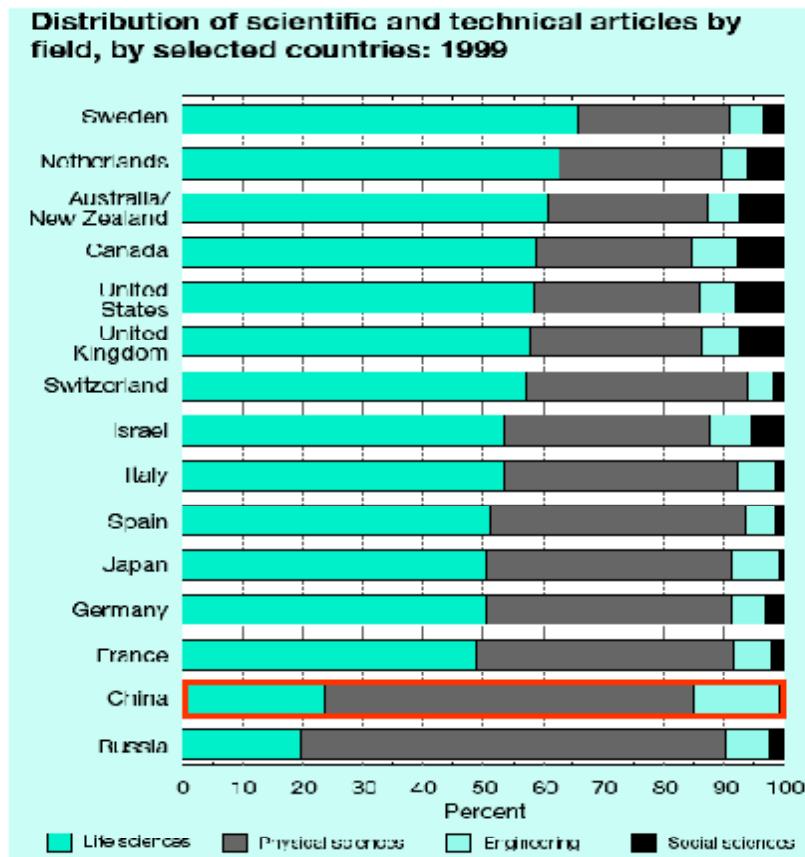
laboratories, 12 botanic gardens, 10 herbaria, 9 databases of herbarium, and dozens of eco-system field stations.



Budget: 15% of CAS' total (2004: 150 M Euro), ½ via competitive channels

Zhu Chen, Minister of Health. China

Biomedical Science-A Priority for the Life Science and Biotechnology in China



Zhu Chen. Minister of Health. China

Production and Quality Control Issues

- **Source of high quality CMM is difficult to control well**
- **Preparation of CMM lacks stringent QC standards**
 - **the quality of CMM is still evaluated based upon experience; physical, chemical and genomic methods must be established**

Challenges in the Development of Chinese Materia Medica: Clinical Issues

- Evidence for efficacy is still not well established
 - Need to establish & develop clinical pharmacology & pharmacodynamics for CMM
 - Need to evaluate potential benefits from combining CMM & Western medicine, as well as the possibility of interactions of these two types of drugs
- Difficult to assure clinical efficacy
 - Lacks placebo-controlled Western-style clinical trials evidence

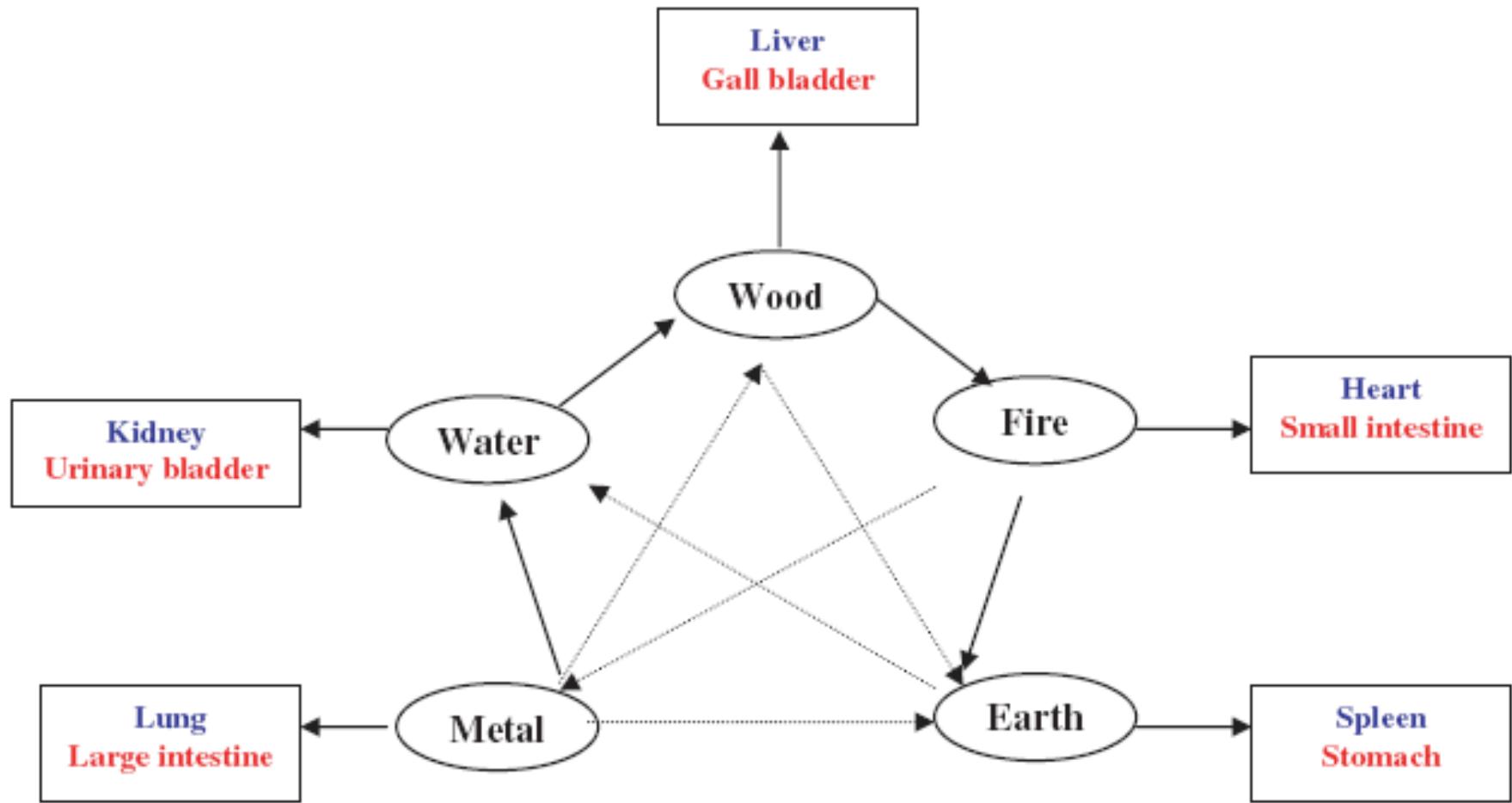
Validation Issues

A suitable screening model for developing new medicines from CMM has not been established

IP & Marketing Issues

- Intellectual patent system has not been well established
- A large international market still has not been established





→ Mutual nourishment cycle

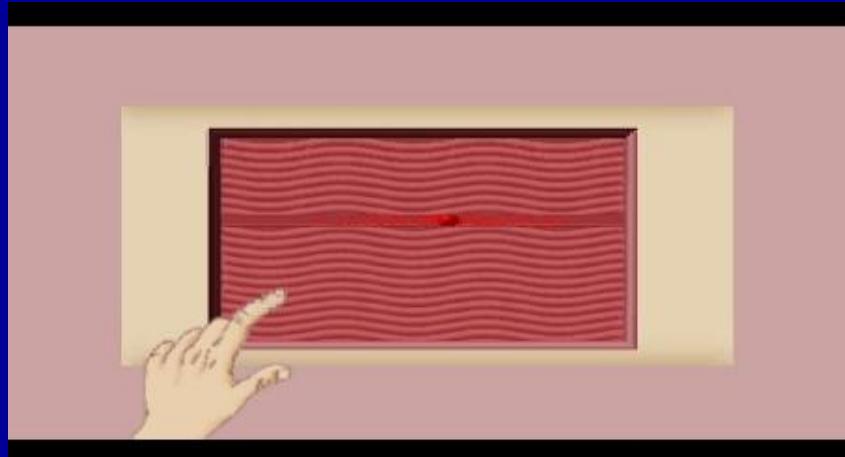
■ - Zang organs

→ Mutual restraint cycle

■ - Fu organs

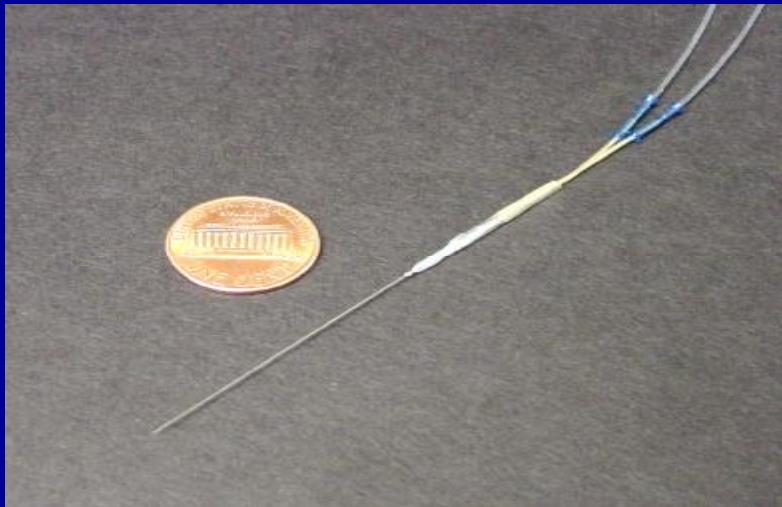
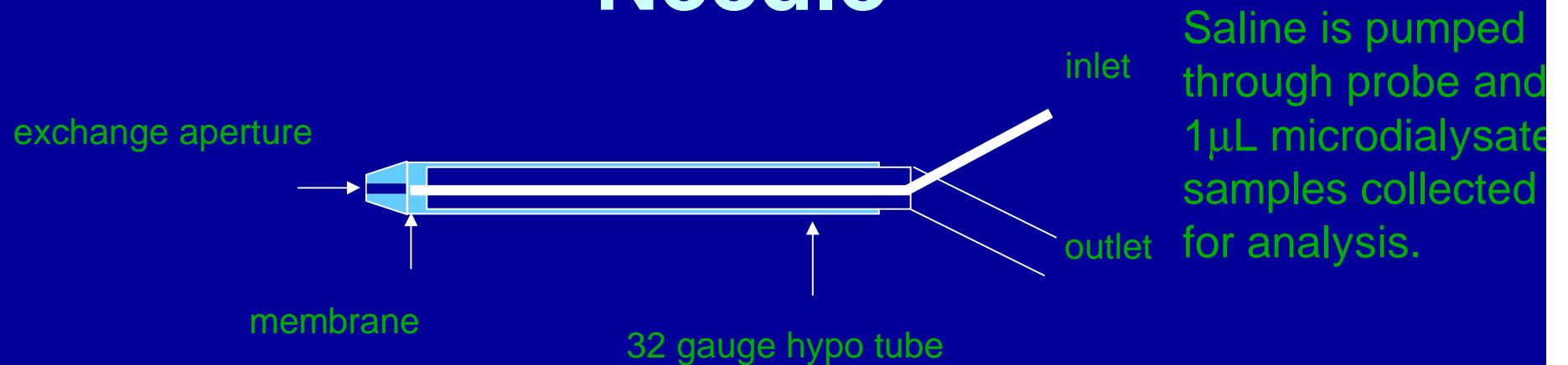
Neurological Muscle Pain

Trigger Points (TP) and muscle knots



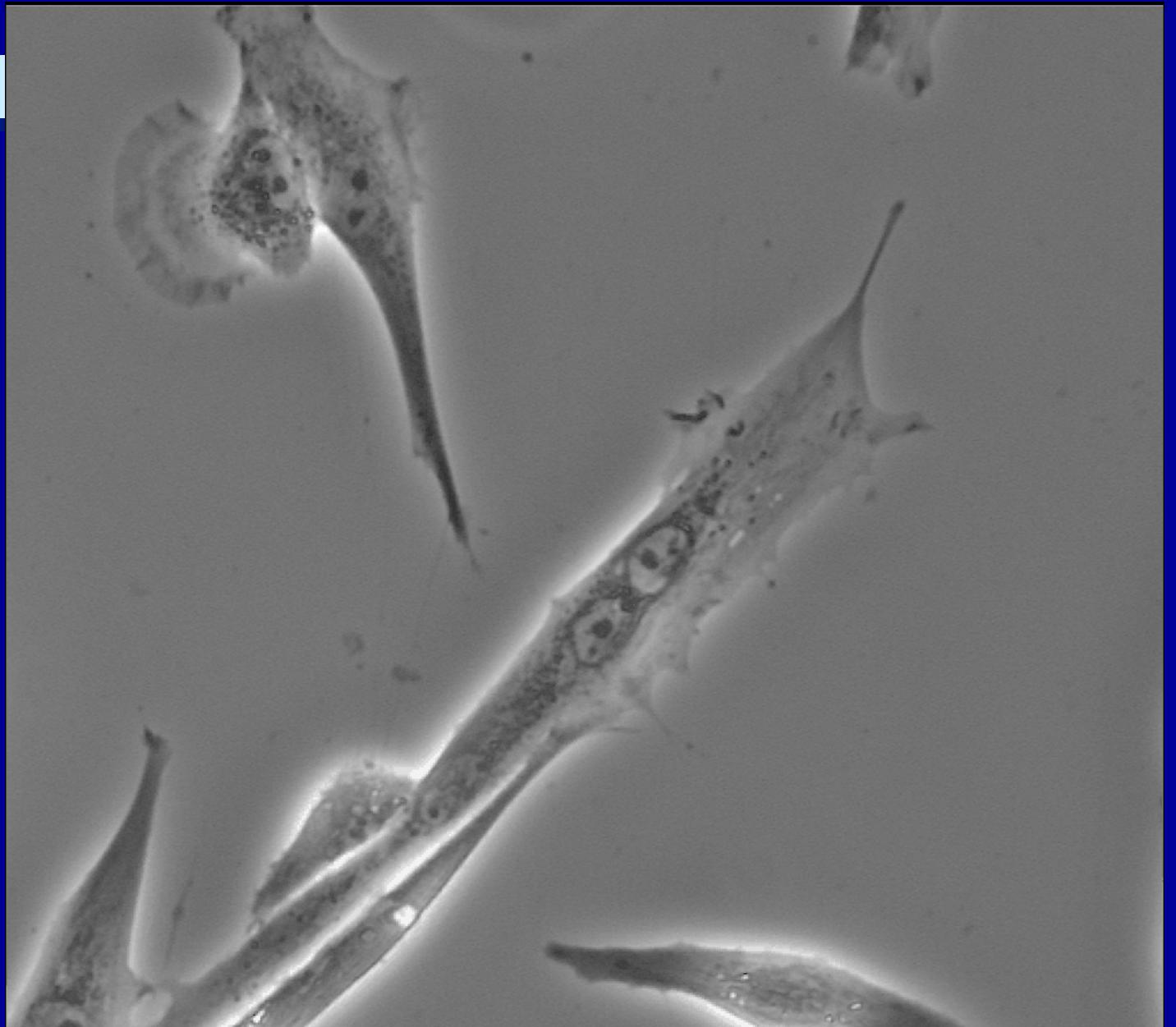
Acupuncture needles are inserted into muscle “trigger point” (yellow areas)

Microdialysis – Acupuncture Needle

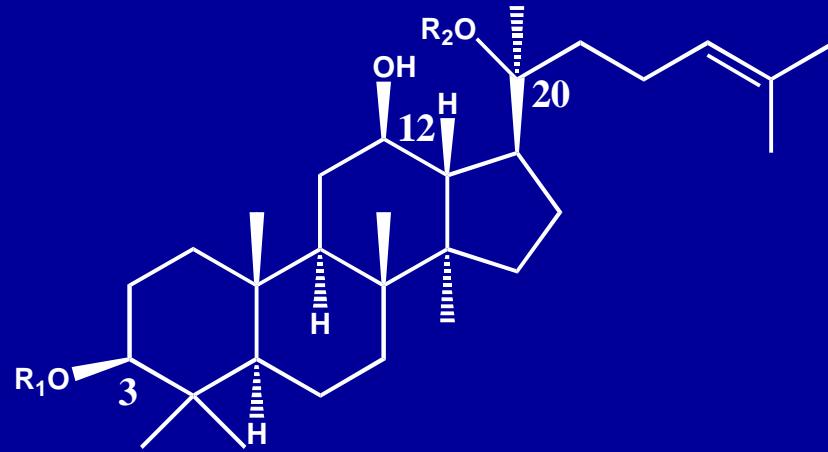


Mechanical Biology of the Muscle Cell

Fusion and ??

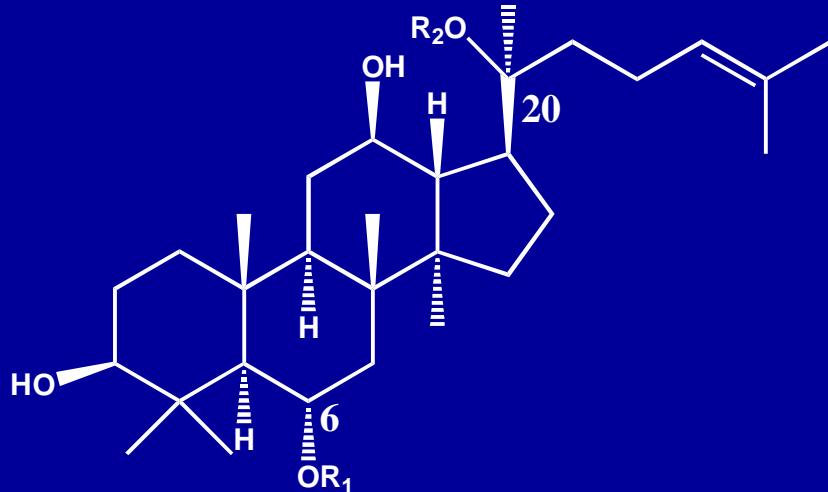


20(S)-protopanaxadiol type



Ginsenoside	R1	R2	Actions
Rb ₁	-glc(2-1)glc	-glc(6-1)glc	
Rb ₂	-glc(2-1)glc	-glc(6-1)arap	Inhibits angiogenesis
Rb ₃	-glc(2-1)glc	-glc(6-1)xyl	
Rc	-glc(2-1)glc	-glc(6-1)araF	alleviates pain by increasing capsaicin-induced inward current; antiarrhythmia
Rd	-glc(2-1)glc	-glc	Antiarrhythmia
Rg ₃	-glc(2-1)glc	-H	Reduce lung tumor incidence, inhibits metastasis
Rh ₂	-glc	-H	inhibits tumor cell growth, antimitogenic
Rs ₁	-glc(2-1)glc(6)Ac	-glc(6-1)arap	

20(S)-protopanaxatriol type



Ginsenoside R1	R2	Actions	
Re	-glc(2-1)rha	-glc	Patented as a treatment for cardiac arrhythmia ¹
Rf	-glc(2-1)glc	-H	
Rg ₁	-glc	-glc	Anti-aging, improves memory, immunoregulator ²
Rg ₂	-glc(2-1)rha	-H	Anti-platelet; Elevating blood pressure ³
Rh ₁	-glc	-H	

1. Court, GINSENG The Genus Panax, p. 169, Harwood academic publishers, 2000

2. Court, GINSENG The Genus Panax, p. 146, Harwood academic publishers, 2000

3. Lu, Lu, Tian, Li, Chin J Chin Mat Med, 26, 556, 2001

Global Herbal Market Outlook:

The global herbal market is estimated to be worth US\$ 62 billion
It is estimated that the global traditional medicine market is growing at the
rate of 7-15 % annually

India

India's current share in the global herbal market is just \$1 billion.
India share is less than 2% of global market share.

China

China occupies nearly 30% of the market.
With total earnings of about \$11.8 billion, the TCM industry accounted for
more than a quarter of China's overall medical industry in 2005

STATUS OF AYURVEDA IN INDIA

- The Indian government and non-government organizations have been collecting statistics on the Ayurvedic system in India and these data about the manpower and institutional aspects of Ayurveda have emerged:
- Number of registered medical practitioners: 366,812
- Number of dispensaries: 22,100
- Number of hospitals: 2,189
- Number of hospital beds: 33,145
- Number of teaching institutions (undergraduate): 187
- Number of upgraded postgraduate departments: 51
- Number of specialties in postgraduate medical training: 16
- Number of pharmacies manufacturing Ayurvedic medicines: 8,400
- In India, there are about 20 well-recognized manufactures of herbal drugs and 140 medium or small-scale manufactures.

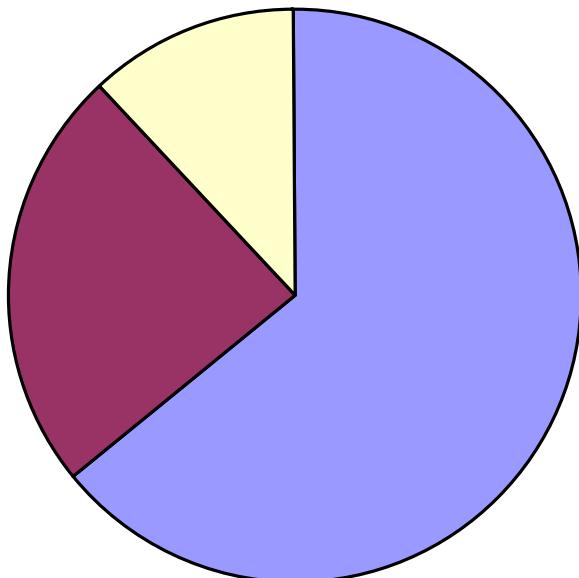
Summary of The Pharmacological Effects of Ginseng

- Even a single ginsenoside has been found to produce multiple effects.
- Diverse effects are induced by multiple active constituents.
- In addition to the most investigated ginsenosides, non-ginsenoside constituents of ginseng also exert pharmacological effects.

Conclusion: the overall activity of a herb is complex, resulting in synergistic effects as well as antagonistic effects so as to maximize the therapeutical effects and meanwhile minimize the side effects.

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The Global Herbal Market



- 64% Pharmaceutical
- 24% Spices and Herbs
- 12% Cosmetics

麻黃湯

Ma-huang
Combination

邱秀麗著《中藥方劑常用圖典》 P. 34
三采文化出版事業有限公司
S. L. Chiu, "Colored Atlas of
Common Chinese Materia
Medica Formula", P. 34
Suncolor Culture Press,
Taipei, Taiwan, 2004

麻黃 (Ma-huang,
Ephedra sinica)

味辛微苦，性溫：
歸肺、膀胱經。



炙甘草

(Baked licorice,
Glycyrrhiza uralensis)

味甘，性平：
歸心、肺、脾、胃經。

桂枝 (Cinnamon twig,
Cinnamomum cassia)

味甘辛，性溫：
歸心、肺、膀胱經。

(Apricot seed,
Prunus armeniaca)

杏仁

味苦，性微溫，有小毒：
歸肺、大腸經。

Traditional Chinese Medicine in China

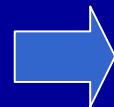
- There are 3009 TCM hospitals accounting for over 16 percent of all hospitals in China.
- There are 35,053 TCM outpatient departments and clinics, or nearly 17 percent of all outpatient departments and clinics in China.
- 92 percent of urban community health centers and nearly 55 percent of community health service stations are able to provide TCM services.
- 75 percent of the 40,907 town hospitals have TCM departments.
- 50 percent of the 58,209 village clinics across China can provide TCM services.
- Among the 864,168 rural doctors, 267,305 practice some combination of TCM and western medicine.
- There are 19,533 practicing TCM “pharmacists” in China.
- 234 million people were treated in TCM outpatient departments (No indication of time period).
- Over 6 million people were discharged from TCM hospitals making up nearly 13 percent of all discharges in China (No indication of time period).

Quality Control for Standardized New Medicines

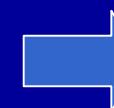
1. CMM –
Origin ID/Authenticity



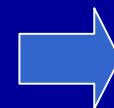
2. Production
Methods/GAP



3. Controlled Inspections
of Contaminants



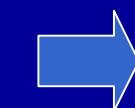
4. Raw Materials
Processing



5. Extraction &
Concentration



6. Chemical
Fingerprinting



7. Pharmacological
Fingerprinting



8. Manufacture &
Dosage Form
(GMP & GMC to maintain
batch-to-batch consistency)

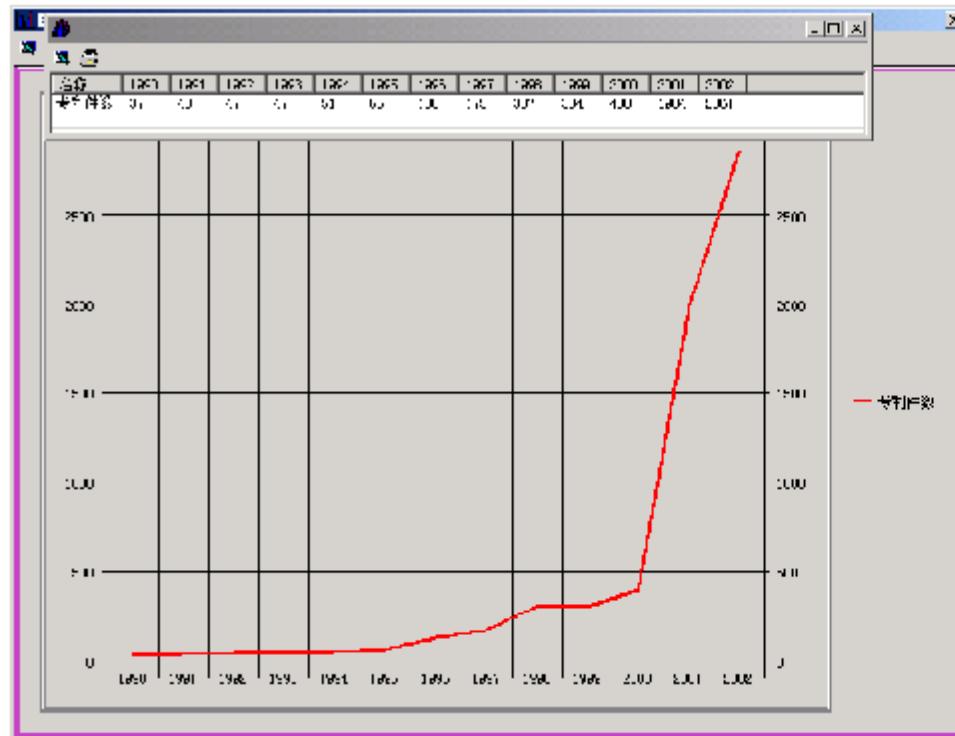


9. Preclinical &
Clinical Trials
(Toxicity, Pharmacokinetic
& Metabolic Studies)



10. Standardized
New Medicines

Published Patents on Bio-technology in China (1990-2002)



Recent highlights in China

In 2002, applications of international patent from the developing countries increased by 11%. Among them China ranked No 2 with 1,205. In 2003, the number of applications of patent in China from the residents for the first time exceeded those of non-residents

Total Sales of Bio-tech Products in China (Unit: Mn Euro)

