

We will start momentarily at 2pm ET



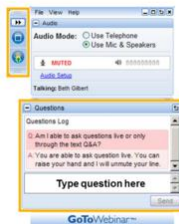
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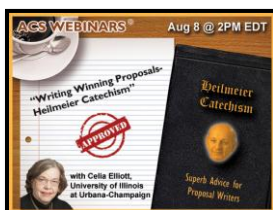
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Advances in Natural Product Chemistry: Benefits of Evidence-Based Chinese Medicine



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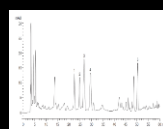
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ACS Webinar - July 25, 2013

Advances in Natural Products Chemistry – Benefits of Evidence-Based Chinese Medicine



Chun-Tao Che

*Norman R. Farnsworth Professor of Pharmacognosy
Department of Medicinal Chemistry and Pharmacognosy
and*

*WHO Collaborating Center for Traditional Medicine
College of Pharmacy, University of Illinois at Chicago
Chicago, Illinois 60612, U.S.A.*



Question 1

Do you use any herbal or traditional medicinal products?

- Yes, regularly
- Yes, but only if recommended by people I trust
- Yes, but only if I have read study reports
- Never

Natural Drugs



VS



- Natural (non-synthetic)
- Crude (undergone only simple preparation procedures)
- **Complex chemical composition** (the "metabolome")
- **Variable in quantities**
- **Many structures unknown**
- **Possibly > 1 active ingredient**
- Unclear pharmacological mechanism
- May act on multiple targets (→ systems biology)
- Possible synergism / antagonism

Natural Products Chemistry

- Isolation / purification of secondary metabolites
- Structural elucidation and characterization of secondary metabolites (spectroscopic properties, stereochemistry, etc.)
- Structural modification
- Chemical synthesis
- Biosynthesis and microbial transformation

Analytical Chemistry
Separation Science
Spectroscopy
Synthetic Organic Chemistry
Biotechnology

New Drug Discovery

Focus of this talk

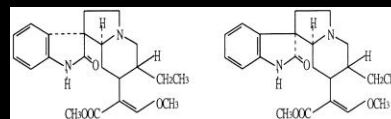
- **Quality and standardization of herbal medicines**
- **Multi-target concept of herbal medicines**
- **Synergy research on herbal medicines**

Contributions of Natural Products Chemistry to Herbal Medicine

- Understanding the chemical composition
- Identification of active principles
- Rationalizing the traditional use



Uncaria rhynchophylla

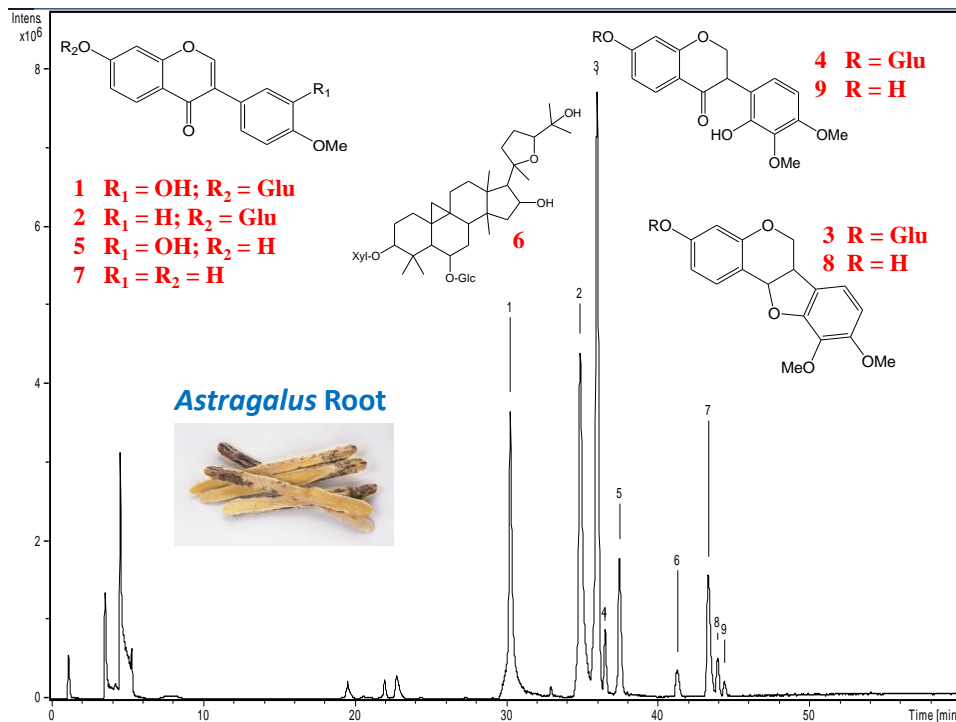


Rhynchophylline

Isorhynchophylline

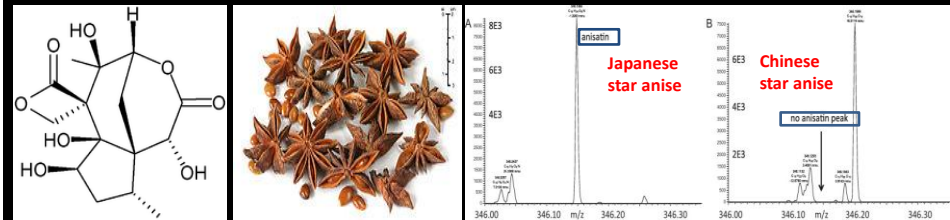
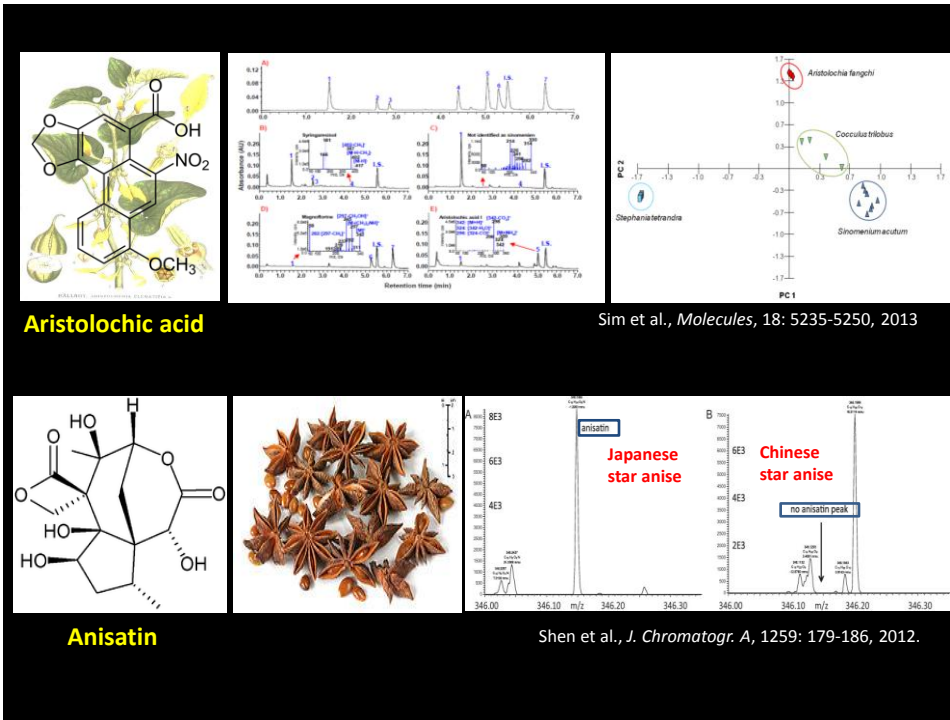
Xian et al., *E-CAM*, 2012, 802625.

- **Setting analytical standards for quality control and assessment**



Contributions of Natural Products Chemistry to Herbal Medicine

- Understanding the chemical composition
- Identification of active principles
- Rationalizing the traditional use
- Setting analytical standards for quality control and assessment
- Detection of toxic components



Question 2

What do you think is the biggest issue that would make people skeptical about the use of herbal products?

- o Unreliable quality
- o Unsafe
- o Unproven efficacy
- o Often not recommended by doctors
- o People have little knowledge about herbal products



Standardization

- **Current practice**
 - Quantitative measurement of small number of marker compounds (often with little biological irrelevance to the clinical effects)
 - Chromatographic profile (TLC / HPLC fingerprints) based on small number of reference peaks (or bands)
- **More appropriate to assess the whole medicine in the context of multiple components**
- **Plant metabolomics analysis provides better analytical methods for standardizing herbal medicines**

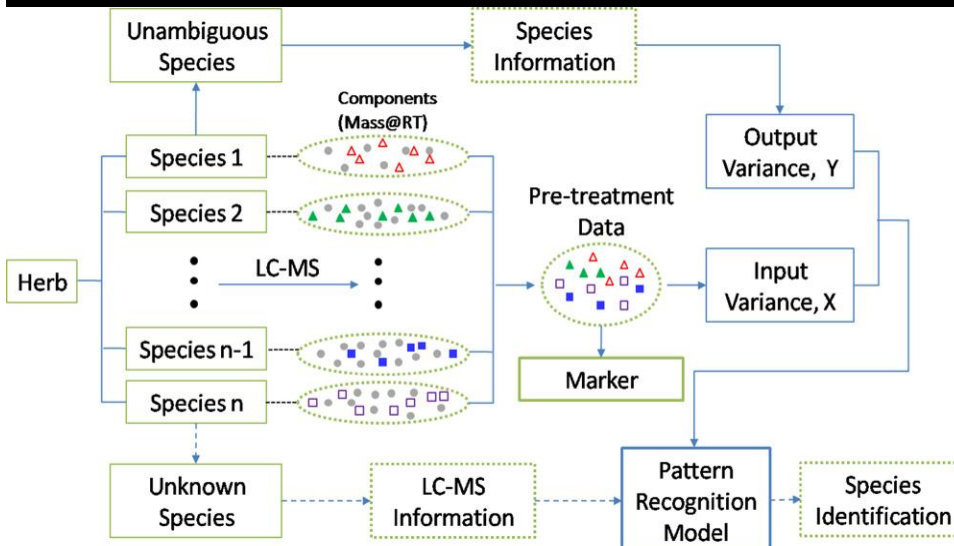
The Metabolomic Approach

- A holistic, simultaneous and systematic qualitative and quantitative determination of plant metabolites
- Dealing with the distribution of metabolites in its entirety (metabolome)
- Allowing quick and efficient identification and quantification of secondary metabolites in a mixture
- A breakthrough to accelerating and streamlining the analytical process of medicinal plant research
- Easily coupled to bioactivity screening data
- Making use of analytical processes such as spectroscopy, chromatography, and multivariate analysis

Applications of Metabolomics in Medicinal Plant Research

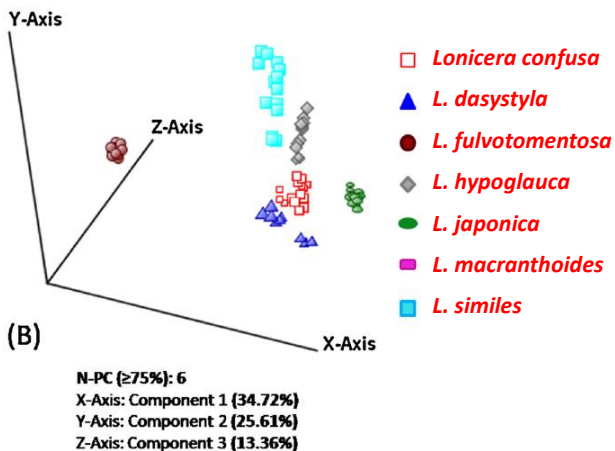
- Classification of medicinal plants
 - Species and varieties
 - Geographical origin
 - Adulterants
- Quality control and standardization
- Characterization of plant cell cultures
- Proof of efficacy of medicinal plants from urine and/or blood samples

A Workflow illustrating the plant metabolomic strategy for herb identification

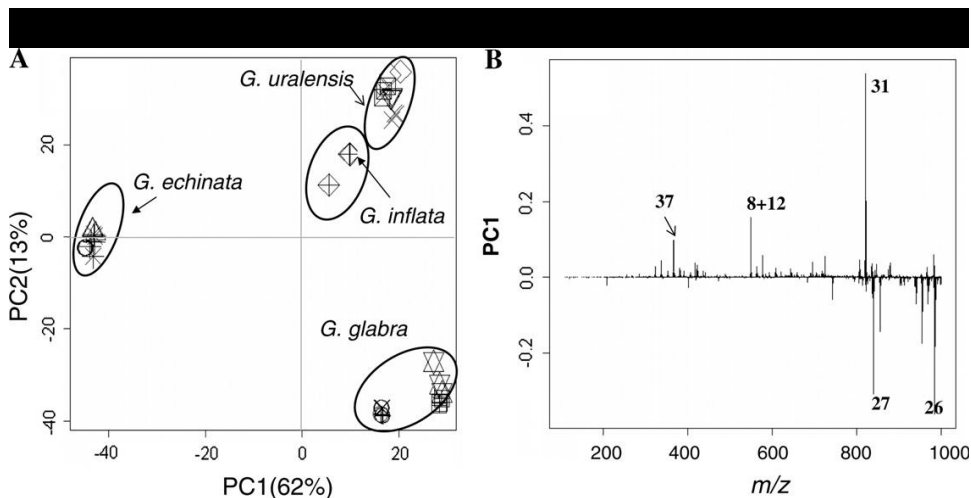


Gao et al., *J Chromatogr A*, 1245: 109-116, 2012.

LC-QTOF MS and PCA-SVM Analysis of seven *Lonicera* (honeysuckle) species flower buds

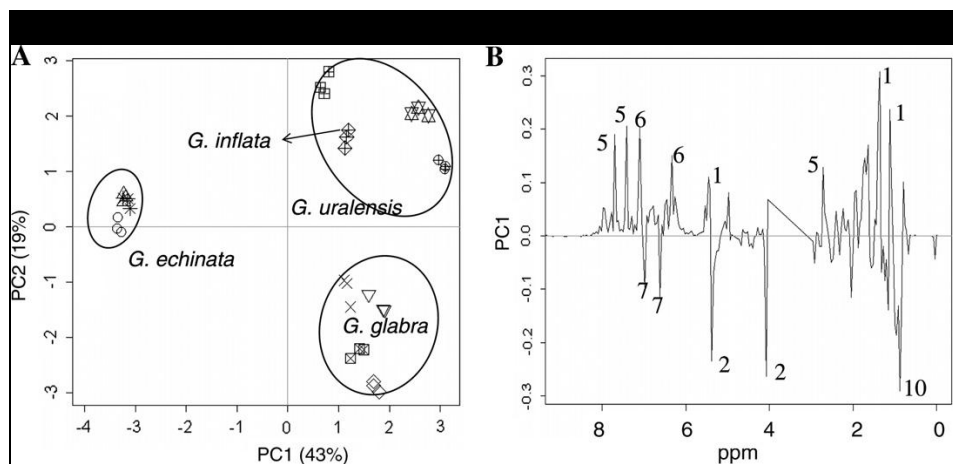


Gao et al., *J Chromatogr A*, 1245: 109-116, 2012.



Principal component analyses of four *Glycyrrhiza* species derived from negative ionization mode LC–MS data (m/z 100–1000). **(A)** Score Plot **(B)** Loading plot for PC1 contributing mass peaks and their assignments: **8** liquiritin apioside; **12** neolicuroside; **31** glycyrrhizin; **37** glycycomarin; **26** yunganoside G1; **27**, yunganoside G2.

Farag et al., *Phytochemistry*, 76: 60-72, 2012.

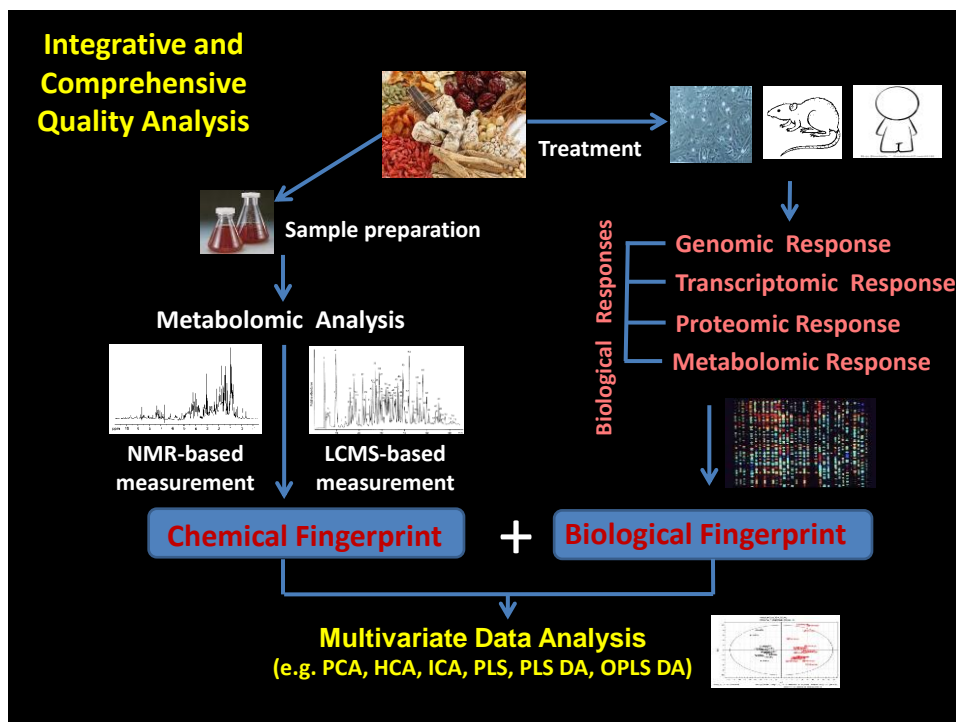


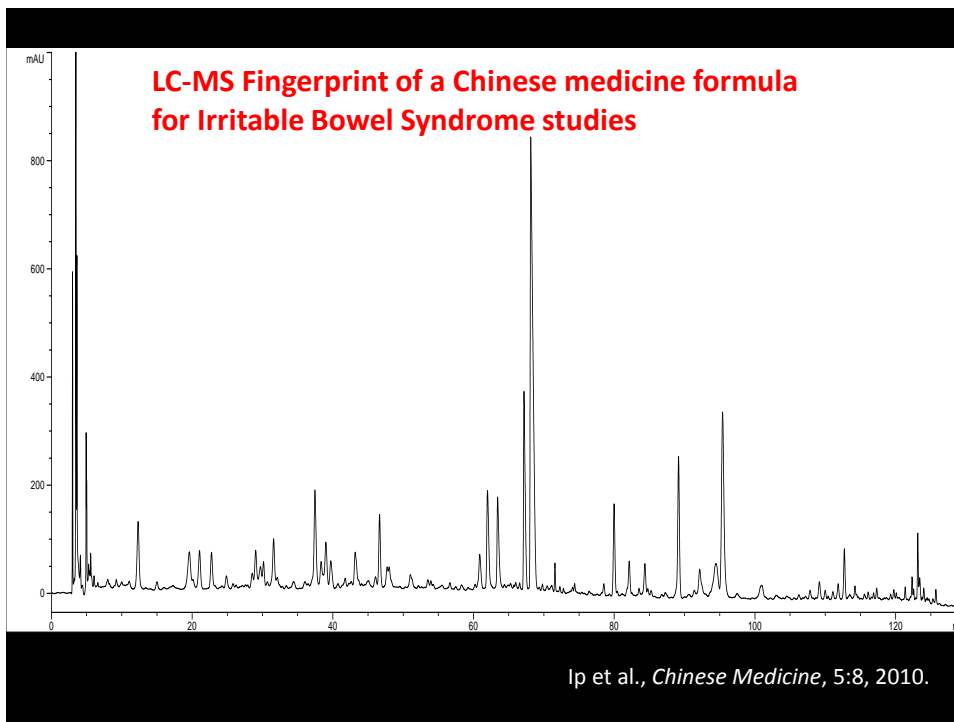
^1H NMR peak based principal component analyses of different *Glycyrrhiza* samples. **(A)** Score Plot. Group discrimination is related to qualitative and quantitative differences in the saponin and flavonoid patterns. **(B)** Loading plot for PC1 components: **1** glycyrrhizin; **2** sucrose; **5** liquiritigenin; **6** isoliquiritigenin; **7** 4-hydroxyphenyl acetic acid; **10** rhamnose moiety.

Farag et al., *Phytochemistry*, 76: 60-72, 2012.

Applications of Metabolomics in Medicinal Plant Research

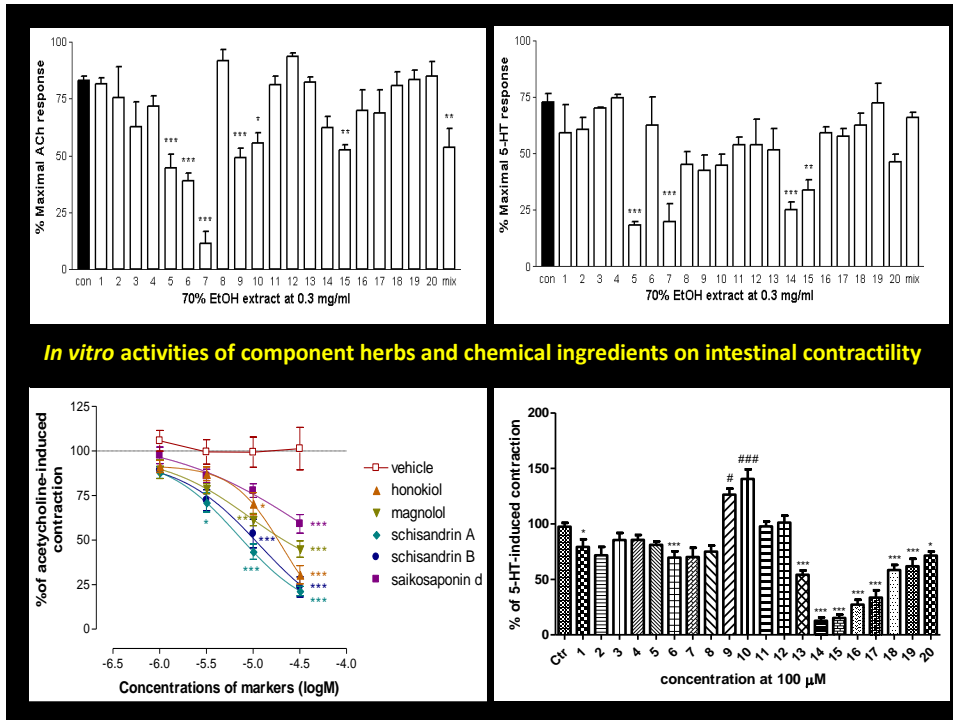
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APCI MS Data (Positive Ion)

Peak Identification	M/QM	Other Peaks	MS2 of M/QMIP
1 Esculin	341 (M+H)+	179	179
2 Chlorogenic acid	355 (M+H)+	163	163
3 Aesculetin	179 (M+H)+		134, 123, 109
4 Paeoniflorin	498 (M+H ₂ O)+	301, 179	301, 179
5 prim-O-Glucosylcimifugin	469 (M+H)+		307
6 Magnoflorine	342 (M)+		297, 265
7 Liquiritin	419 (M+H)+	307, 257	
8 5-O-Methylvisamminoside	453 (M+H)+	291	290
9 Hesperidin	610 (M)+	465, 449, 303	463
10 Columbamine	338 (M)+		323, 294
11 Jatrorrhizine	338 (M)+		323, 294
12 Epiberberine	336 (M)+		
13 Coptisine	320 (M)+		304, 292
14 Palmatine	352 (M)+		337, 308
15 Berberine	336 (M)+		321, 292
16 Glycyrrhizic acid	823 (M+H)+	647, 471, 453, 406	
17 Schisandrin	433 (M+H)+	415	
18 Honokiol	266 (M)+	263	
19 Magnolol	266 (M)+	261	
20 Schisandrin A	417 (M+H)+		402, 347, 316



Applications of Metabolomics in Medicinal Plant Research

- Classification of medicinal plants
 - Species and varieties
 - Geographical origin
 - Adulterants
- Quality control and standardization
- Characterization of plant cell cultures
- Proof of efficacy of medicinal plants from urine and/or blood samples

Question 3

What do you believe is more effective?

- Mixture of herbal ingredients in a natural or semi-purified form
- Mixture of conventional drug with herbal drug
- Pure chemical compound

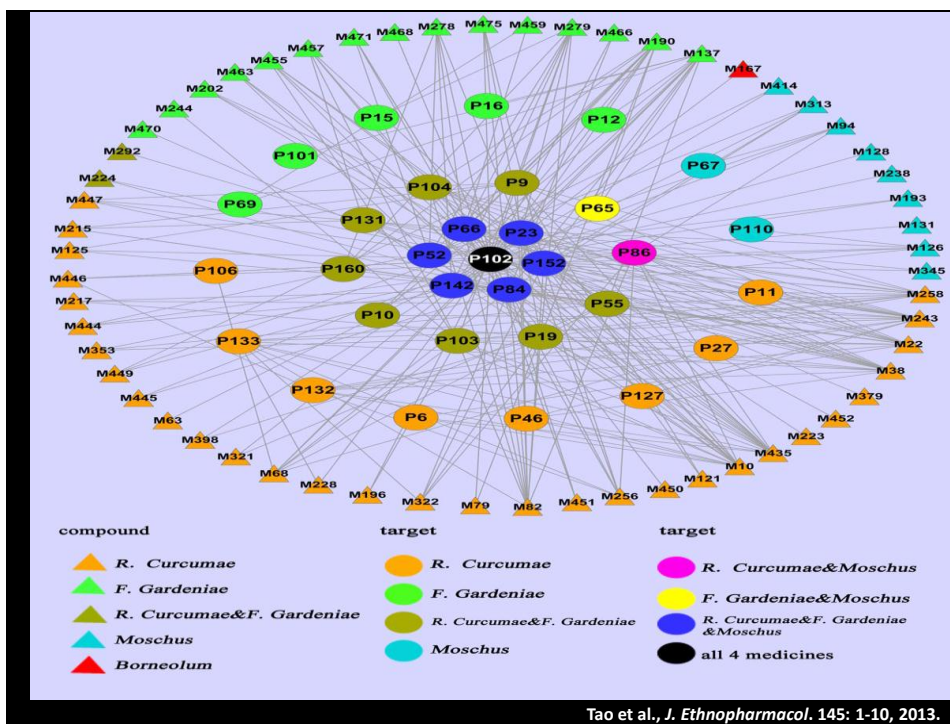
Therapeutic Approaches

Reductionistic Approach

- Mainstream approach
- One target – one drug
- Selective ligand (single substance) acts on a single disease target
- Aiming for highly specific and safe drugs
- Not quite effective for diseases of multi-factorial pathogenesis
- Subject to development of resistance

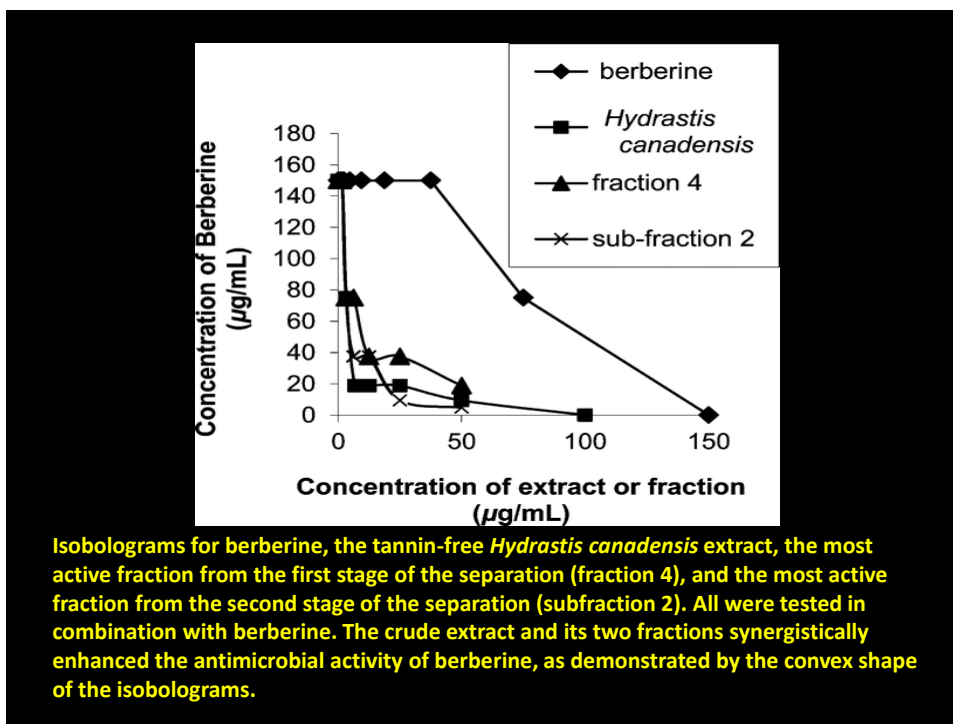
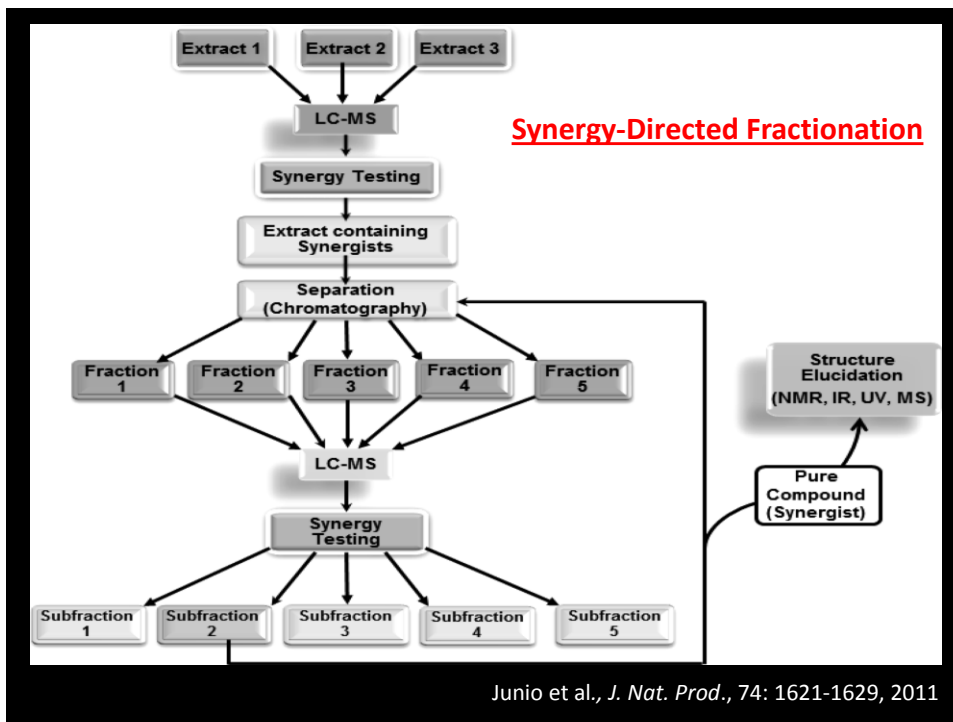
Holistic Perspective

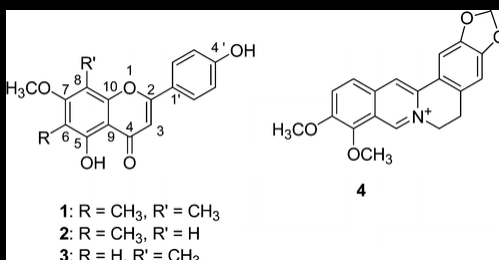
- Many diseases possess multi-causal etiology and a complex pathophysiology
- Multi-drug therapy
- Most traditional medicinal systems make use of combination of herbs
- Mixture of compounds (multi-component) act on multi-targets
- Network Pharmacology would help explain the mechanisms of multi-component herbal medicines



Synergy Effect

- The efficacy of herbal medicines may be a result of the combined action of multiple constituents.
- Studies have shown the therapeutic superiority of herbal drugs as compared with single constituents.
- The practice of Chinese medicine is built upon the concept of synergistic or polyvalent effects among various plant metabolites present within the herbal decoction.
- The specific components responsible for these effects, and the fundamental mechanisms by which they interact, have rarely been demonstrated.
- A synergy-directed fractionation approach was developed to probe into the possible mode of synergy.





1. Sideroxylin
2. 8-Desmethyl-sideroxylin
3. 6-Desmethyl-sideroxylin
4. Berberine

- **Compounds 1-3 were identified as synergists that enhance the antimicrobial activity of berberine.**
- **They act by inhibiting the NorA multidrug resistance pump, and possess no inherent antimicrobial activity.**
- **They could have been missed using traditional bioactivity-directed isolation .**

Junio et al., *J. Nat. Prod.*, 74: 1621-1629, 2011

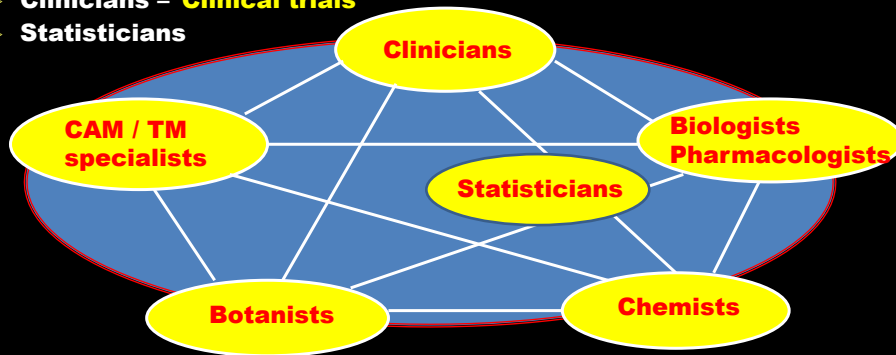
Closing Remarks

Natural Products Chemistry play important major roles in advancing the evidence-base of herbal medicine :

- Bioactivity-directed isolation of novel compounds from natural sources will remains an important and useful approach in new drug discovery. New analytical and spectroscopic techniques are needed to provide better tools for the isolation and identification of minor constituents.
- The emergence of metabolomics has opened up new opportunities to answer the challenges in the area of medicinal plant development. A unique feature is the capability of integrating and correlating the chemical data with biological data.
- New tools to probe into network pharmacology will enhance the modern development of herbal medicine by providing in-depth understanding of the complex pharmacology involved.

Important !! -- Interdisciplinary Collaboration

- CAM / Traditional medicine specialists – **Selection of herbs**
- Botanists – **Procurement and authentication of herbs**
- Chemists – **Standardization and quality control; Isolation and identification of active principles; Structural modification / Synthesis**
- Biologists / Pharmacologists – **Biological assays, pharmacology, and mechanistic studies**
- Clinicians – **Clinical trials**
- Statisticians



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Alternative Careers: Chemistry and the Art Detective

Dr. Suzanne Lomax, Organic Chemist, National Gallery of Art
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