



Traditional Chinese Medicine – does it have a future in the EU?

Peter Hylands

25 March 2011

Traditional Chinese medicine seeks to adjust the circulation of **qi** (metabolic energy flow) in the body using a variety of therapeutic techniques

Some of these techniques include

Special diets

Physical training regimens (*qigong*, *tai chi chuan*, and other martial arts training)

Massage

Acupuncture

Moxibustion

Herbal medicines

Revenues of the Traditional Chinese Medicine (TCM) industry have grown 20 percent annually in the past decade

With total earnings of 15 billion U.S. dollars, the TCM industry accounted for more than a quarter of China's overall medical industry in 2005

China currently has about 3,000 traditional medicine hospitals that dispense medical treatment to nearly 234 million people each year.

China exports 1 billion U.S. dollars worth of traditional medicines to 164 countries

The Five elements:

Tree, traditionally **Wood** (Chinese: 木,
pinyin: *mù*)

Fire (Chinese: 火, pinyin: *huǒ*)

Earth (Chinese: 土, pinyin: *tǔ*)

Metal (Chinese: 金, pinyin: *jīn*)

Water (Chinese: 水, pinyin: *shuǐ*)

Complex prescriptions

One main ingredient – said to be ‘the **Emperor**’,

Two or three others have a similar activity – ‘the **Ministers**’

One or more others included to aid absorption and delivery to the required site - ‘the **Guides**’

The fourth group utilized because they reduce side-effects of the major active herbs - ‘the **Assistants**’

**melon peel (300g),
poria (300g),
quince fruit (100g),
perilla leaf (100g) and
tangerine peel (100g)**



TCM in the UK

Conventional drugs bill £11 billion

30-70% not used as directed

Public dissatisfied with western medicine

Turn to Complementary and Alternative
Medicine

Diseases with complex aetiology:

respiratory conditions (asthma)

sexual health (gynaecological complaints, infertility)

skin diseases (eczema)

allergies; immune system disorders;
chronic pain; psychological problems;
addictions; children's diseases

3,000 TCM clinics in UK

Duration of consultation

Cost

Personalised 1 to 1 consultation and
prescription

Most do not tell gp

What does the regulator think about this?

Regulation of herbal medicines

Safety, quality and efficacy

MHRA: If to be sold with an indication of use, the product is treated as any other medicine

Marketing authorisation

Safety

Quality

Efficacy

Evidence based therapy

In order to obtain robust clinical data,
need closely controlled and
standardised material

Summary of some current work at King's College London

1. Problems and solutions in standardisation and quality control of plant medicines
2. Biological and mechanism studies
 1. *in-vitro*
 2. *clinical*
3. Bioinformatics

Changing emphasis of medicinal plant research

In last 15 years phytochemical and pharmacological studies being complemented by clinical trials

Verifying efficacy and safety
Substantiation of synergy

Complex evolution of pharmacopoeial monographs

Digitalis leaf

Irrational bioassay

colour reaction

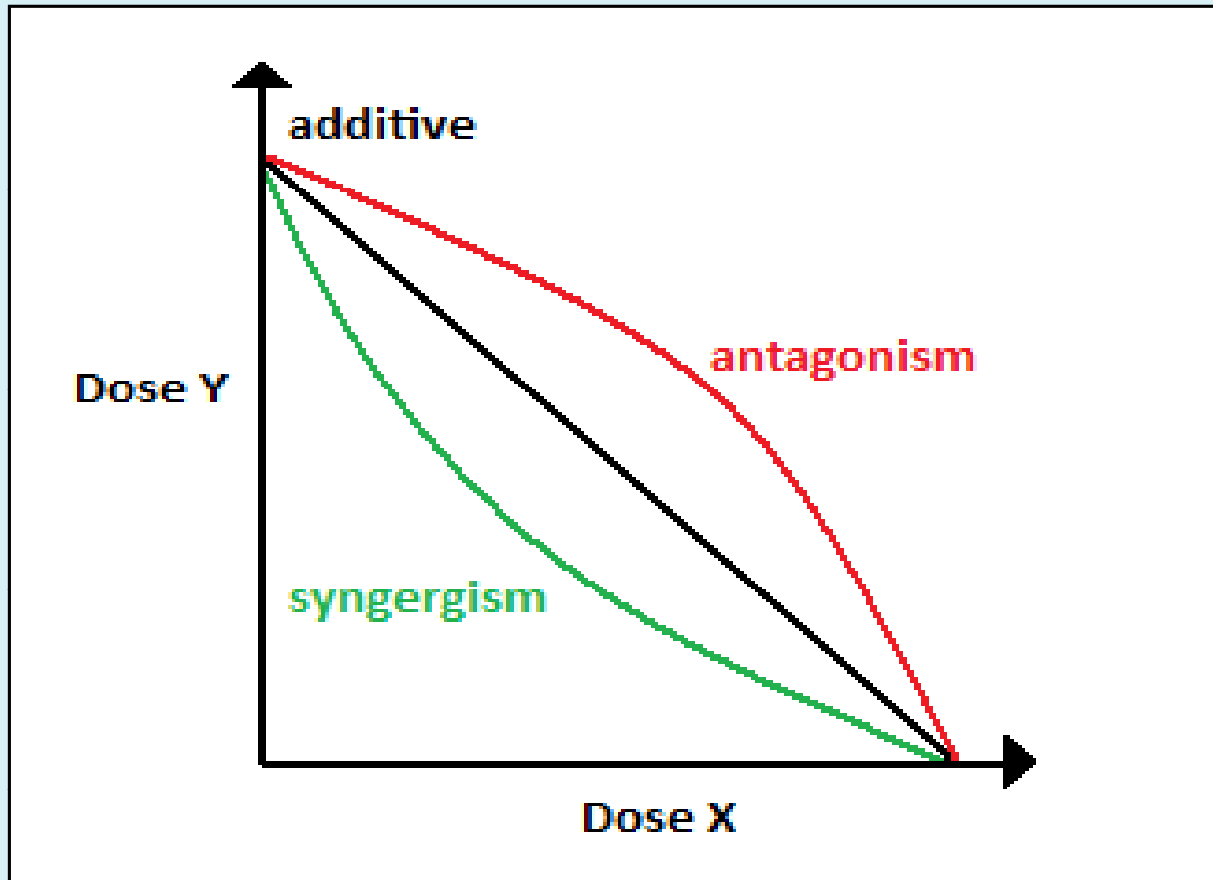
hplc but ignoring saponins/steroids which
influence absorption

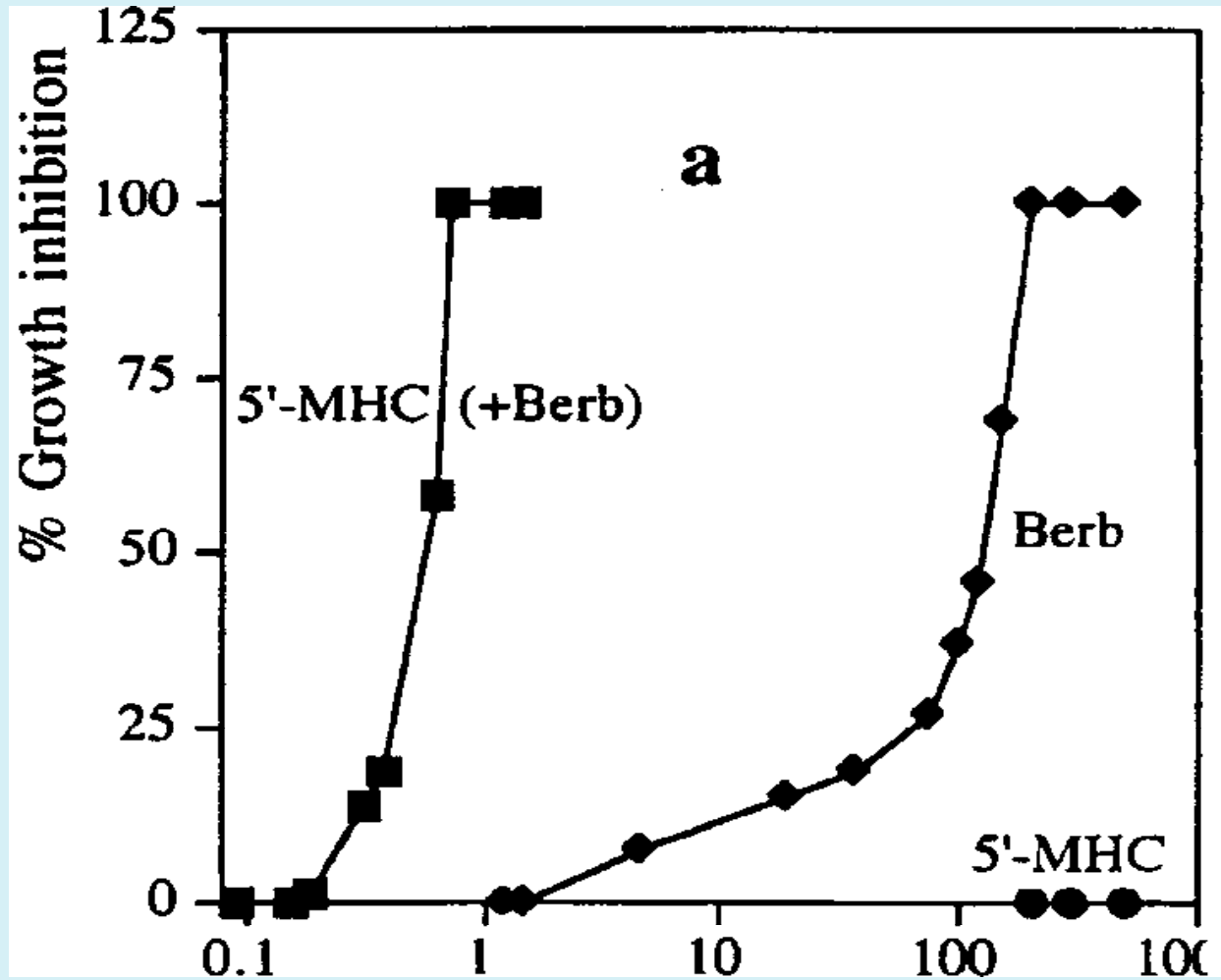
Verification of synergy

Bioactivity-guided fractionation of a plant with
reputed antimicrobial activity

Berberis species

Anti-infective modulators





Antimicrobial activity of a *Berberis* sp

Stermitz FR, Lorenz P, Tawara JN, Zenewicz LA and Lewis K, *PNAS*, 2000, **97**(4), 1433-1437

Widely used herbal medicines

Efficacy established – but ‘actives’ and mechanism still unknown:

—*Hypericum, Echinacea, Crataegus, Humulus, Valeriana*

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How can we standardise?

We need to, because if we do not.....

Problems in use

Incorrect identification

Efficacy, toxicity issues

Variable quality

Efficacy issues

FDA and EMEA and other national authorities
introducing new guidelines

Distinguishing feature of phytomedicines

Extracts (mixtures of compounds) *not single compounds*

Accepted conventional pharmaceutical methods not really applicable to plant extracts

Nonetheless, standardisation often uses single actives or markers

This produces significant difficulties

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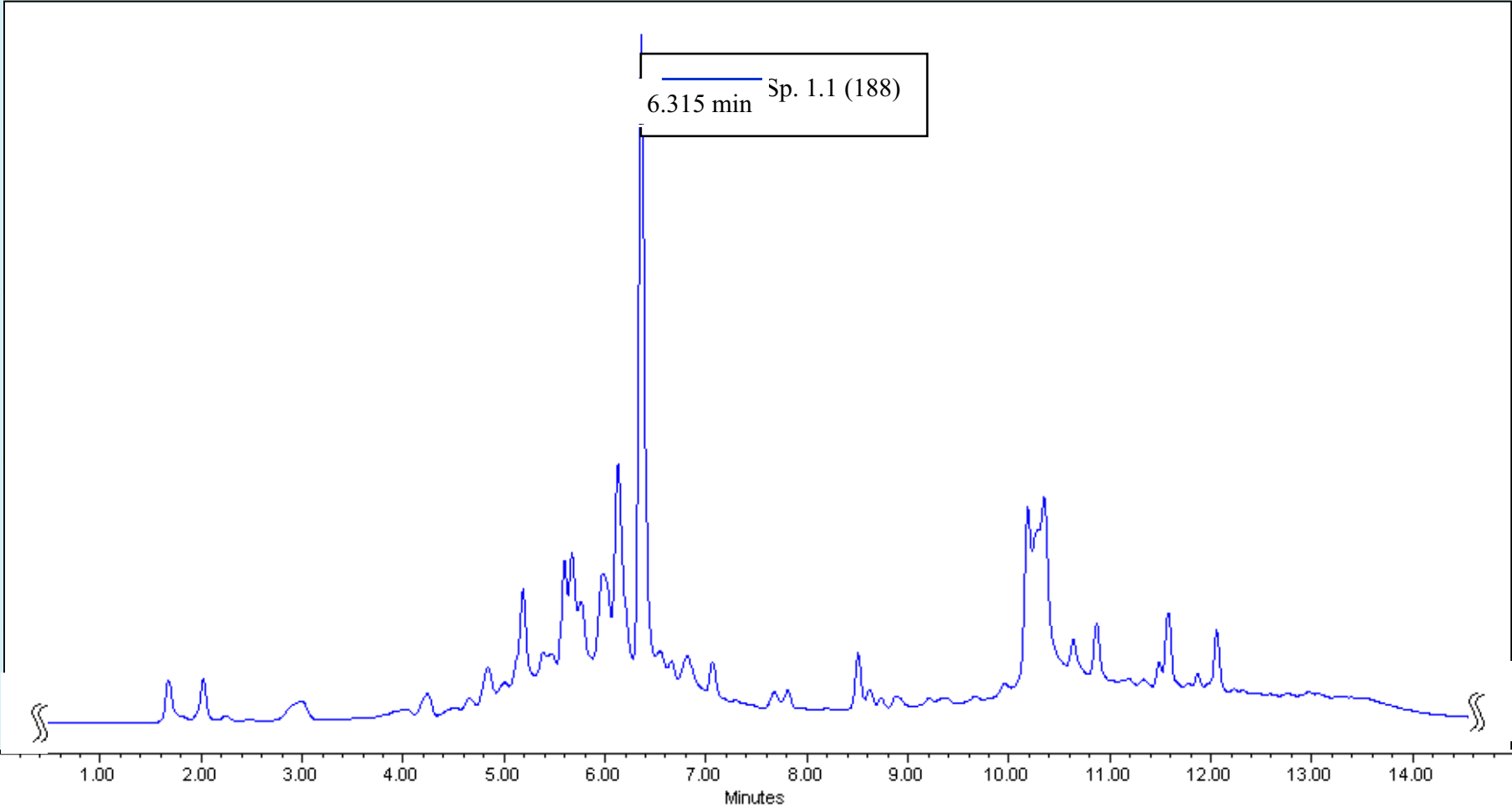
TCM products are mixtures of mixtures

Accepted conventional pharmaceutical methods not really applicable to plant extracts

Nonetheless, standardisation often uses single actives or markers

This produces significant difficulties

ONP-22 whole chromatogram





Metabolite profiling

metabonomics
metabolomics

What is metabolite profiling?

Investigating and describing genetic expression by **non-targeted** measurements of all metabolites in a biological sample

Profiling complex matrices such as *biofluids (plasma and urine)*

Biomarkers for metabolic studies and diagnosis
environmental samples
plant matrices (identification)

Tools available for metabolite profiling are several and can be hyphenated:

Chromatographic

HPLC or GC

GC-MS; HPLC-MS; HPLC-MS-MS

Detection: selectivity

Derivatization

LC-UV-SPE-NMR-MS (cryogenic flow probe)

Spectroscopic

ESI-MS

ionisation and fragmentation variability

IR

data information limited

peak deconvolution algorithms necessary

High field ^1H nuclear magnetic resonance spectroscopy

Data rich fingerprint; requires

Data reduction/simplification

Statistical analysis:

Treatment of metabolic profile data by multivariate analysis:

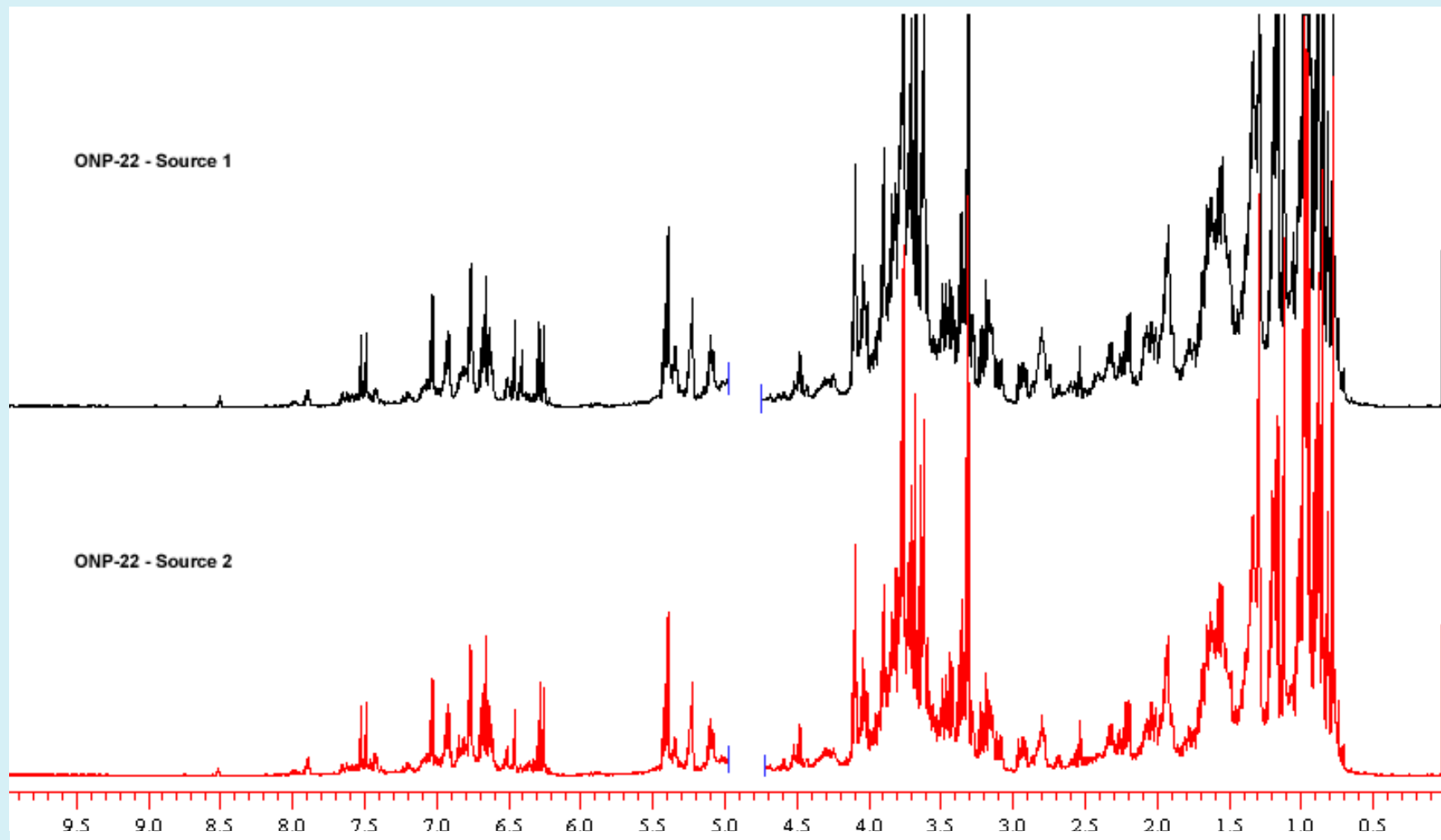
Principal Components Analysis:

Finds basic vectors which maximize separation between classes

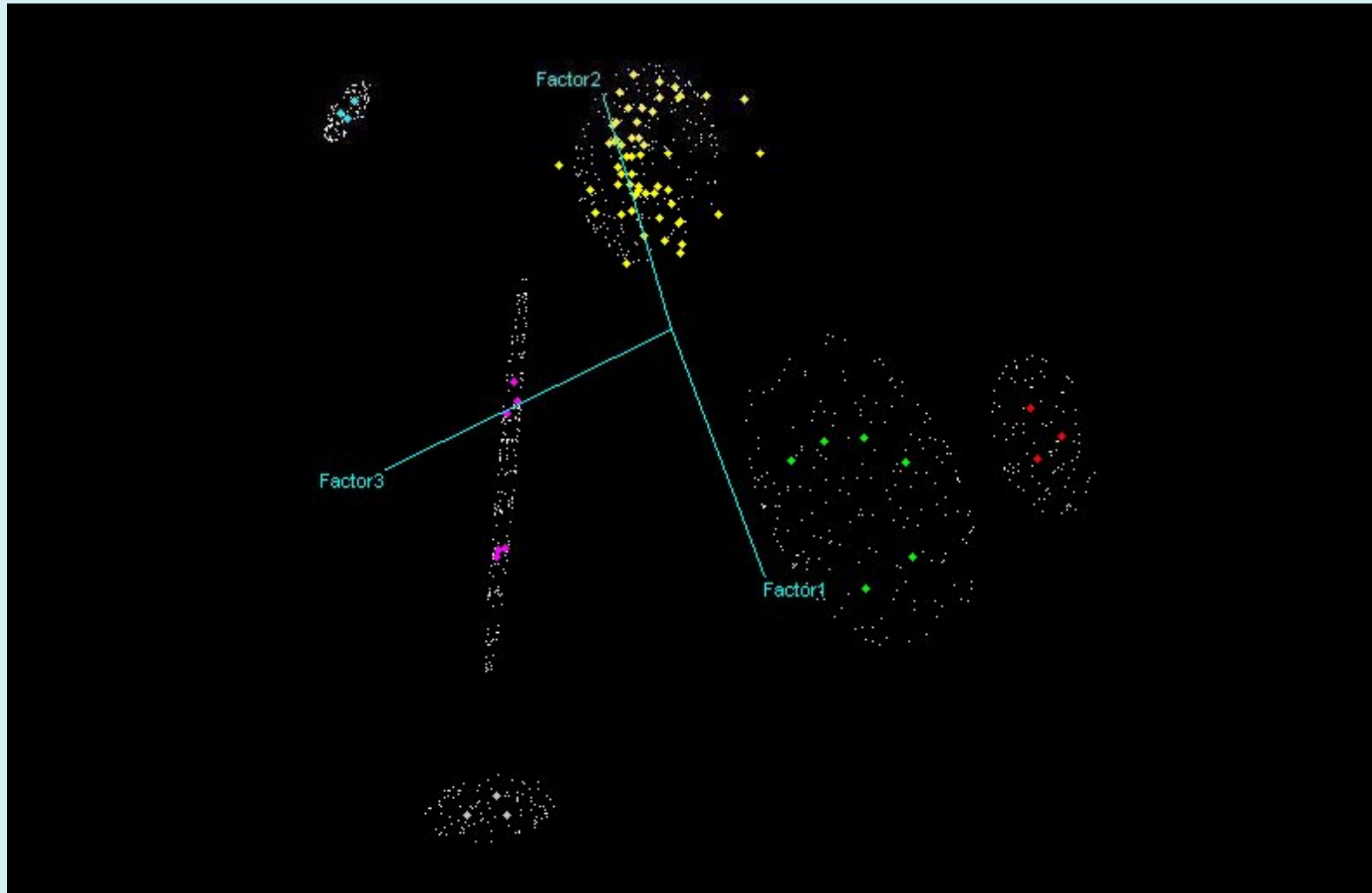
Vectors ordered by decreasing total variance

Visualization in 2- or 3-dimensional presentations

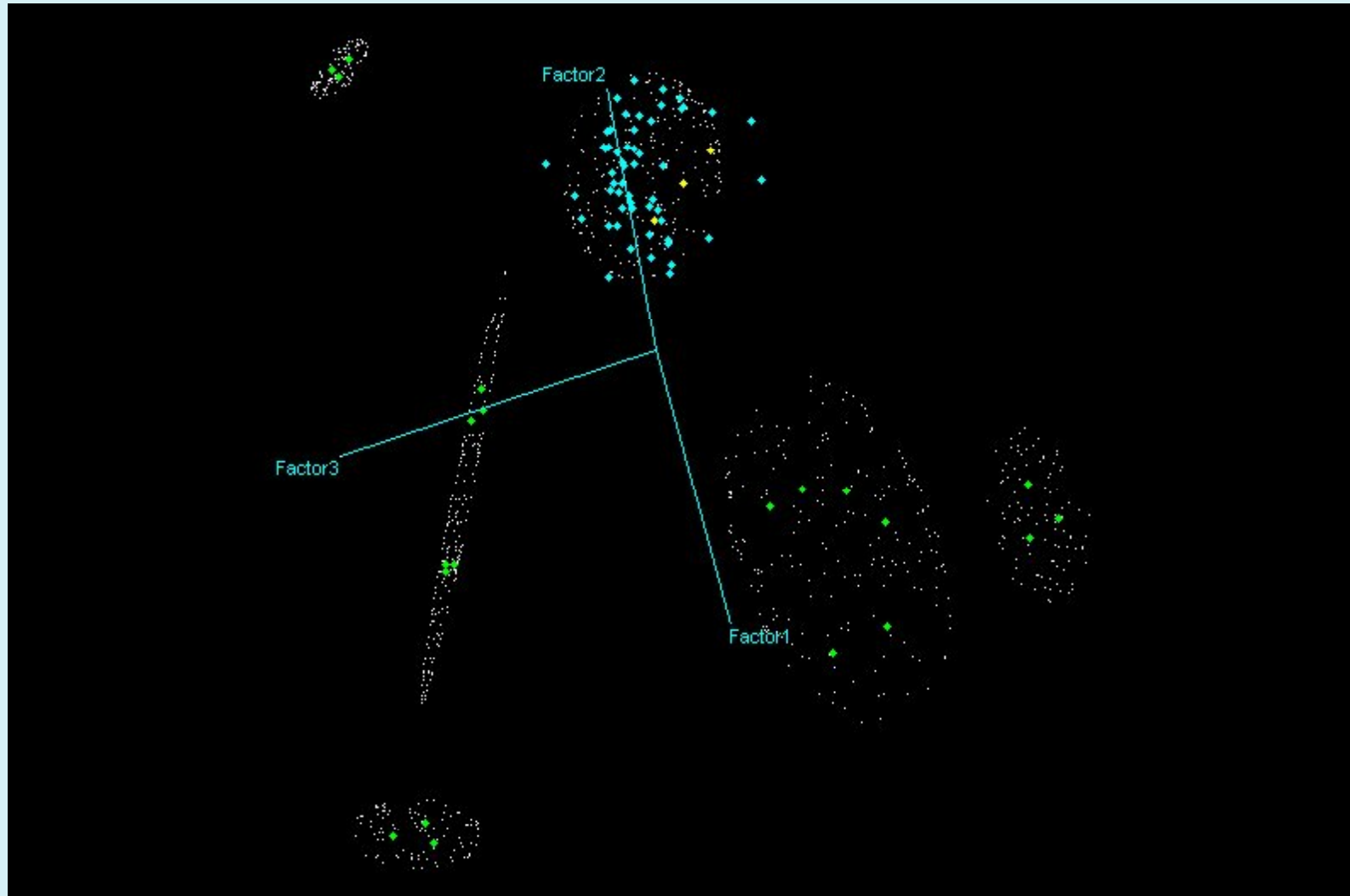
Cluster represents specific metabolic profile – leading to enhanced definition and thence, eventually, specification



PCA – Intraspecific variation: target (field samples) and non-target accessions



PCA – Intraspecific variation: target and non-target accessions + Year 1 Harvest



Conclusion

'Fingerprinting' approaches already recognised by
WHO

Chinese [State Food and Drug Authority](#)

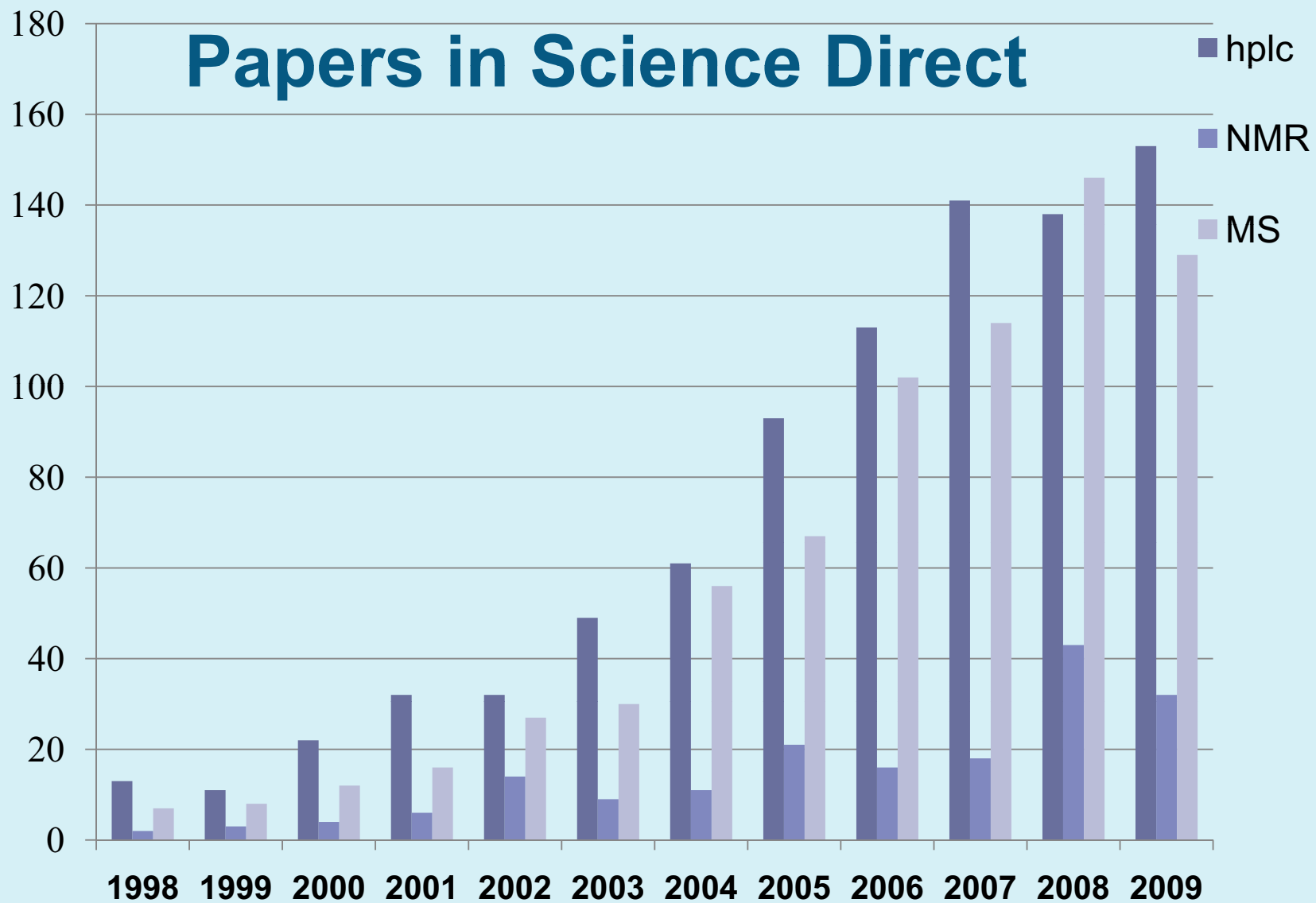
Only HPLC profiles considered

Reductive (not all compounds taken into account)

Subjective in operation (impossible to set criteria for
more than one peak)

NMR and PCA gives an approach to
[fuzzy fingerprints](#)

Papers in Science Direct



2. Biological and mechanism studies

ii clinical methods

Application of metabonomics to detect metabolic effects of plant products

High field nmr spectroscopy to analyse urine
to investigate effects of chamomile tea
ingestion

Experimental design

Human volunteers

Matricaria chamomilla *tea*

- 5g dried flowers infused in 200ml hot water (10 minutes)
- Resultant tea drunk

3 phases

- Pretreatment or control
- Treatment
- Post-treatment or washout

Urine collected 2 hours after dosing

Urine examined by 600MHz nmr spectroscopy

Data analysed by partial least squares analysis

Metabonomic Characterization of Chamomile Ingestion

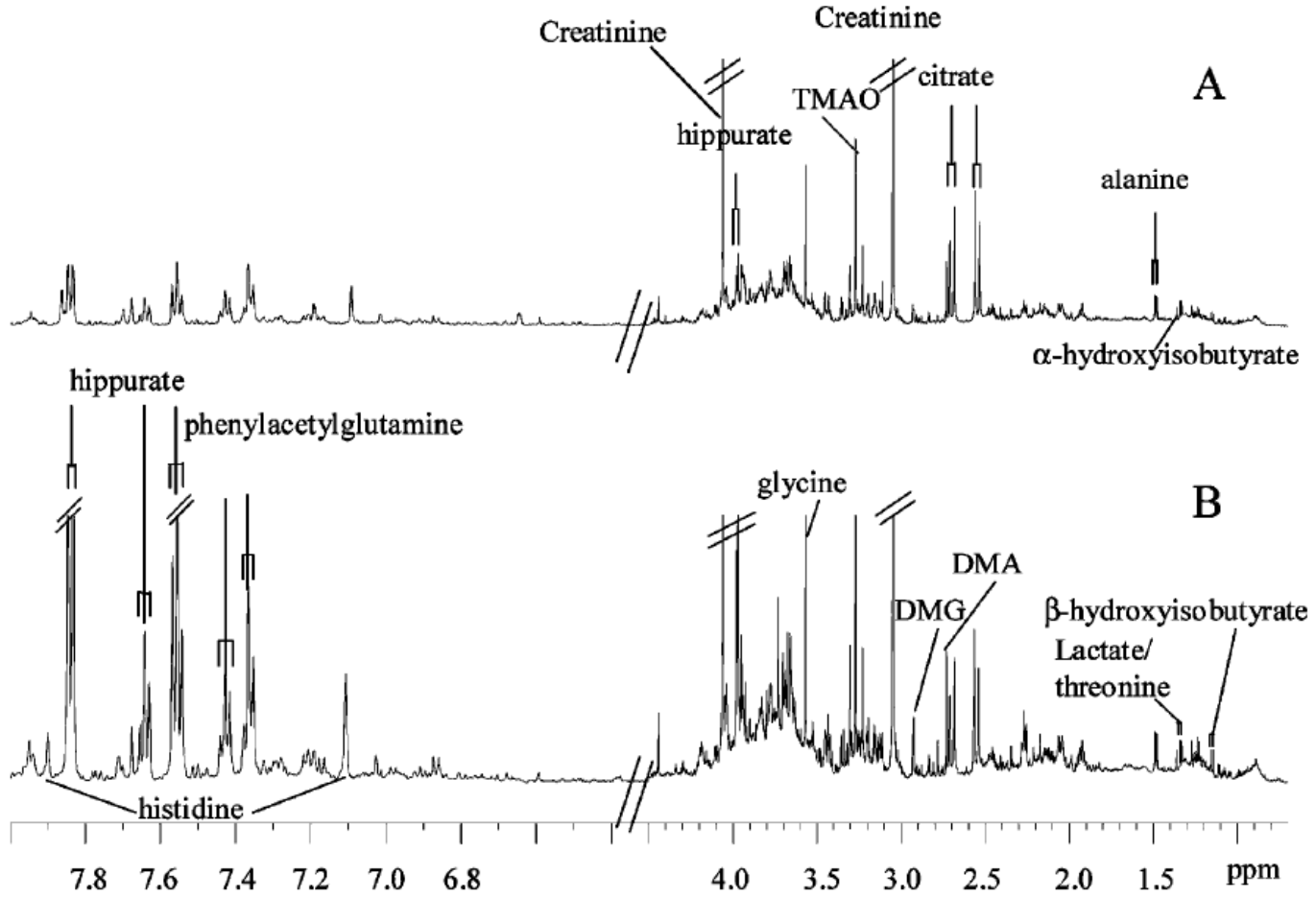


Figure 1. 600 MHz ¹H NMR spectra of urine sample obtained from a healthy male (A) before chamomile intake and (B) during chamomile intake.

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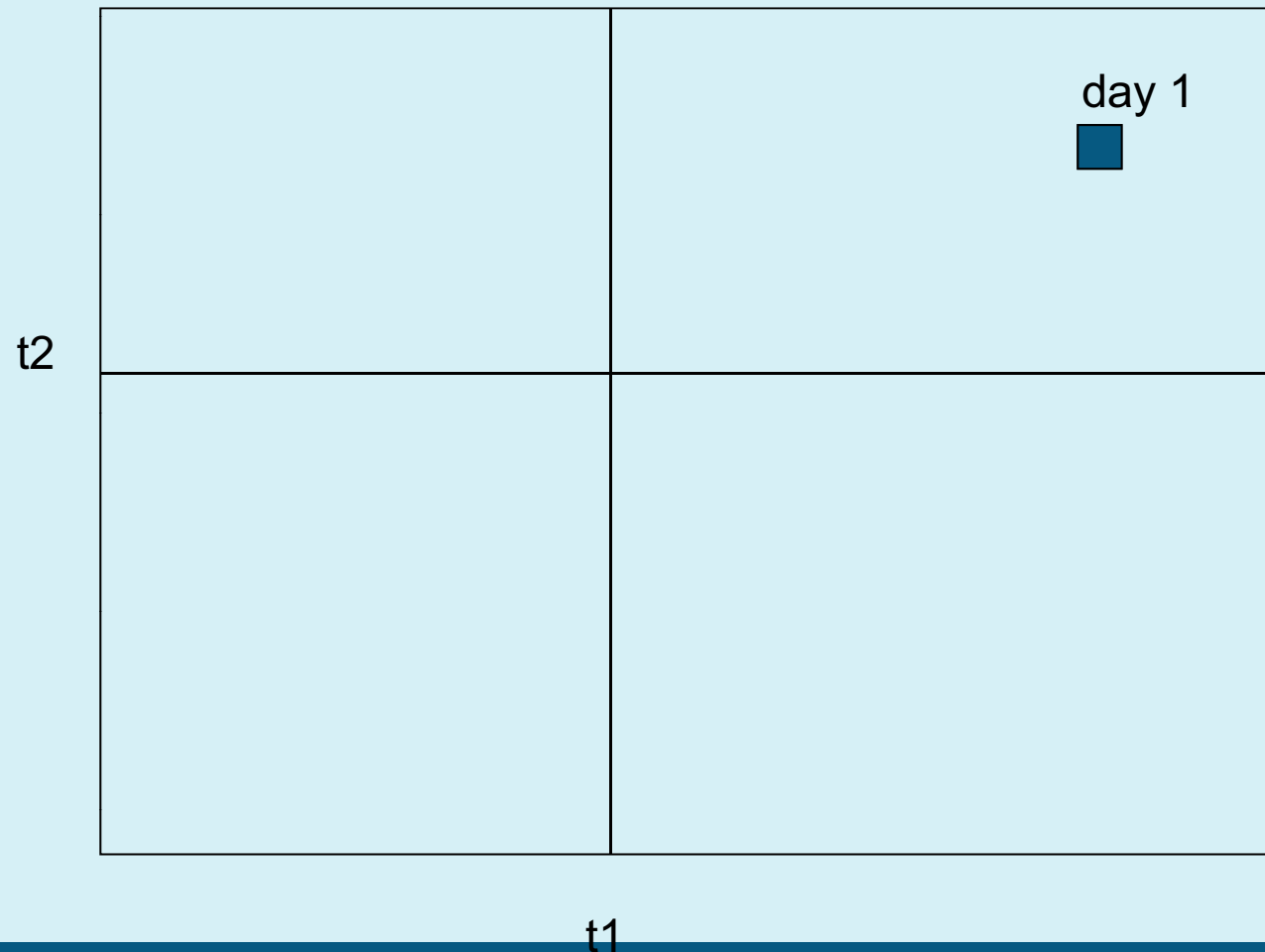
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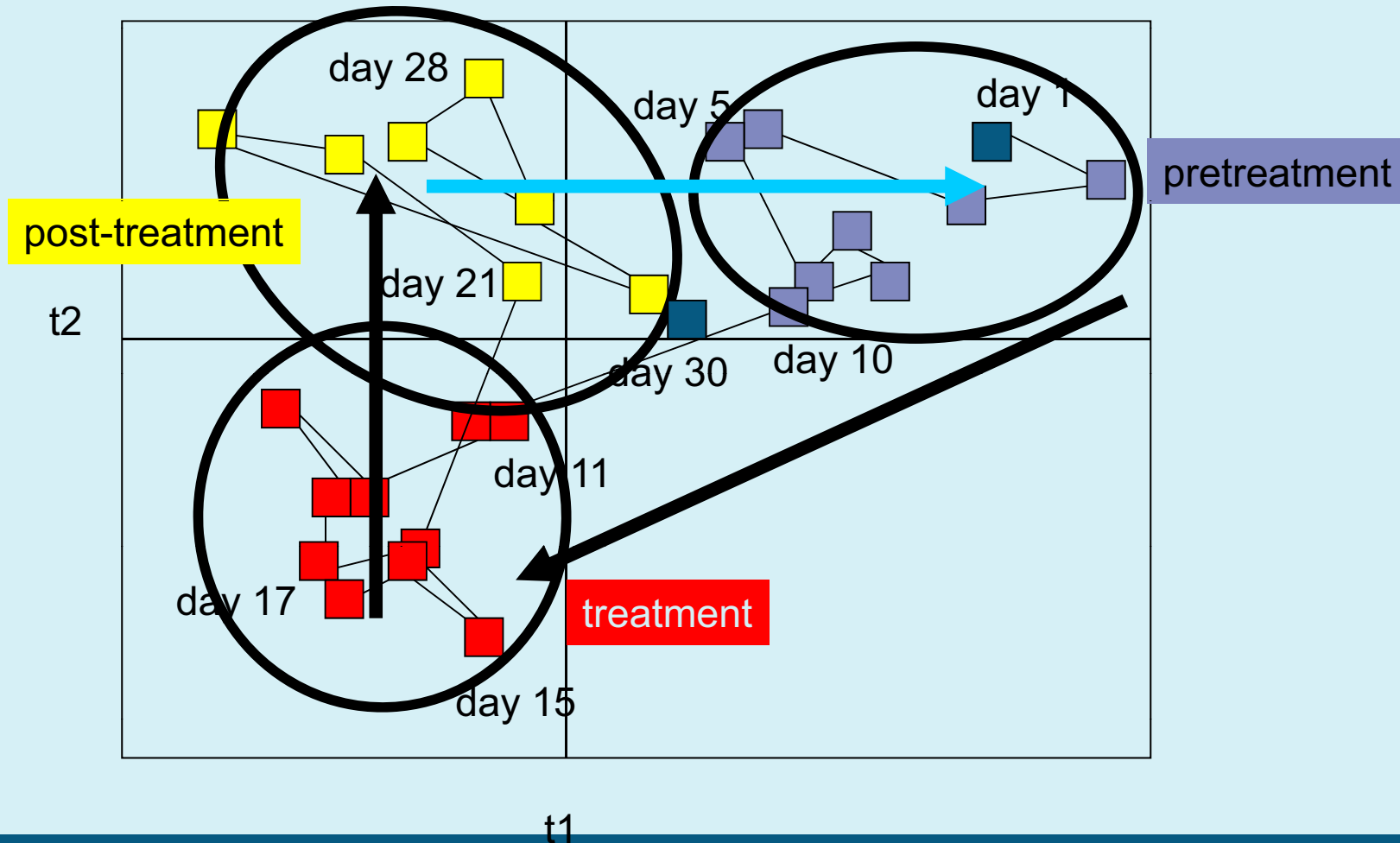
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Trajectory analysis of scores plot



Trajectory analysis of scores plot



Summary of results of chamomile study

Clear differentiation of untreated urine spectra before, during and after chamomile ingestion despite significant subject variation

Changes interpreted as

- increased urinary excretion of hippurate and glycine
- reduced excretion of creatinine

Trend demonstrated, returning to normal over time

Demonstration of prolonged activity of plant medicine

Highlights potential of metabonomics in analysis of effects of plant medicines, including TCM

J Agric Food Chem, 2005, **53**:191-196

3. Bioinformatics and Traditional Chinese Medicine

Traditional Chinese Medicine

| <i>TCM category</i> | <i>Western Equivalent</i> | <i>Signs and Symptoms</i> |
|---------------------|--|---|
| Tonify Yin | Endocrine agent, Antidiuretic, Antihypertensive, Anticholesterolaemic | Dizziness, tinnitus, weak lower back and knees, low-grade fever, menopausal symptoms, scanty dark urine, red dry tongue, thin pulse |
| <i>Shen</i> | Tranquillizer, Sedative, Nerve Tonic | Palpitations, anxiety, insomnia |
| Wind Cold | Diaphoretic, Antiviral, Antibacterial | Chills, headache, body & neck pain, no fever/mild fever |
| Heat (<i>Qi</i>) | Refrigerant, Antipyretic, Anti-inflammatory, Antimicrobial | High fever, irritability, thirst, delirium, certain skin diseases |

Drug discovery from TCM plants

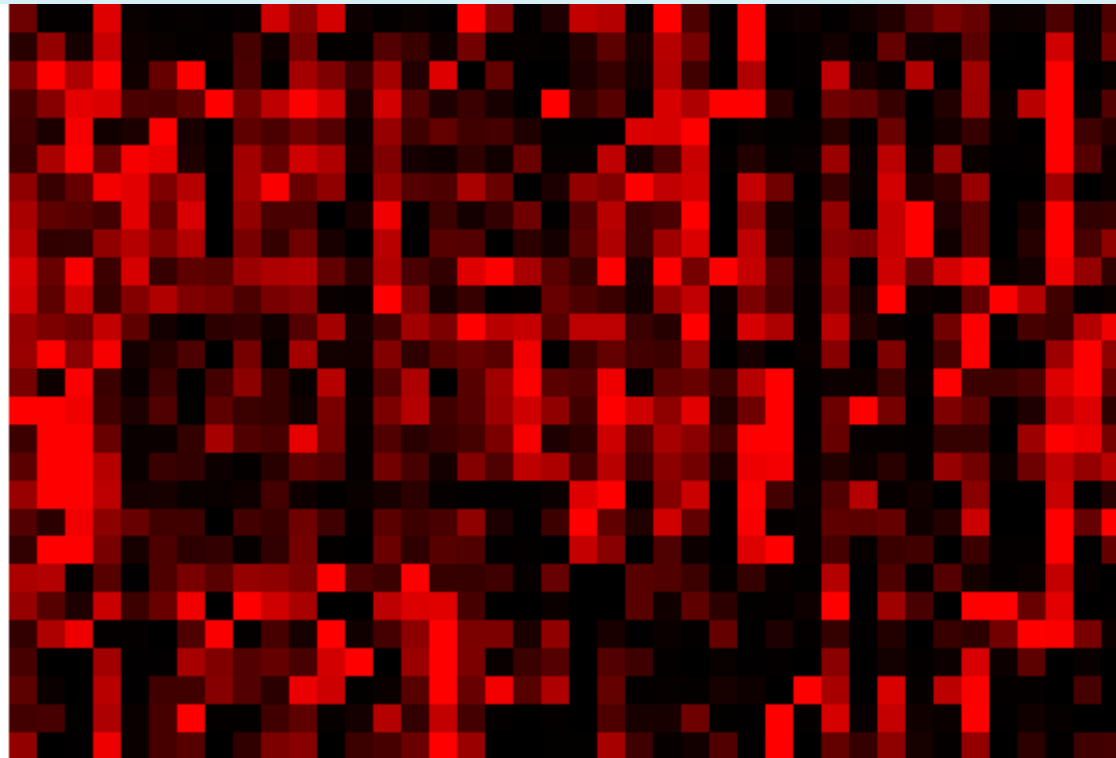
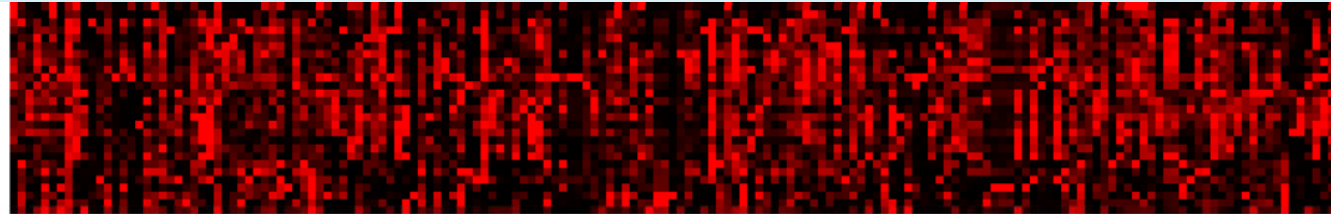
Construction of Two Novel Databases:

Chinese Herbal Constituents Database
(CHCD)

Bioactive Plant Compounds Database (BPCD)

J Chemical Information & Molecular Modeling, 2007, **47**, 254-263

Random ordering of compounds

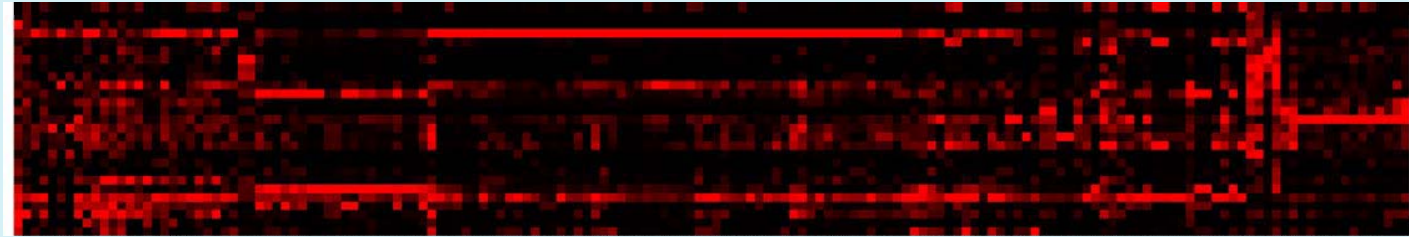


- nACh receptor
- GABA receptor
- Na K ATPase
- Voltage dependent Na channel
- Alpha-1 adrenergic receptor
- Dopamine receptor
- Acetylcholinesterase
- Monoamine oxidase
- iNOS expression
- NO in vivo
- cAMP dependent phosphodiesterase
- Calmodulin dependent protein kinase
- MLCK
- Protein kinase A
- Protein kinase C
- Topoisomerase II
- Apoptotic
- HIV-1 reverse transcriptase
- HIV-1 protease
- HIV-1 integrase
- Testosterone 5 alpha reductase
- Oestrogen receptor
- Aromatase
- Phospholipase
- Cyclooxygenase
- Lipoxygenase
- Aldose reductase

← Herbal constituents →

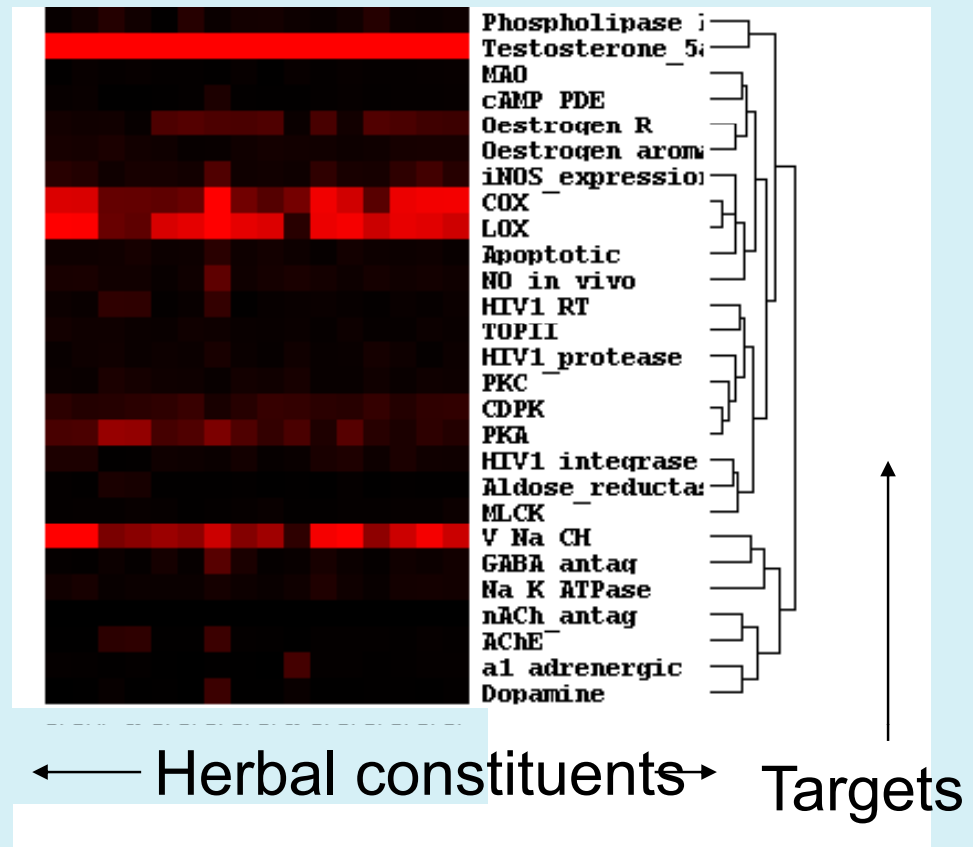
↑
Targets

Compounds ordered by TCM profile/usage



Constituents of Herbs in the **Invigorate Blood** TCM Category

For treating severe pain and ulcer

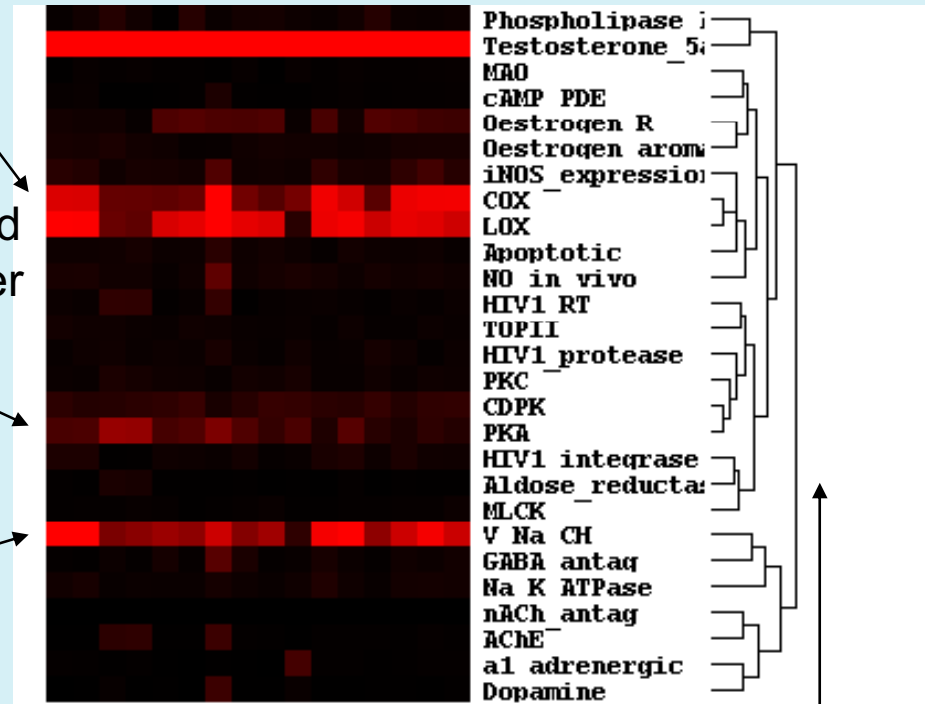


Compounds ordered by TCM profile/usage

5-lipoxygenase & cyclooxygenase-2 inhibitors - anti-inflammatory & analgesic

Protein kinase A & calmodulin dependent protein kinase - implicated in *H. pylori* potentiation of peptic ulcer

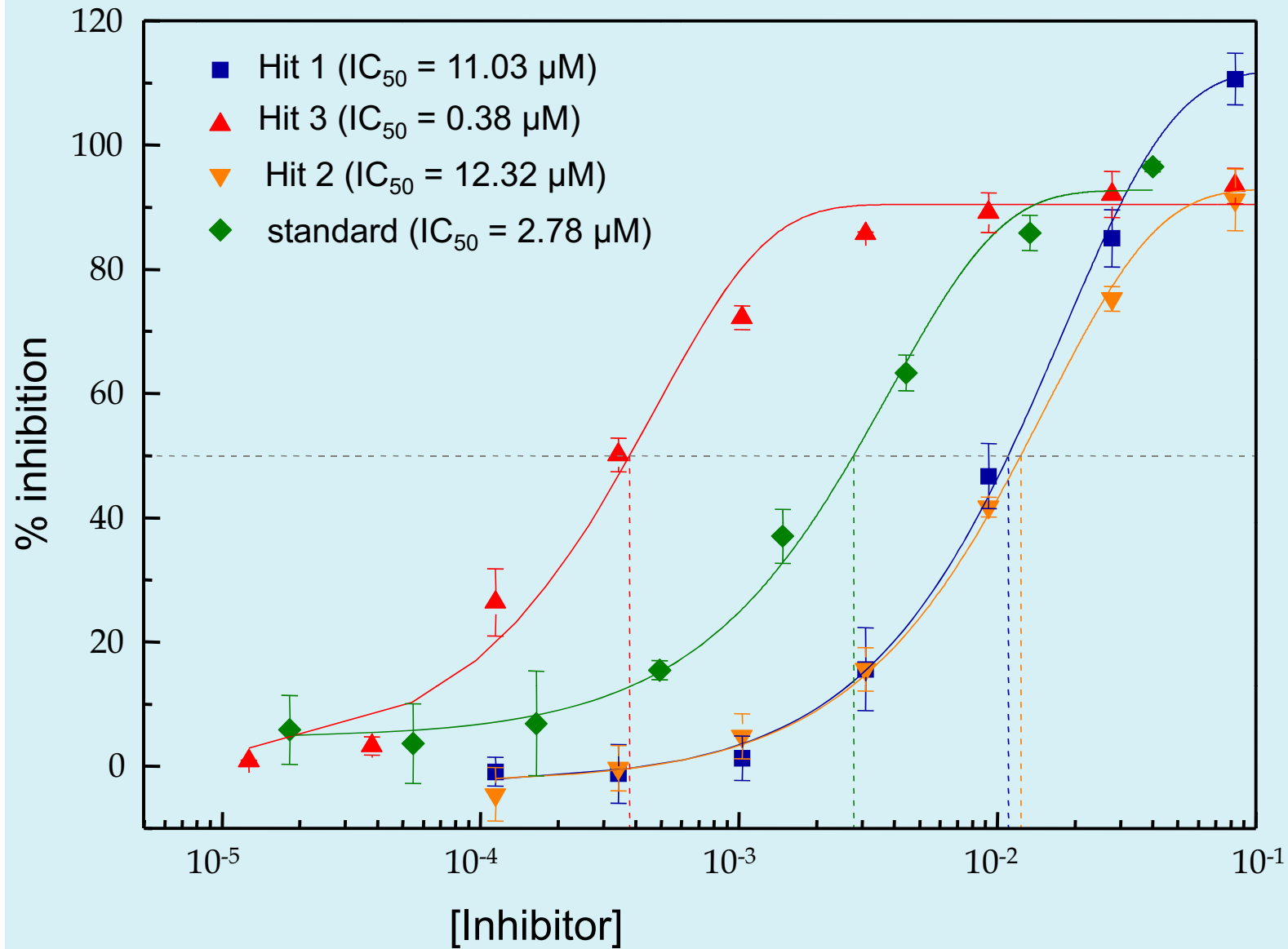
Voltage sensitive Na⁺ channel blockers - effective in treating inflammatory pain



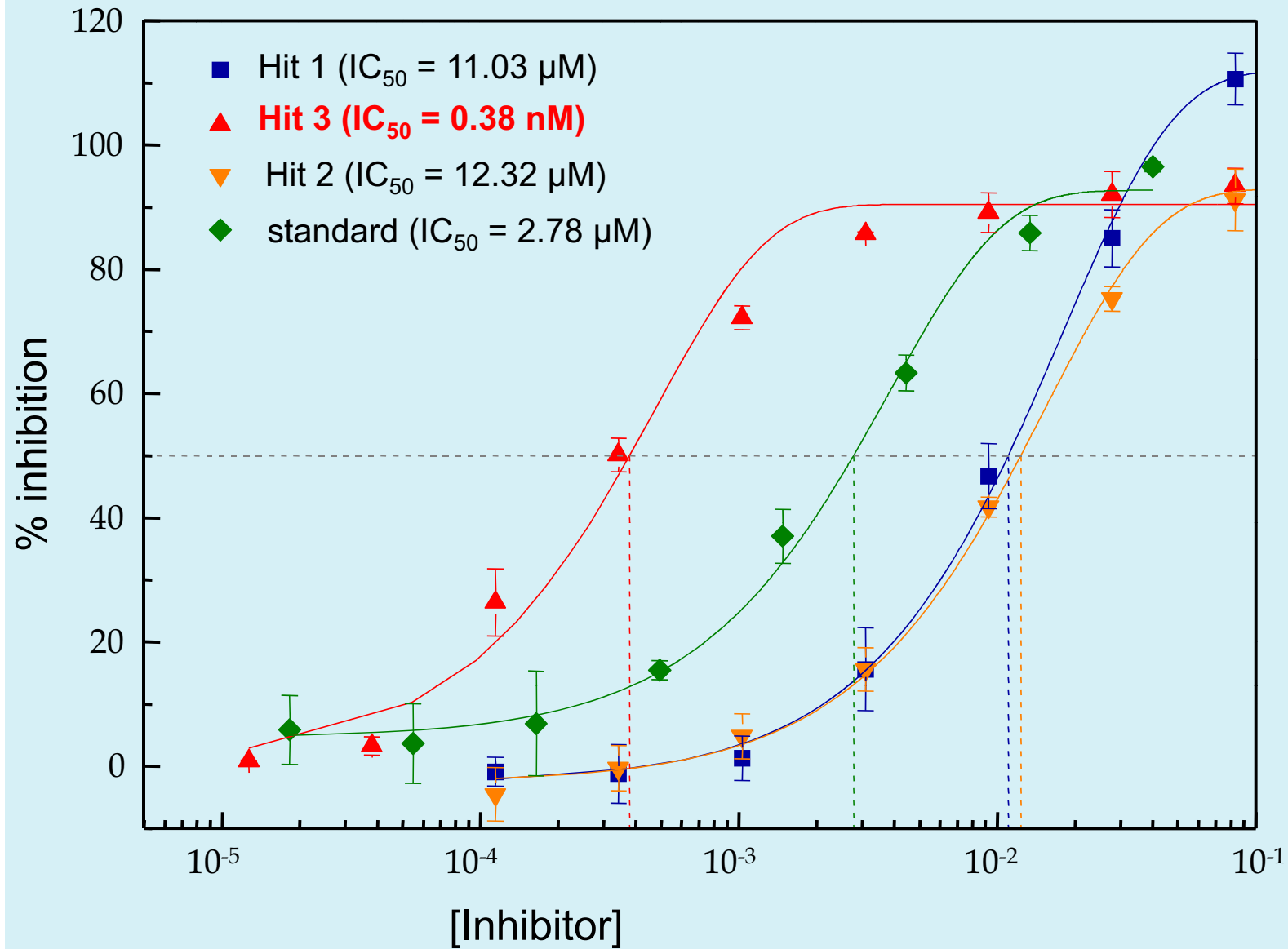
← Herbal constituents → Targets

Drug Discovery prediction verified by laboratory study

Aromatase inhibition



Aromatase inhibition



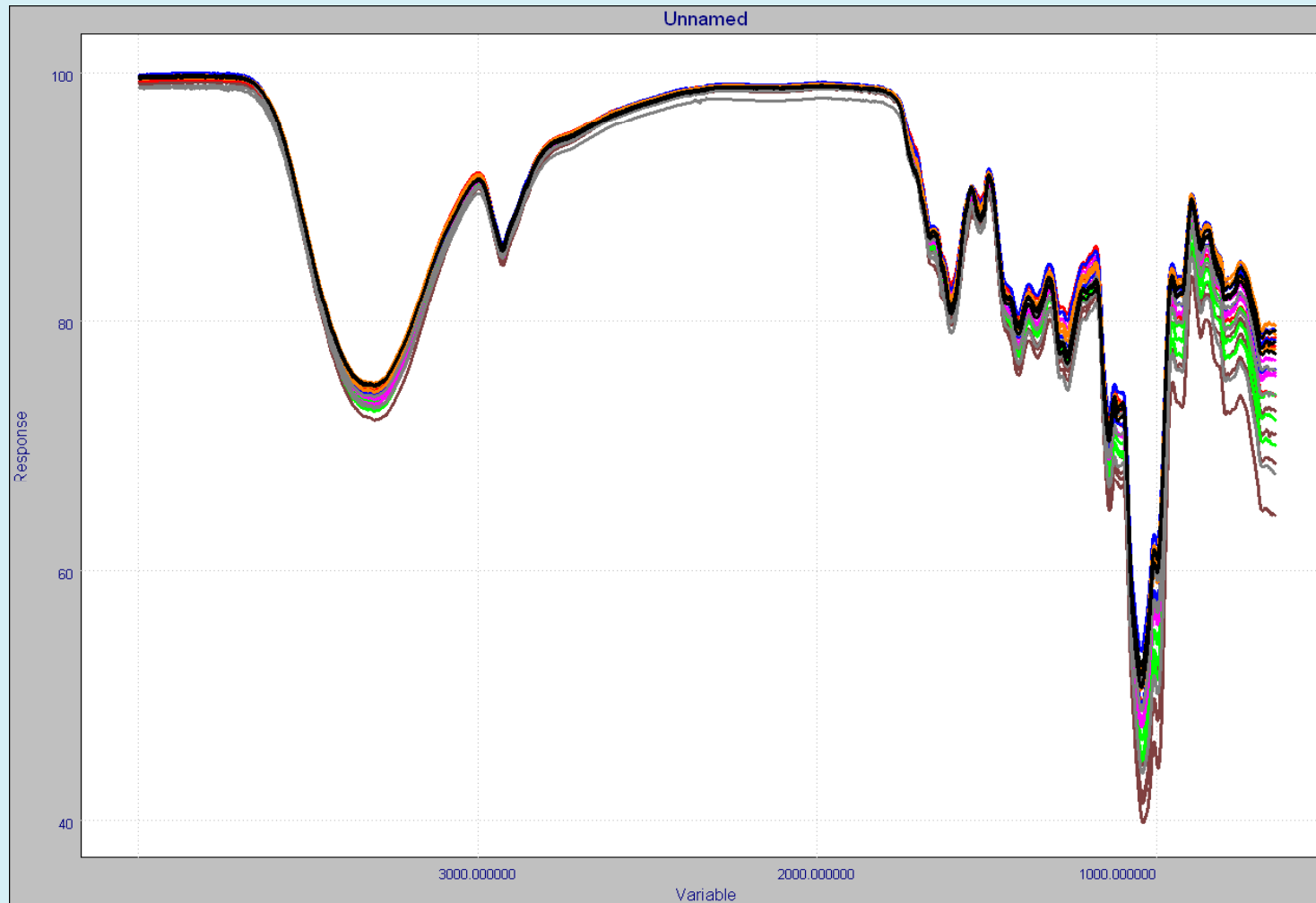
Summary

1. TCM
2. Problems and solutions in standardisation and quality control of plant medicines
3. Chemical, biological and mechanism studies
 1. *in-vitro*
 2. *clinical*
4. Bioinformatics
5. Drug discovery



Much more data is
coming....

Infrared profiles



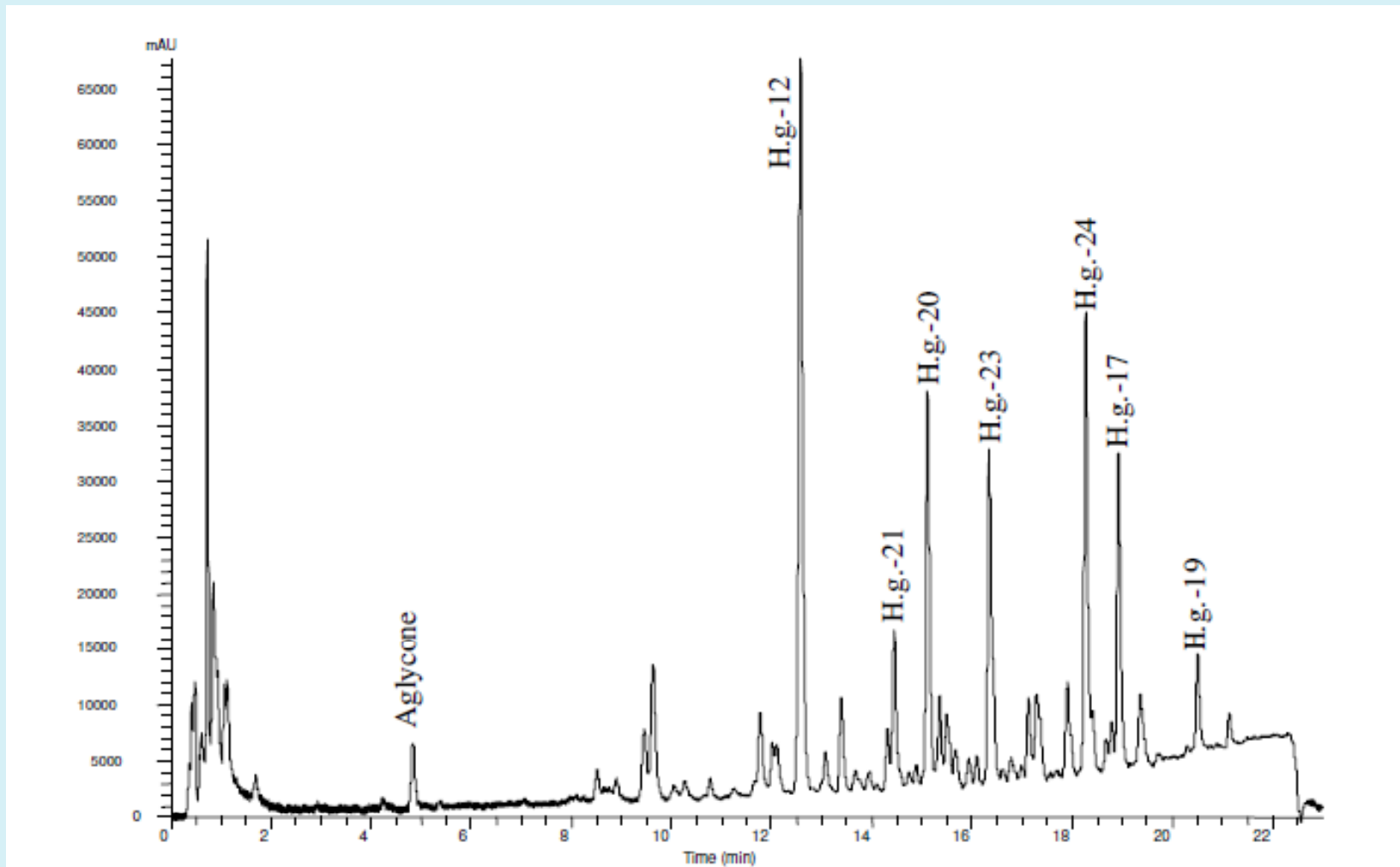


Figure 3.9 Typical UHPLC-UV (220 nm) Chromatogram of extract.

Russell, thesis, 2010

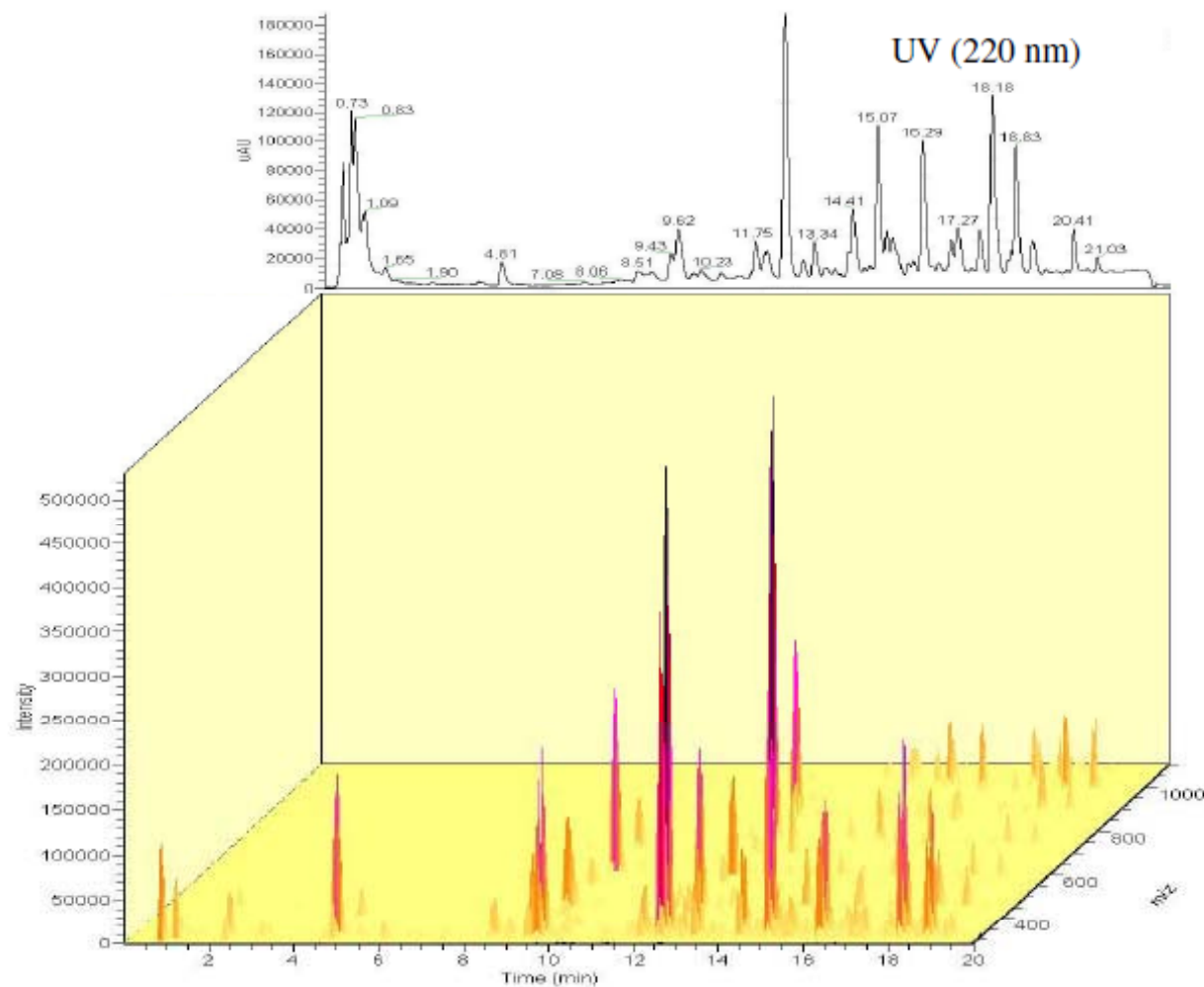
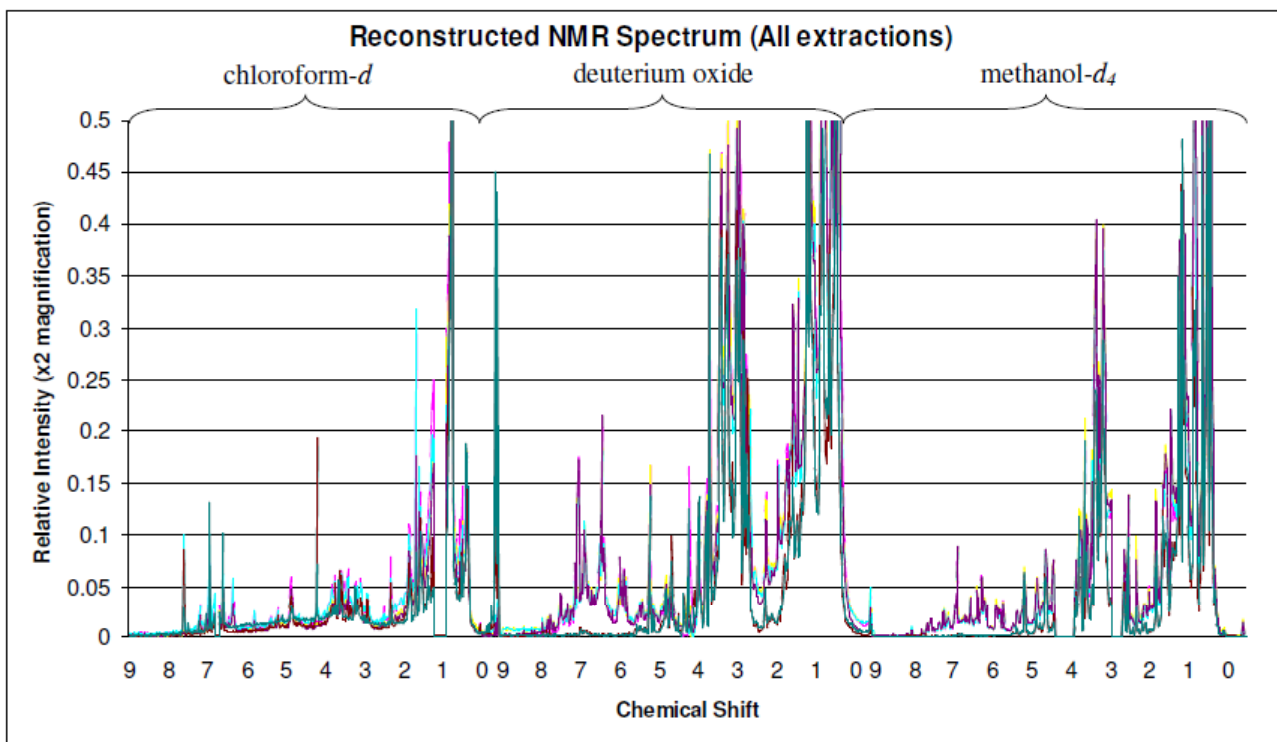


Figure 3.13 Typical UHPLC-UV (220 nm) profile of [redacted] extract and data dependent acquired MSⁿ fragment ions for individual peaks obtained by linear ion trap MS.

Russell, thesis, 2010



Key:

1

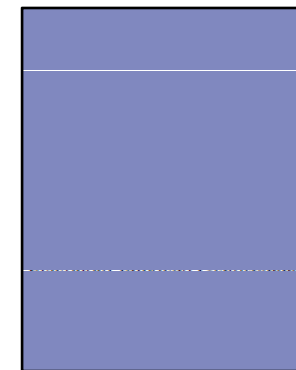
2

3

4

A

B



Russell, thesis, 2010

We can add biological and mechanism data

Method analogous to total 'chemistry'

No single active

No single mechanism

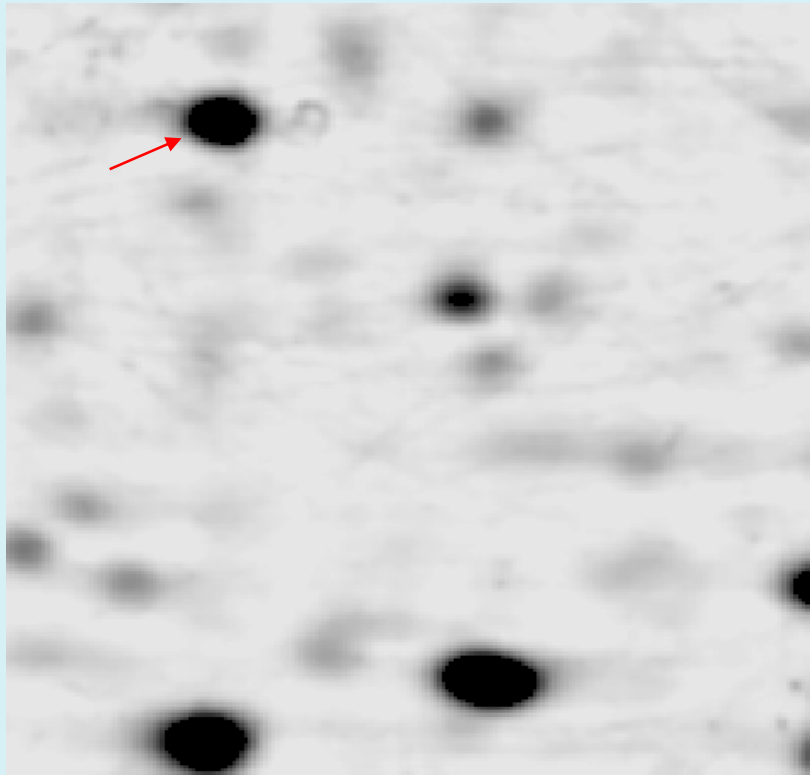
'Omics technologies'

Proteomics

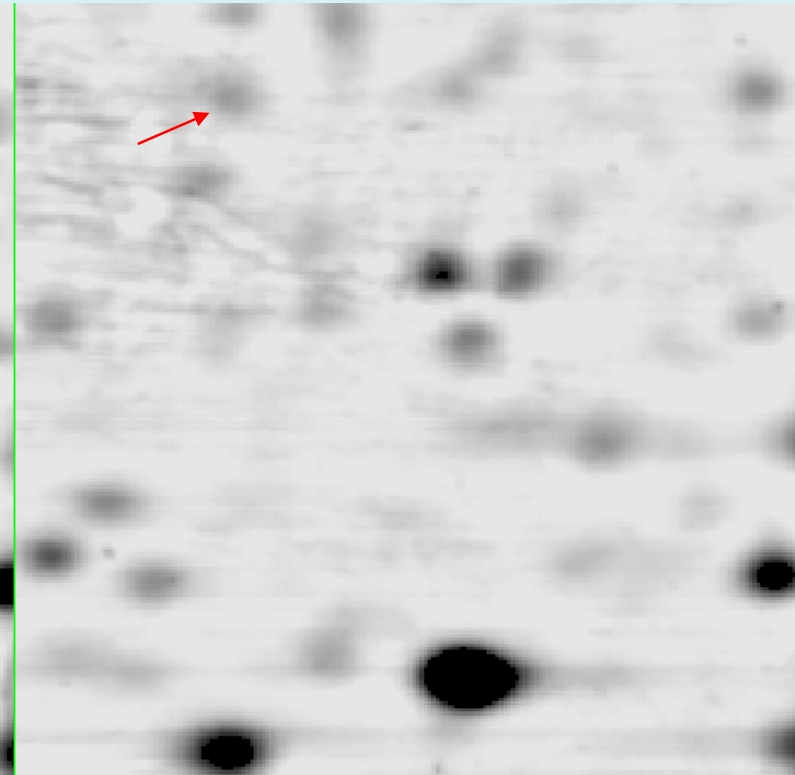
Gene expression

2D-gel analysis

Treated - test



Untreated - control



Principal applications of fingerprinting

origin identification

indication of stability

Can we use the data more wisely
to help in standardisation and
quality control?

How similar is similar?

Substantial equivalence

Similarity index

Centre for Natural Medicines Research

Expertise

Pharmaceutical Science

Chemical biology

Pharmacology

Clinical Pharmacology

Medicine

Academic Health Science Centre

King's Health Partners

Clinical trials - Quintiles

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€1 million EU funding for Chinese medicine research

05 May 2009, PR 87/09



King's College London successfully led a consortium bid for €1,100,000 of EU funding for a ground-breaking research project that will play an important role in the unification of Western and Chinese approaches to medicine.

The project entitled 'Good Practice in Traditional Chinese Medicine Research in the Post-genomic Era' (GP-TCM) will review the current status of Traditional Chinese Medicine (TCM) research, identify problems and propose solutions by applying modern methods of investigation, as well as providing a forum for the exchange of opinions, and expertise among scientists in the EU and China.

The three-year project aims to propose guidelines and priority areas for future research, and will lead to the formation of a new academic society, the European Society of TCM Research, which is to facilitate and foster sustainable EU-China collaboration in this area.

The research consortium consists of 29 beneficiary partner institutions and small-and-medium-sized enterprises from the EU and China. Partnerships with more than 20 additional non-beneficiary institutions, companies and independent experts are further strengthening its research.

Holistic approach

Dr Qihe Xu, Lecturer in the Department of Renal Medicine, Division of Gene and Cell Based Therapy, and coordinator of the project, explains: *'In contrast to the reductionist approach of Western medicine that is based on modern anatomy and cell and molecular biology, TCM uses a unique theory system and an individualised holistic approach to describe health and disease, which is based on the philosophy of Yin-Yang balance. These two medicine systems disagree with each other in many situations since they observe health from their own limited perspective. GP-TCM aims to inform best practice and harmonise research of the safety and efficacy of TCM, especially Chinese herbal medicines and acupuncture, in the EU.'*

'The project will be divided into ten parts, which will review aspects of quality control, extraction and analysis of Chinese herbal medicines. Discussion fora that explore the role of functional genomics methodology in researching the safety, efficacy and mechanisms of action of Chinese herbal medicines and acupuncture are at the core of this project. New guidelines about good practice and agreed protocols in related research areas will harmonise future TCM research in the EU, and online tools and research resources will be made available to all EU member states. As an open-start and open-ending consortium, we will invite more organisations to become involved in the work.'

Share our experiences

Professor Peter Hylands, Head of the Department of Pharmacy and Director of the Centre for Natural Medicines Research, continues: *'We are delighted to be part of this unique group. In the Centre for Natural Medicines Research at King's we are examining the application of emerging technologies to the solution of difficult problems in the use of traditional medicines. This*

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Good Practice in Traditional Chinese Medicine - Windows Internet Explorer

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Good Practice in Traditional Chinese Medicine Research in the Post-genomic Era

About

- The project
- Partners
- Deliverables



Welcome to GP-TCM

GP-TCM is a European Coordination Action funded under the 7th framework programme. The overall aim of the project is to inform best practice and harmonise research of the safety and efficacy of Traditional Chinese Medicine (TCM) in EU Member States using a functional genomics approach through exchange of opinions, experience and expertise among scientists in EU Member States and ...more

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WP4 and WP7 Joint Phase II Meeting

The joint phase II meeting of WP4 and WP7 was held on 26th - 27th July 2010 at Kings College London, Waterloo Campus, UK. Number of WP4 and WP7 members ...more

WP1 and WP2 Joint Phase II Meeting

The joint Phase II meeting of WP1 and WP2 brought together 17 participants across Europe and China in Düsseldorf, Germany. ...more

The 1st GP-TCM Annual Meeting

The 1st GP-TCM Annual Meeting was held on 27th-30th July 2010 at Henley Business School, Henley-on-Thames, ...more

WP10 Kick-off Meeting (the Sino-EU GP-TCM Workshop)


GP-TCM Workshop was held in Beijing on 11th -13th January ...more

More

- » WP3 Kick-off Meeting
- » WP6 Phase I Kick-off Meeting
- » WP4 Phase I Kick-off Meeting
- » WP5 Kick-off Meeting
- » Joint WP1 and WP2 Phase I Kick-off Meeting
- » WP7 Phase I Kick-off Meeting

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GP-TCM is a Coordination Action funded by the European Union's 7th Framework Programme under the grant agreement No. 223154.



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Acknowledgements

Paul Russell
Huiying Zhao

Jue Zhou

David Barlow
Tom Ehrman



Thank you for your attention