HERBAL MEDICAL PRODUCTS – EVIDENCE-BASED OR TRADITIONAL MEDICINES?

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PLANT SCIENCE

Evidence and herbal medicines

- The best available (clinical) evidence is obtained using well developed scientific protocols for clinical decision making, but often limited to those products which have been shown to be efficacious and safe in large(r) clinical trials.
- Yet, in many countries most of the usage of herbal medicines is based on self-treatment and often relies on OTC (Over-the-counter) products or a diverse group of health care practitioners.
- HMPs (Herbal Medical Products) are normally more complex phytochemically and require a much higher level of analytical assessment.

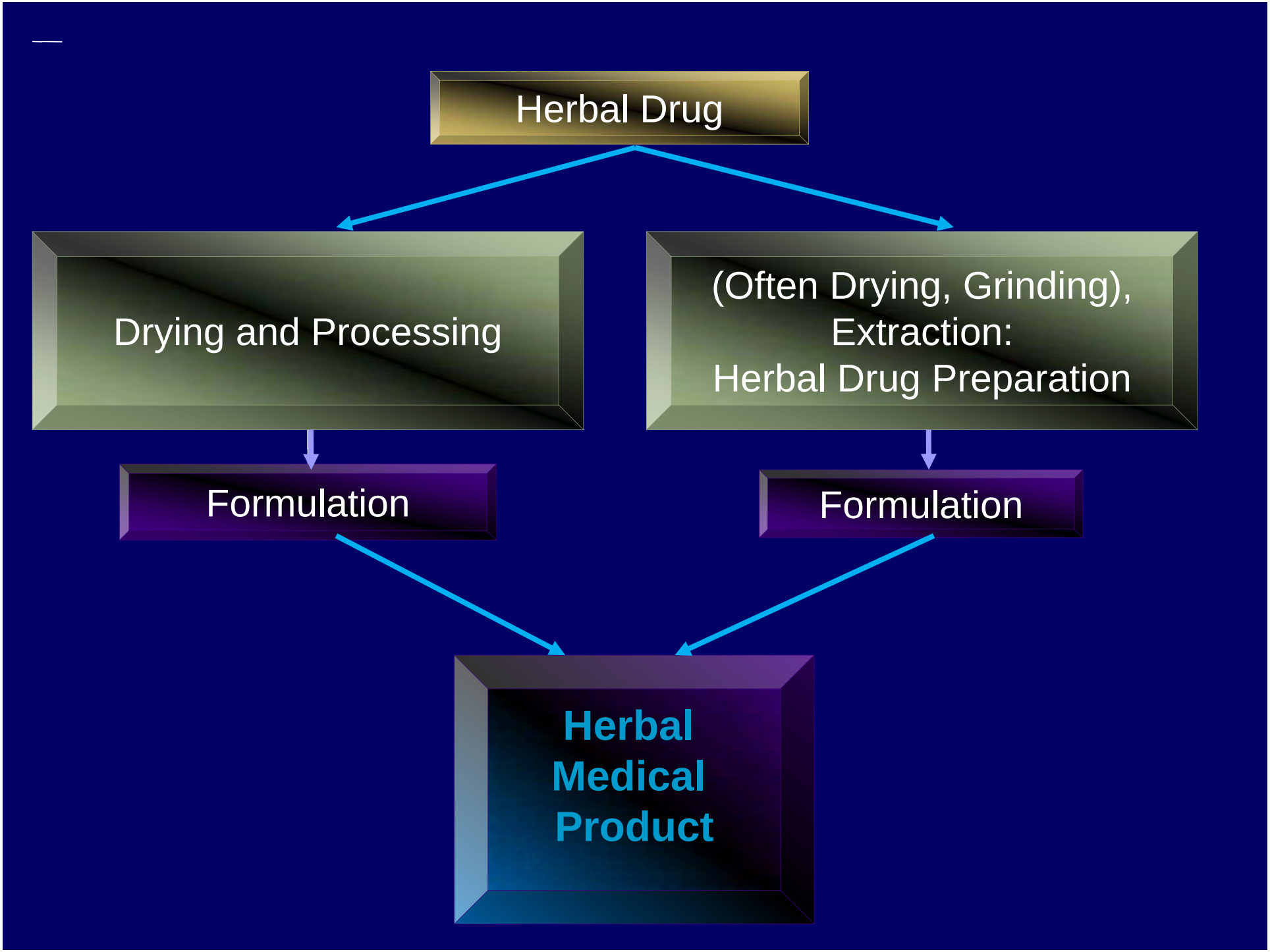
We know it, but how do we deal with it?

Aspirin tablets contain:

- Aspirin
- *(excipients)*

Tablets containing extract of St John's wort herb, contain:

- Hyperforin, adhyperforin, hypericin, pseudohypericin, isohypericin, protohypericin, protopseudohypericin, kaempferol, quercetin, luteolin, hyperoside, isoquercitrin, quercitrin, rutin, bi-apigenin, amentoflavone, catechins, tannins, other phenols etc.
- (excipients)


Herbal Drug
Drying and Processing
(Often Drying, Grinding),
Extraction:
Herbal Drug Preparation
Formulation
Formulation
Herbal
Medical
Product

From (botanical) drugs to (standardised phyto-)medicines

Drug	Botanical drug	Botanical drug
⇓	⇓	⇓
	Extraction	Extraction
⇓	⇓	⇓
		Standardisation
		⇓
Formulation	Formulation	Formulation
⇓	⇓	⇓
Medicine	Phytomedicine	Standardised phytomedicine

Standardisation

- Standardisation is achieved by adjustment of the extract with inert materials or by blending batches of extracts (Eur. Phar. Suppl. 4.3 01/2003-0765), all this has to be achieved on the basis of high quality material!
- Clinical, (placebo or verum) controlled, double-blind studies have become the gold standard of drug assessment. In the context of phytomedicines it is only meaningful if the composition is known and meta-analysis is only meaningful if identical extracts have been used
- *Often it is not known which compounds contribute to the activity or the pharmacological effects of the extract* ⇒ Lead compounds for assuring reproducible quality, *but cannot be used to standardise an extract*
- **Special extracts** - extracts which are enriched in desired bioactive compounds and have reduced concentrations of unwanted (inactive or toxic constituents , e.g. *Ginkgo biloba*)
- See Fundamentals of Pharmacognosy and Phytotherapy , esp. chapter 9; European Pharmacopoeia, esp. Suppl. 4.3 - 2937

LOCAL MEDICINES IN THE TREATMENT OF MALARIA IN MALI

What is the effectiveness of a traditional treatment?

- Mali: A prospective, dose-escalating, quasi-experimental clinical trial with a traditional healer using a decoction of *Argemone mexicana for the treatment of malaria*
- Symptoms of malaria
- *Plasmodium falciparum parasitaemia >2000/l but no signs of severe* malaria.

Figure 1 Chief Tiemoko Bengaly holding *Argemone mexicana*, the plant his grandfather taught him to use as a treatment for malaria. ©Merlin L. Willcox.

Wilcox et al., Trans. R. Soc. Trop. Med. Hyg. (2007) 101, 1190—1198

What is the effectiveness of a traditional treatment?

- Three treatment regimens: once daily for 3 days (Group A; *n = 23);* twice daily for 7 days (Group B; *n = 40); and four times daily for the first 4 days followed by twice* daily for 3 days (Group C; *n = 17).* → *80 patients / 80% aged* <5 years and 25% aged <1 year.
- The proportions of adequate clinical response (ACR) at Day 14 were 35%, 73% and 65% in Groups A, B and C, respectively (*P = 0.011*

Wilcox et al., Trans. R. Soc. Trop. Med. Hyg. (2007) 101, 1190—1198

What is the effectiveness of a traditional treatment?

- *At Day 14, overall proportions of* adequate clinical response *were* lower in children aged <1 year (45%) and higher in patients aged >5 years (81%) (*P = 0.027*). *Very* few patients had complete parasite clearance

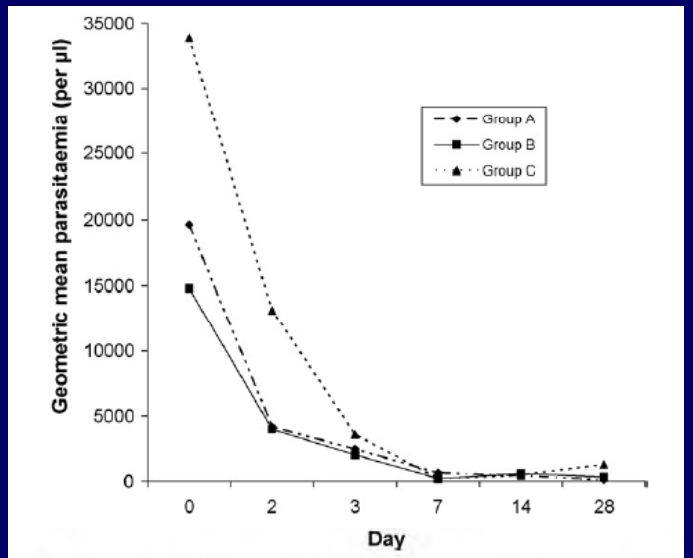


Figure 2 Parasitaemia in all patients during treatment with *Argemone mexicana*.

- On Day 14, 67% of patients with ACR had a parasitaemia <2000/l. No patient needed referral for severe disease. Only minor side effects.
- Further research: Can this local resource be at a first-aid home treatment in remote areas.

- This is evidence, but is it sufficient?
- Should /can we dismiss this?
- Other studies focus on pharmacological effects? Evidence?
- Safety?
- How much would it cost to do it for all the key ‘traditional remedies’ of the world?
- Who will fund this?

EUROPE: HMPS IN A REGULATED FRAMEWORK

UK's Regulatory framework: herbal medicines (1968)

- Product Licences of Right (PLRs) granted to all existing products when Medicines Act came into force (1968)
  At PLR review, traditional herbal medicines used for minor, self-limiting conditions were permitted to draw on bibliographic evidence of efficacy and safety rather than carry out controlled tests and trials ⇒ product licence (PL number); about 600 licensed herbal medicines in the UK
- Section 12 of Medicines Act 1968 provides two crucial exemptions from licensing for herbal medicines:

  (1) supplied by 'herbal practitioner' following request for treatment

  (2) herbs only subjected to simple processing, sold under common/botanical name, no written uses

⇒ Many herbal products (> 5000?) sold as unlicensed 'food/dietary supplements', without direct medical claims (→ 'Female Aid', Sleep Well)

- Only licensed herbal medicines are required to comply with regulatory provisions on quality and pharmacovigilance

The new regulatory routes

- **1. Unlicensed herbal remedies (unprocessed crude drugs)**
- In the last decades most herbal medicines in the UK have reached the consumer as unlicensed herbal remedies. Where these are not industrially produced (= they are crude drugs), they are still exempt from the normal requirements for a medicine to hold a product licence or marketing authorisation through an exemption set out in Section 12. 1 and 12.2 of the Medicines Act 1968. Currently without any quality control or safety evaluation

- **2. Registered traditional herbal medicines (Traditional Use Directive)**
- .... [It] will help protect public health by requiring specific standards of safety and quality for traditional herbal medicines. This scheme is required by the European Directive on Traditional Herbal Medicinal Products (2004/24/EC).

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON024001

The new regulatory routes
(continued)

- **Registered traditional herbal medicines (Traditional Use Directive)** (cont'd)

  Unlicensed manufactured herbal medicines placed on the market under Section 12 (2) of the Medicines Act after 30 April 2004 will need to comply with the requirements of the scheme or, alternatively had to obtain a marketing authorisation, by **30 October 2005**. Unlicensed manufactured herbal medicines placed on the market under Section 12(2) of the Medicines Act before 30 April 2004, will need to comply with the requirements of this scheme by **April 2011** or obtain a marketing authorisation (see below). With quality control, safety evaluation/ pharmacovigilance

- **3. Licensed herbal medicines**

  Around 600 herbal medicines hold a product licence or marketing authorisation after meeting safety, quality and efficacy (or effectiveness) criteria in a similar manner to any other licensed medicine, for example aspirin. Fully regulated medicinesl

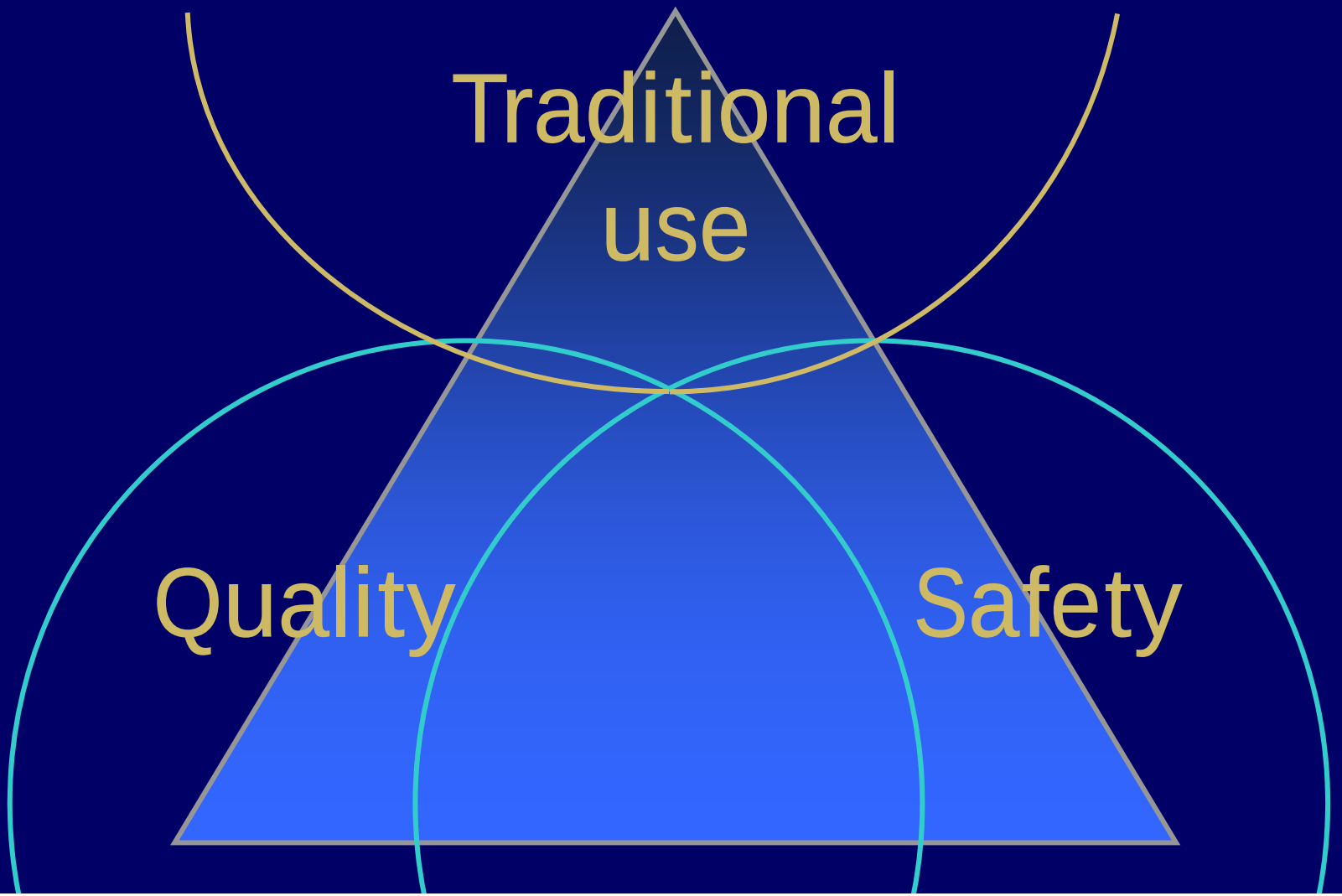
The new regulatory routes
(continued)

- The transition period ends next month, and products on stock may be sold off in the next months

Traditional Herbal Medicinal Products Directive (THMPD) of the European Union

- EU-wide binding regulation based on previous directives with the overarching goal to harmonize the regulatory framework for herbal medical products
  - Implemented October 2005; 7 year transition period, requires member states to set up new national scheme for registration of traditional herbal medicinal products
  - Quality and safety have to be demonstrated
  - No requirement to demonstrate efficacy, instead traditional use (min 30 years, incl. 15 in EU)
  - Registration required; manufacturing under GMP
  - Currently (Sept 2010: > 50 registrations with more than 20 different herbal drugs)

Medicines registered under the EU's *Traditional Use Directive*



Quality and safety of *licensed herbal medicines*

CLINICAL EVIDENCE AND PRODUCT VARIABILITY

Echinacea (*E. purpurea* (L.) Moench, *E. pallida* (Nutt.) Nutt., *E. angustifolia* (DC.) Hell.)

- 3 species used medicinally
- Black sampson; purple coneflower (*E. purpurea*); pale coneflower (*E. pallida*)
- Part used: rhizome, root; aerial parts of *E. purpurea*
- Constituents differ between the different species and plant parts
- Modern uses: Prophylaxis and treatment of common cold, influenza and other upper respiratory tract infections (URTIs)

Clinical evidence : ***In two meta-analyses the benefit of Echinacea preparations in decreasing the incidence and duration of the common cold were demonstrated*** (Shah SA et al. Lancet Infect Dis 2007; 7:473-80; Schoop, R, et al. Clin Therapeut 2006; 28: 174 – 83.)

The effect of Echinacea on the incidence / duration of the common cold

Shah et al: Good basis for clincial evidence.

Overall, three meta-analyses highlight that Echinacea preparations are effective in reducing the incidence and duration of the common cold

Problem: Variability of products

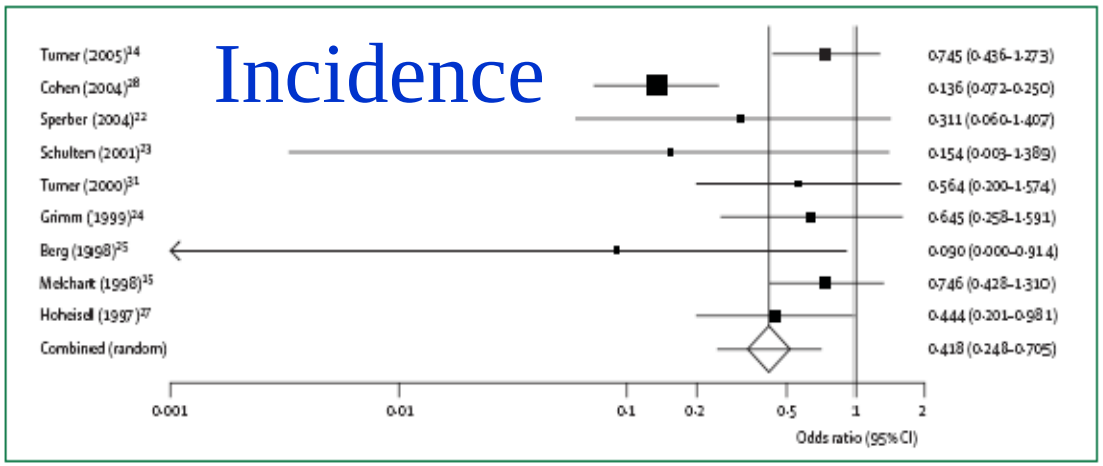


Figure 3: The effect of echinacea on incidence of common cold
The squares represent individual studies and the size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% CIs. The diamond represents the combined result. The solid vertical line extending upwards from 1·0 is the null value.

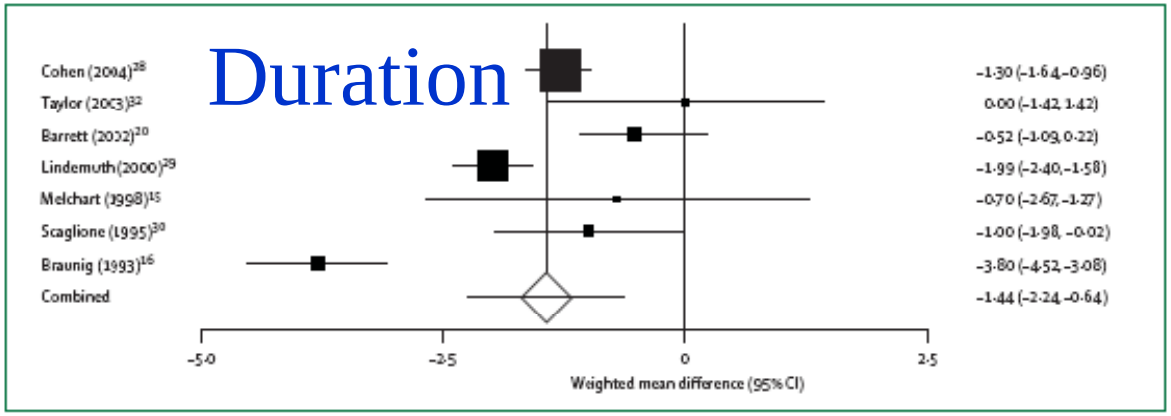


Figure 4: The effect of echinacea on duration of common cold
The squares represent individual studies and the size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% CIs. The diamond represents the combined result. The solid vertical line extending upwards from 0 is the null value.

Shah SA et al. (2007) *Lancet Infect. Dis.* 7: 473-480

Echinacea (*E. purpurea, E. pallida, E. angustifolia*)

- Most (but not all) trials found that echinacea, compared with control, had beneficial effects (reduced frequency or duration of colds/URTIs or severity of symptoms),

  but: several trials poorly designed; tested different preparations of echinacea and/or combination preparations
- Linde and colleagues (2009, Cochrane Review), attempted to determine whether there is evidence from randomised controlled trials that the results of *Echinacea*-only treatment (combination studies were excluded) are different from placebo or no treatment, or treatment with other extracts.
  Conclusion: *Echinacea* preparations tested in clinical trials differ greatly. There is some evidence that preparations based on the aerial parts of *E. purpurea* might be effective for the early treatment of colds in adults but the results are not fully consistent. Beneficial effects of other *Echinacea* preparations, and *Echinacea* used for preventative purposes might exist but have not been shown in independently replicated, rigorous RCTs.
- Linde K et al. (2009) *Cochrane Database Syst Rev* 1: CD000530

Key issues

- Generally, the size of the studies is small
- The evidence is often not accepted by health care professionals or by bodies regulating the access to medicines (NIH, NICE)
- The limitations of the evidence are often not accepted by alternative health care professionals and by many consumers
- Such natural remedies is either seen as potentially dangerous (often because of lack of knowledge about the products) or as always and intrinsically safe.
- There has been a constant and considerable concern about adulteration and poor quality-products (not covered today)

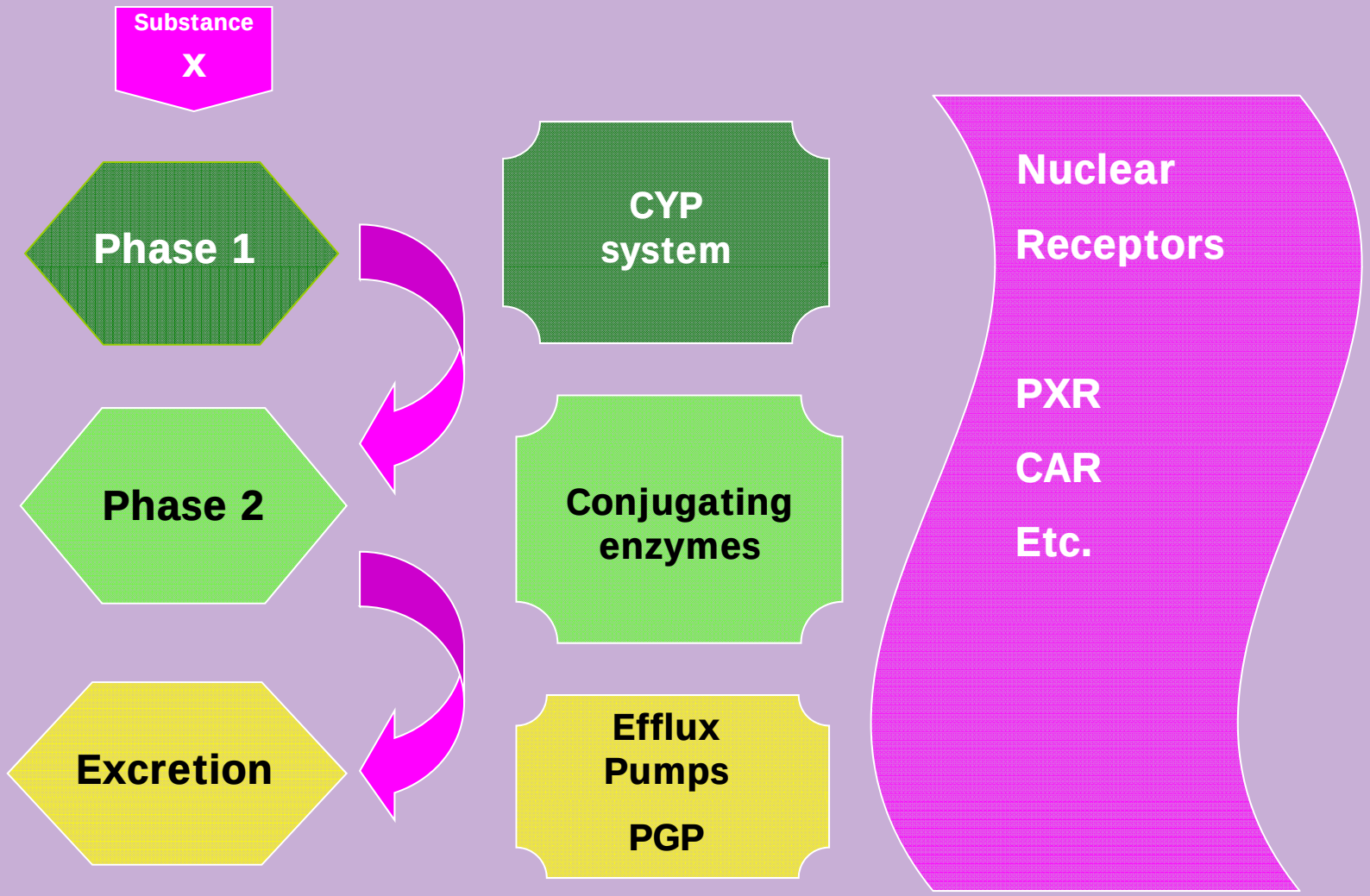

Lack of interaction
risks with Echinacea

Herb Drug Interactions

- Herb-Drug Interactions – BfArM (Germany) Draft Document (2004) on the **Evaluation of potential pharmacokinetic drug interactions with herbal medicines** :
  "If the medicinal product is commonly used in combination with other medicinal products, information is to be submitted concerning concomitant administration studies performed to detect possible alterations of pharmacological action. Pharmacokinetic interactions between the active substance and other medicinal products or substances are to be investigated".

  On this basis, studies or bibliographic information on interactions are automatically required for medicinal products that are, for example, usually taken by elderly, multi-morbid patients who frequently take other medicinal products.

Xenobiotics – the Defence System



HMP-drug interactions

- Cytochrome P450 enzyme system (CYP)
- CYP1A2, 2C9,2C19,2D6,3A4 and others – Echinacea liquid preparations were evaluated in an in vitro system and the effects on CYP 3A4 were compared for ten preparations
- Other targets – conjugation and excretion

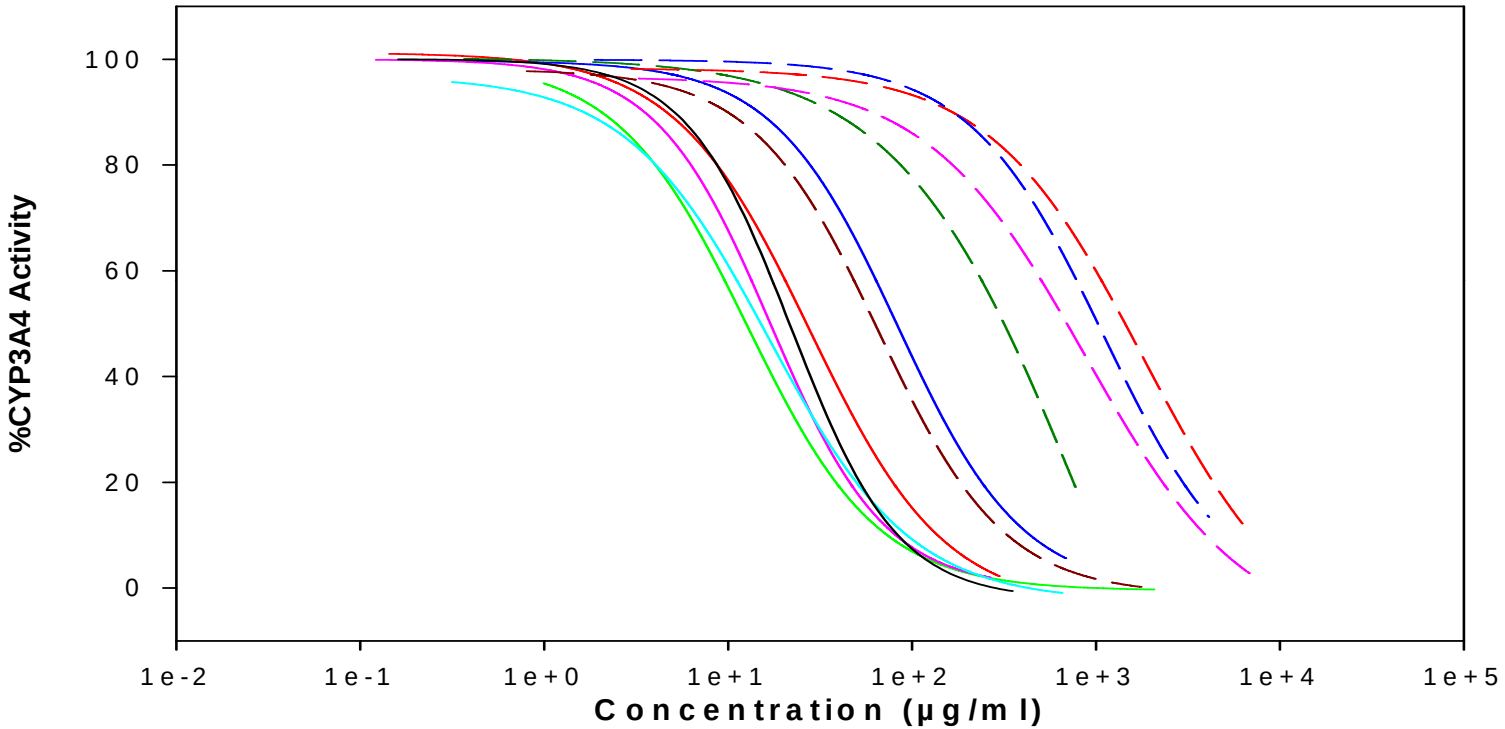
Aims: Assess the interactions of commercially available Echinacea liquid preparations on the CYP system

Echinacea

Extract name/ manufacturer	Ethanol (%)	Echinacea species (tincture/fresh plant pressed juice)
Madaus	22	*E. purpurea* (juice)
Ratiopharm	22	*E. purpurea* (juice)
Schonenberger	0	*E. purpurea* (juice)
Hervert Purpforte	22	*E. purpurea* (juice)
Viridian	22	*E. purpurea* (tincture)
Salus	50	*E. pallida radix* (juice)
Echinaforce Bn: 018451 Bn: 015232	 65 65	*E. purpurea (herb and root)* (tincture)
Holland and Barrett	65	*E. purpurea* (tincture)
Healthaid	45	*E. angustifolia* (tincture)
Echinagold	50	*E. purpurea* (tincture)

Echinaceae and Inhibition of CYP3A4

Modarai et al. (2007) J. Pharm Pharmacol.59: 567-573



96-well plate
fluorescence based assay
Single CYP isoforms

Metabolomics

- …..the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind" - specifically, the study of their small-molecule metabolite profiles (1). *The metabolome represents the collection of all metabolites in a biological organism, which are the end products of its gene expression.*

→ Ideal for studying extracts!

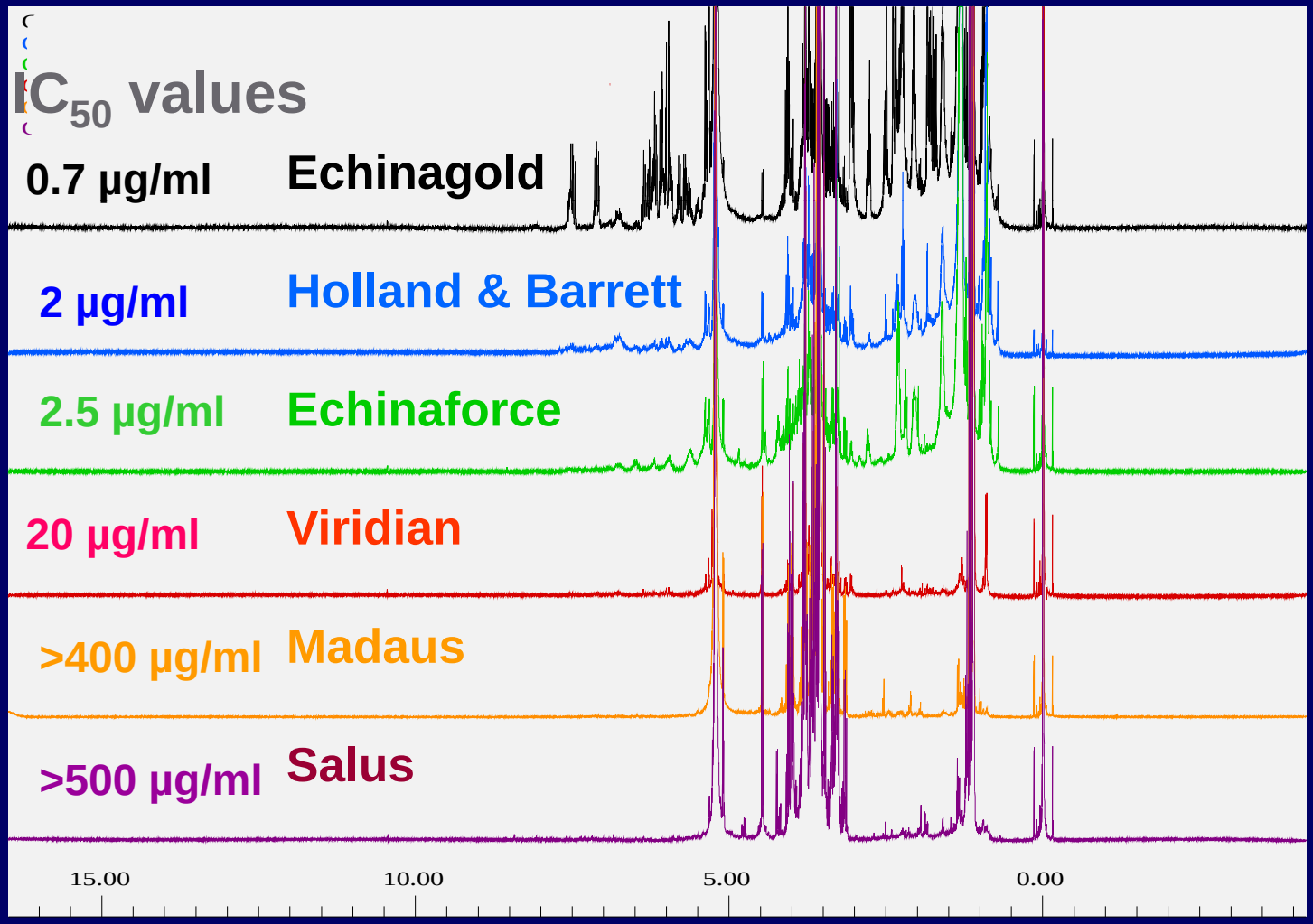
(1) B. Daviss, "Growing pains for metabolomics," *The Scientist*, 19[8]:25-28, April 25, 2005

Metabolomic of Echincea preparations

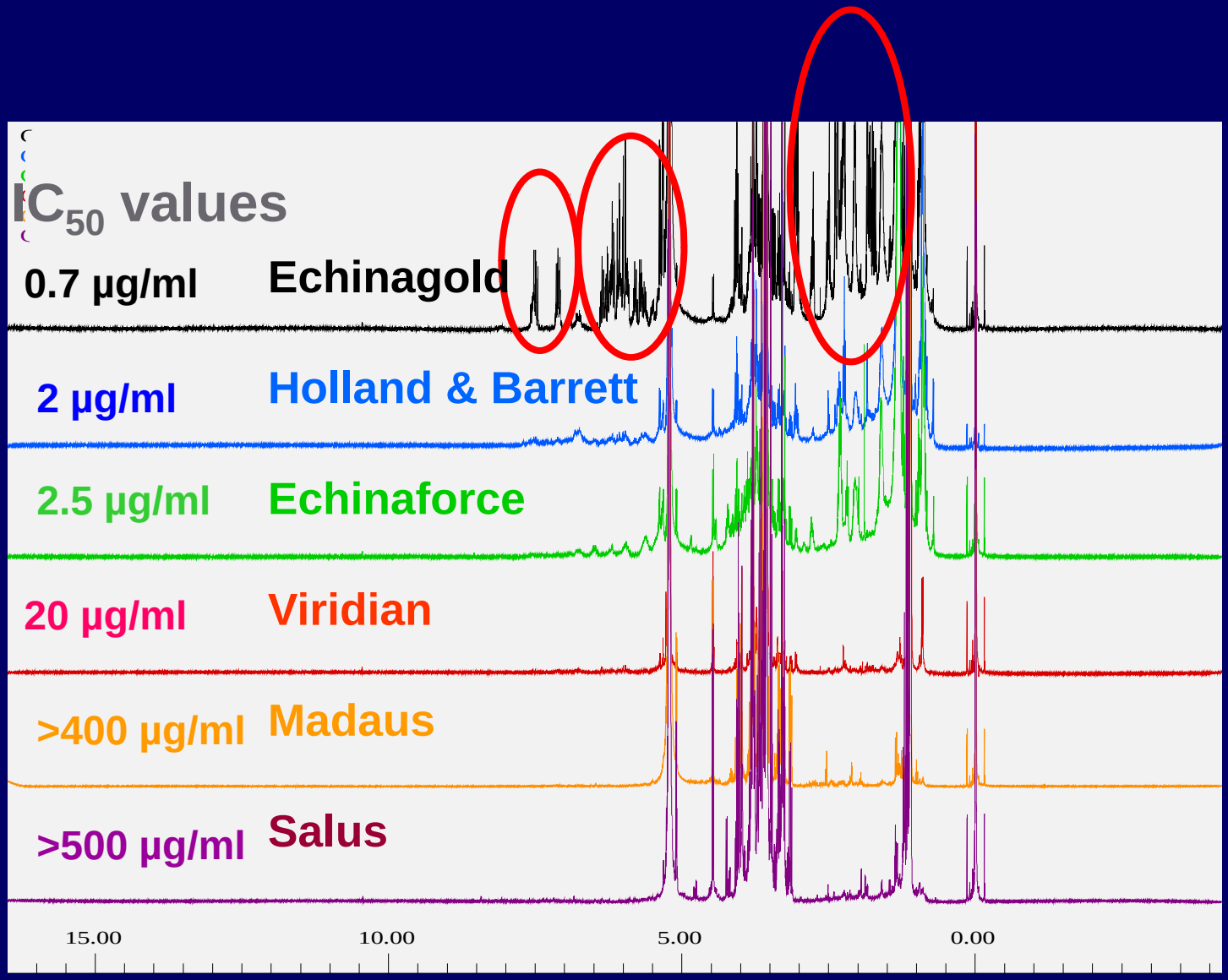
Aims:

- Identify differences between the Echinacea liquid preparations
- Determine whether these differences can be related to their inhibitory activity on CYP3A4.
- Identify compounds responsible for CYP3A4 inhibition.

Results -^{1}H Ethanol fractions



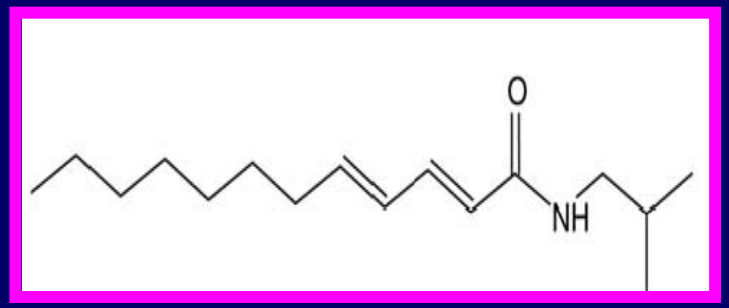
Results -^{1}H Ethanol fractions



The safety of Echinacea:

- A range of compounds co-responsible were identified
- Overall, alkylamides contribute to the inhibition CYP1A2, 2C19, 2D6 & 3A4?

Dodeca 2E, 4E,8Z,10E/Z tetranoic acid isobutylamide (mw = 247) (TAI)



Dodeca 2E, 4E-dienoic acid isobutylamide (mw = 251) (DAI)

- The extract is the active 'constituent'

Effective or not

- Mounting evidence points to good levels of evidence for some products, which, however, are below the level generally expected by regulatory agencies in the UK
  Other examples of of HMPs with well documented effectiveness for certain indications include *Ginkgo biloba*, *Hypericum perforatum*, *Andrographis paniculata*, *Harpagophytum procumbens*, to name just a few

- Key is the quality of the products as well as their safety!
  ⇒ Phytochemical Analysis and Quality Control
  ⇒ Lack of interaction risks and other safety parameters have to be evaluated
  - …
- The variability of the products' composition makes an assessment of an HMP's 'effectiveness much more challenging.

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