Rational and irrational phytotherapy
Modern medicine - rational phytotherapy - folk medicine

- Medicinal plants in the past and in modern medicine
- Unified medicine: reality or fiction?
  - Standards, guidelines
  - Safe and effective
  - Efficient (financial aspect)
- Does phytotherapy meet these criteria?
  - In principle
  - In practice
  - And what we experience…
Medicinal systems applying herbal remedies

Western medicine

Phytotherapy

Ayurvedic medicine

TCM

Anthroposophy

Traditional medicine of Africa, South America, and Australia

Homeopathy

Aromatherapy

Bach flower therapy
Why are herbal remedies different?

1. Origin

- Empirical knowledge
- Followed by modern experiments and trials (efficacy, safety)
  - Some exceptions (paclitaxel, galanthamine)
  - Difficulties:
    - Raw material, processing
    - Traditional indications hard to interpret

- Synthetics
  - Time, expenses, risk
Why are herbal remedies different?

1. Composition

- One or several herbal components
- Chemically multicomponent
- The active principle
  - Known
  - Partly known
  - Not known
- Hard to warrant unvarying quality, safety, efficacy
Plant constituent - active agent - marker compound

- **Plant constituent**
  - Number: unknown
  - Influence on effect

- **Marker compound**
  - Not necessarily active
  - One ore several („fingerprint”)

- **Active agent**
  - Chemical entity, responsible for the effects of the herbal drug (quantitatively and qualitatively)
  - One
  - Or several similar (pl. *Silybum*) or different (pl. *Chamomilla, Hypericum*) compounds
Content of camptothecin (%) from bark extracts of *N. nimmoniana* collected from various localities during different seasons

Traditional medicinal plant -
traditional herbal remedy

- Most widespread products: tisanes (medicinal teas)
  - Home remedies: chamomile, rosehip etc.

- Further home-made extracts: prepared with spirits
  - Melissengeist in Austria/Germany
  - Unicum in Hungary

- Home-made ointments
  - Calendula (marigold) + fat = antiphlogistic ointment
Traditional medicinal plant - herbal extract-containing medicine

- Most typical in Europe
- Advantages
  - Price
  - Reproduction of traditional application
  - Advantages of complex mixtures
    - Synergism
- Ca. 300 products in Hungary
What is complexity in reality?

← Multicomponent herbal extract with anti-allergic effect
What is complexity in reality?

Separation of components with chromatographic methods
What is complexity in reality?
Traditional medicinal plant-concentrated active components

- **Purpose of concentration**
  - Decrease the dose of the extract
  - Get rid of inert (or unfavourable) components
  - Eg. Milk thistle (*Silybum marianum*)

![Chemical structures of silybin, isosilybin, silychristin, and silydianin]

**silymarin**
Pure (herbal) components as medicines

- One ore more compounds
  - Of natural origin
  - Semisynthetic
  - Synthetic
- Substance = pharmacon (effect, risk)
- Constant quality
- Reproducible efficacy - easy task

- Herb-derived components
  - Original: galanthamine
  - Semisynthetic derivatives (butyl-scopolamine)
Traditional medicinal plant - active components

- Advantage:
  - Easy to dose
  - One active component - specific effect
- Foxglove - digoxin
Traditional medicinal plant-lead molecule

- Lead molecule: more effective molecule with similar structure (with less side effects)
Medicine from a toxic plant

- Yew tree and taxol® (paclitaxel)
  - National Cancer Institute screening programme for anticancer compounds - 2000 herbal extracts
  - Most active: yew tree bark
  - Active component: taxol
  - Yield: 1 mg from 24 kg bark
  - Industrial production: from a precursor in the leaf
  - Nowadays: one of the most important drugs in breast cancer
Drug - from a weed

- *Euphorbia peplus* - ingenol-mebutate - Picato®
  - Keratosis (precancerous state)
Quality

- Primary goal

- Propagation, collection

- Processing

- Standardization (active component), quantification (marker compound)

- Quality control

- Highly depends from the product category
Why are herbal remedies different?

3. Efficacy, safety

- Same methods as in the case of synthetic drugs
  - *In vitro*
  - *In vivo* animal experiments
  - Clinical studies
  - Meta-analyses

- Usually less health risk, side effects
  - Natural ≠ safe
  - New side effects (processing, concentration)
  - Interactions of plant substances
Efficacy: are there clinical trials?

- Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2014
- There are 268 results from 763865 records for your search on 'hypericum in Title, Abstract, Keywords in Trials'

Authors' conclusions

- The available evidence suggests that the hypericum extracts tested in the included trials a) are superior to placebo in patients with major depression; b) are similarly effective as standard antidepressants; c) and have fewer side effects than standard antidepressants. The association of country of origin and precision with effects sizes complicates the interpretation.
Safety and adverse effect: plant, product or human?

Herbal does not mean innocuous: Ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife® products

Alain M. Schoepfer¹, Antoinette Engel², Karin Fattinger³, Urs A. Marbet⁴, Dominique Criblez⁵, Juerg Reichen⁶,*, Arthur Zimmermann⁷, Carl M. Oneta⁸
Side effects

- Severity, frequency
- Traditional application is not the evidence
  - Carcinogenic, hepatotoxic plants (pirrolizidine alkaloids)
- Side effect $\neq$ abuse
- Side effect $\neq$ toxic effect
Interactions: possible, probable, confirmed

- Based on misconceptions
- Possible theoretically
- In vitro confirmed
- Probable even in human organism
- Confirmed

Rational therapeutic decision
- Assessment of the relevance of interaction
- Benefit-risk analysis
Type of interactions

- **Pharmacodynamic**
  - agonism, antagonism
    - On receptor level
  - Easy to predict and handle

- **Pharmacokinetic**
  - absorption
    - p-Gp, binding of pharmacons
  - Metabolism
    - Induction or inhibition of liver enzymes
  - Hard to predict
Why are herbal remedies different?

4. Product categories

- Medicine
- Trad. herbal medicinal product
- Homeopathic medicine
- Medical device
- Food supplement (food!)
- Illegal products
Medicine (allopathic)

- Efficacy and safety confirmed in clinical trials
  - OGYI or EMA authorization

- Established indication

- Controlled quality
  - Raw material, production, end product

- Controlled distribution
Traditional herbal medicinal products

- OTC
- At least 30 years tradition, at least 15 years in the EU
- Per os, externally or for inhalation

Cons:
- It is not necessary to confirm efficacy
- It is not possible to introduce new indications, new plants
- Innovation is killed in this area
Homeopathic medicines: herbal, but not phytotherapy

- **Critics are right, but**
  - The efficacy of some products has been investigated in clinical trials
  - Not all the products are free from active component

- **Supporters are right, but**
  - Efficacy is not confirmed convincingly
  - Products are not necessarily free from side effects
  - Some products contain measurable herbal components

- **80-90% of the preparations is based on plant extracts**
A special case: chasteberry

- Vitex agnus-castus
  - Premenstrual syndrome
  - Efficacy clinically confirmed
  - Mode of action only partly elucidated
    - $D_2$-receptor agonism
    - $\mu$- and $\delta$-opioid receptors
  - Dose: 40 mg dry fruit(!)
  - Clinical trials: both allopathic and homeopathic medicines

- European market
  - AgNUcaston (allopathic)
  - Mastodynon (homeopathic)
Chemical analysis of *Vitex-agnus castus* products

**Mastodynon**

*Vitex agnus-castus* mother tincture 324,0 mg  
*Caulophyllum thalictroides* D4 162,0 mg  
*Cyclamen europaeum* D4 162,0 mg  
*Strychnos ignatii* D6 162,0 mg  
*Iris versicolor* D2 324,0 mg  
*Lilium lancifolium* D3 162,0 mg

**Agnucaston**

*Vitex agnus-castus* fruit extract 3,2-4,8 mg  
(DER 8,3- 12,51:1; extracting solvent 70 (V/V%) ethanol)

Agnuside: 25,19 µg vs. 100,82 µg  
Casticin: 47,03 µg vs. 42,95 µg
Food supplements

- Definition
- No therapeutic indication
- Composition
  - Vitamins, trace elements
  - Other compounds with physiologic activity
  - The number of herbal products increasing
- No registration, only notification
  - No guarantee for quality
- Health claims
Adulterated products

- Aphrodisiacs, slimming agents
- Efficacy cannot be explained by the presence of plants
- Adulterants
  - Medicines
  - Withdrawn medicines
  - Derivatives
- In some cases overdosed
Abuse: grapefruit seed extract for medicinal purposes

- **What is it used for?**
  - Common cold, prevention

- **What is it good for?**
  - In EBM: for nothing
    - In vitro antibiotic effect
    - Nigerian case study

- **Grapefruit seed or peel? Or something else?**

- **Analysis of 6 product**
  - 2 : peel (furocoumarins!)
  - 1 : ?
  - 1 : benzalkonium derivative
  - 2 : seed
Conclusions

- Plant ≠ product
  - Efficacy, safety
  - Dose, quality
- Product category
- Modern phytotherapy is the part of modern medicine (EBM)
  - Application of plants is not necessarily phytotherapy