## NATURAL MEDICINES

Medicines from plants

- Fresh plants or their parts (Myrtilli fructus recens)
- Dried plants or their parts = drugs
- Isolates from fresh plants and drugs (chemically defined compounds)

Medicines from animals (mostly isolates)

Medicines from marine organisms (Plexaura homomala – prostaglandins)

Medicines obtained by biotechnology (enzymes, hormones, cytokines, monoclonal antibodies, inhibitors of tyrosinkinase…)

## PHYTOPHARMACEUTICALS

„Pharmaceuticals exclusively or predominantly composed from plants, plant parts and content compounds from plants, if they are not listed in homeopathic or anthroposophic groups“. Rudolf Hänsel

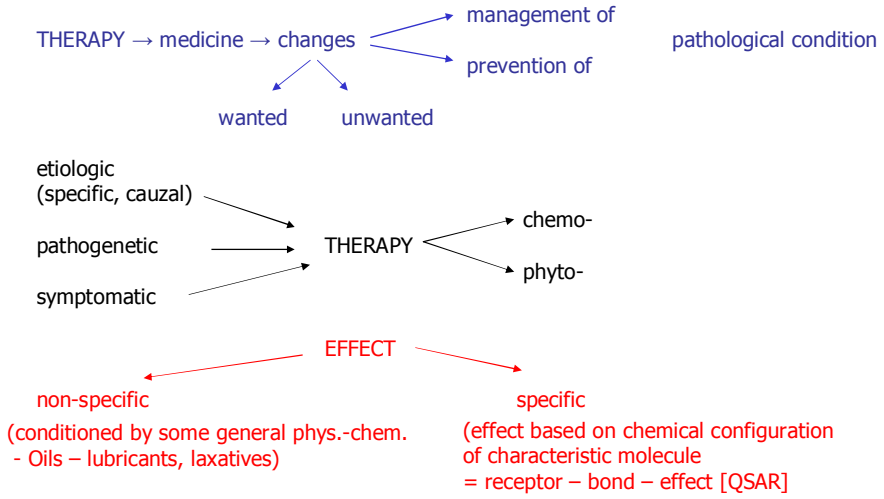
- Chemically uniform compounds (atropine, VLB, taxol …)
- Chemically nonuniform (drugs, essential oils, resins, oils …)

Key importance for quality has a technological process for manufacturing

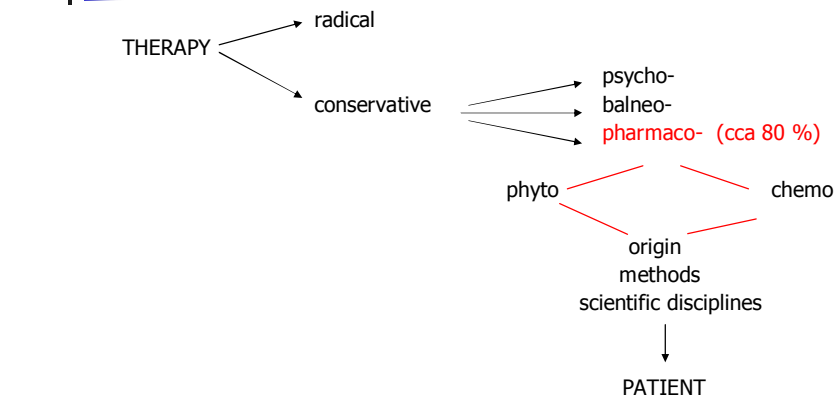
Valerianae radix water = hydrophilic compounds without sedative effect
chloroform = sedative valepotriates

Pharmaceutical and medical research intensively make a point of identification of main active content compound and its quantification in final medicinal formulation.

## THERAPY – EFFECT




## THERAPY



## PHYTOPHARMACEUTICALS

No law-defined definition for phytopharmacuticals.

Germany:

- Medicines exclusively or predominantly composed from plants, palt parts, plant content compounds (generaly drugs with non-organised structure as it is resine or essential oil) if these are not listed in homeopatic anad anthroposophic groups of compounds.
- Medicines of plant origin including plant isolates (chemical individua) with defined structure.

## PHYTOPHARMACEUTICALS, PHYTOTHERAPY

EMA (EMEA) – European Medicines Agency
FDA - Food and Drug Administration

Phytopharmaceuticals – exclusively or predominantly composed from plants, plant parts, plant content compounds

1. Effect proved
2. Proof of effect missing

WHO – phytopharmaceuticals are not belonging to essential drugs
¨range of products in individual countries different

PHYTOTHERAPY – part of therapy overall. Phytodiagnostic does not exist. Phytotherapy is chemotherapy which uses compounds biosynthesized by plants. Phytopharmaceuticals possess wide therapeutic range – indication according to the „officinal" medicine.

## NATURAL MEDICINES AND MATERIAL FOR THEIR PREPARATION

- MEDICINAL PLANT – such as plant, which is used whole or its parts in different forms directly for treatment of diseases, or as a material for medicaments preparation. Fresh medicinal plants, their parts or products are used for therapy exceptionally.

- DRUG – dried, alternatively conserved by different way, modified or un-modified plant (animal), or its organ or part, alternatively its product, which serves for manufacturing medicaments or technically important compounds, or directly used for therapeutical, technical, or other purposes.

- PARTES USUALES – collected and used parts of plants, in which the biologically active compound is in the highest amount.

## NOMENCLATURE OF DRUGS

Nomenclature of drugs is usually binomic (similarly to the nomenclature of botany)

- First word represents the genus, to which the mother plant belongs (Malvae folium, Strychni semen, Stramonii folium).
  - incial letter big, genitive
- Second word represents the name of plant organ (Betulae folium, Ononidis radix)
  - inicial letter small, singular
- Mother plant precisely named in drug definition (*Malva silvestris* L., *Malva neglecta* WALLR.)
- Names of essential oils, oils and starches are derived in cited way: Anisi etheroleum – Anise essential oil; Olivae oleum – olive oil; Solani amylum – potatoe starch
- Exceptions:
  Name is created from one word only: Lupulinum, Lycopodium
  Traditional name, which is not in correspondance with name of plant: Liquiritiae radix – Lycorice root
- Previously used nomenclature is still in use for balms: Balsamum peruvianum – Balsam of Peru

# DRUG DIVISION

**ACCORDING TO THE ORIGIN**

- plant (vegetabile)
- animal

**ACCODING TO THE STRUCTURE**

- Drugs with organized structure
  majority of plant drugs and partly animal drugs, showing cellular constitution – from one cell to set of tissues in constant order: Lupulinum, Lichen islandicus, Belladonnae radix

- Amorphous drugs
  different plant and animal drugs, without cellular organization. Are derived as:
  physiologic products: Resina mastix,
  pathologic products: Balsamum peruvianum
  products obtained from raw material by destillation (Menthae etheroleum), melting (Adeps suillus), stamping (Olivae oleum), extraction (Chrysarobinum), thickening (Liquiritiae succus)

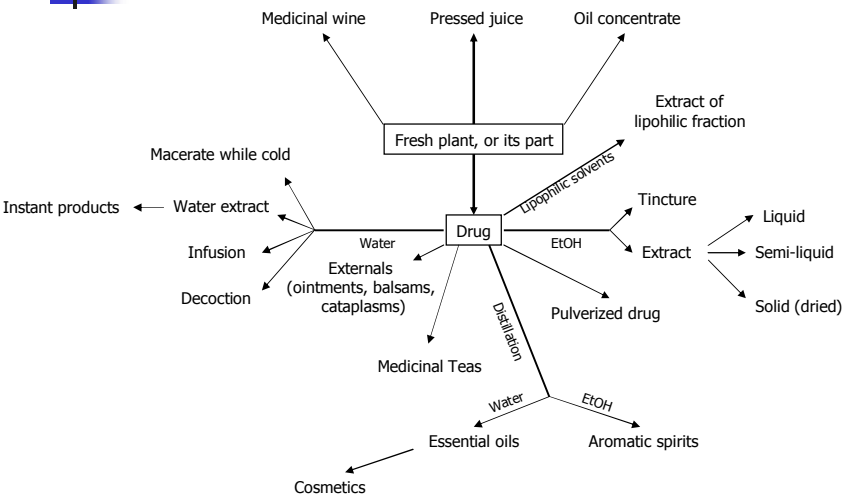
**ACCORDING TO THE USAGE**

- Drugs therapeutical (used for medicaments preparation or for isolation of effective compounds)
- Drugs utilitarian (manufacturing of colors, tannery, food industry, cosmetics)

# CONTENT COMPOUNDS

- Compounds effective, active principles, main compounds (pharmacodynamics)
- Co-effectors, affecting main compounds (pharmacokinetics)
- Dietetics (sugars, fats, proteins)
- Adjuvants (starches, gums)
- Accompanying compounds (lignine, pigments, Ca oxalate)
- Balast compounds

## Treatment Of Fresh Plants, Their Parts And Drugs




## PREPARATION FROM FRESH PLANTS OR THEIR ORGANS

### PLANT JUICES

- Maceration in water, pressing, pasteurization, uperization
- Containing hydrophilic compounds (sugars, vitamins, amino acids, organic acids…)
- Do not contain strongly effective compounds
- Freely distributed, self-treatment

### HOMEOPATIC TICKTURES

- Maceration in 90% EtOH, pressing ⟶ URTINCTURE (allopatic)
- Preparation according to HAB and Ph.Eur.
  for example Nux vomica Φ = D1 equivalent Strychni tinctura
- dilution, potentiation, dynamisation, infinitesimal doses

## WATER EXTRACTS

Drug(s) : water = 1:3; 1:5; 1:10

Boiling → Decoction *Decoctum* (ligna, radices, semina, fructi)
30 min. at 90 $^0$C (water bath)

- drug + cold water, slow increase of temperature, boil 10 – 15 min, next 15 min. extraction

Infusion → *Infusum* (extraction at temperature decreasing from boiling point to room temperature)

Maceration → *Maceratum* (maceration (soaking) of drug in liquid to extract soluble parts and to get extract (macerate)

Drugs containing mucilage – pass with defined amount of water at temp. cca 20 $^0$C, 30 min. maceration, decantation

## INSTANT TEAS

*Extracta aquosa sicca* = granulations (vacuum, lyophilisation)

*Extracta aquosa spissa seu fluida* = paste

Additional compounds – lipophilic compounds (essential oil)

Most often preparations for treatment of stomach disorders

## SPECIES – TEAS

1. *Remedium basis*
2. *Remedium adjuvans* → maximum 4 to 6 drugs
3. *Remedium corrigens*

Effect of medicinal tea is ensured by qualitative parameters of drugs (effective compounds quantified) and keeping the recommended conditions for preparation and usage.

Drugs for tea mixtures

1. Prescription only
2. Without prescription
3. Marketed out of pharmacy (without indication)
4. Cannot be used

1-4: Qualitative criterions according to ČL 2002; ON

Back to nature:
Plant medicines are not almighty and are not harmless!!

## ALCOHOL EXTRACTS

ČL 2002 – Suppl. 2003

EXTRACTS – extract from drug (macerate, percolate) with more or less removed extraction medium.

Extracts can be divided:

- **Liquid** (liquid extracts and tinctures) - drug : EtOH = 1:5; 1:10; *Extractum fluidum* (extractive compounds from 1 portion of drug are contained in 1, maximally 2 portions of extract.
- **Semi-liquid** (thick extracts) *Extractum spissum* (original, non-modified extracts, containing 15 – 25 % residual solvents.
- **Solid** (dried extracts) - *Extractum siccum* (with max. content of 5 % of residual solvents).

## TYPES OF EXTRACTS

- **Standardized extracts** – are modified to contain required of compounds with known therapeutic potential; standardization is carried out using inert compounds or by mixing different extracts (different batch).
- **Quantified extracts** – corrected to required content of desired compounds.
- **Other extracts** – are defined especially by manufacturing procedure (characteristics of plant or animal drug used for extraction, type of solvent and extraction conditioning) and its properties.

## THERAPEUTIC EFFECT IS AFFECTED BY:

- Type of drug and by content of effective compounds
- Manufacturing of drug into final preparation
- Changes of effective compounds in GIT
- Specifity of effective compounds
- Kinetics of effective compounds
- Dosage and tolerance
- Accumulation of effective compounds in organism
- Synergism or antagonism
- Status of patient

## FOLK MEDICINE, SELF-TREATMENT

Risks of ignorance

- Impossibility of correct diagnose?
- Choice of medicament?
- Dosage?
- Period of therapy?

- Knowledge of practical experience

## REQUIREMENTS ON PHYTOPHARMACEUTICALS REGISTRATION

Development in area of pharmaceuticals is very intensive.

Research → materials → pharm. industry → medicaments → authorized use

→ deceptions

→ tragedies (thalidomid)
Contergan - terathogenic

REGISTRATION IN CZECH REPUBLIC – STATE INSTITUTE FOR DRUG CONTROL

## REQUEST FOR REGISTRATION AS LARGE SCALE MANUFACTURED DRUG

1. BASIC DATA
Name of preparation
Drug form
Name and address of manufacturer, applicant
Company responsible for marketing
Datum, signature

2. BASIC CHARACTERISTICS
Composition (Czech, Latin, INN
of effective compounds and adjuvants)
Pharmacologic data (indication,
contraindication, dosage, exceptional data
– pregnancy, breast-feeding…)
Pharmaceutical data (description of preparation,
type of package, size of package, expiration,
storage)

3. PHARMACEUTIC-TECHNOLOGIC DOCUMENTS
quantitative composition of medicament
manufacturing description
drug specification according to Eur. Ph. Or branch norm
determination of pesticide residues

4. CONTROL OF FINAL PREPARATION
Assays and procedures for phys.-chem. methods
according to Eur. Ph.
Microbial assays
Biological assay

## REQUEST FOR REGISTRATION AS LARGE SCALE MANUFACTURED DRUG

5. STABILITY STUDIES
Description
Possible products of decomposition
Results according to different conditions of keeping and storage

6. TOXIKOLOGIC AND PHARMACOLOGIC DOCKUMENTATION

7. CLINICAL DOCUMENTATION

8. CERTIFICATION ABOUT REGISTRATION

9. CERTIFICATION OF MANUFACTURER ABOUT GMP

10. MISCELANEOUS
Original package including leaflet
Samples (including referential standards) for 3 full analyses

## CLINICAL ASSAYS OF PHYTOPHARMACEUTICALS

All rules for clinical pharmacology are valid:

1. Definition of disease and symptoms
2. The matter of clinical assay, the time limits
3. To know the exact composition of phytopharmaceutic, chemical structure of compound, presumed therapeutic effect
4. To determine if the test will be individual, with placebo, or with known therapeutic
6. To determine daily doses, time of administration with regard to possible effect of feeding
7. Number and selection of patients (ambulant – hospitalized / acute – chronic
8. Type of study (opened, simply or double blindened)
9. Definitions of criterions for effect evaluation (value of blood pressure, level of serum lipoproteins….)
10. The way of analysis of acquired results, definition of criterions of effectiveness
11. Exclusion of extra pharmacological effects
12. To monitor the time of start and duration of effect
13. Topic preparations – dermatotropic activity

## CLINICAL ASSAYS

- For all newly used drugs
- For plant species till present not used for medicals preparation
- Drug with unknown content compounds
- Known drug till present does not used as medicinal
- New indications of known phytopharmaceuticals
- Foreign drugs non-registered in Czech Republic

## APPROVAL OF NEW MEDICINES

New drug is important factor, which can affect improvment of health status and quality of life, and possibly to safe the life. Therefore the attention is laid also on duration of approval process to imply new drug on market. This is defined as overall number of calendar days from application to issue the approval. From the monitoring of duration of approval process for 70 new chemical entities, which were under approval process 1995-1999 can be deduced: median of duration of approval process in Australia (43 new drugs) was 25,3 of month,

in Canada (70) 29,4 of months, in Sweden (48) 27,3 months, Great Britain (54) 11,7 of months and in USA (57 ne drugs) 25,5 of months.

Duration of approval process is not significantly affected by therapeutic classification, number of required and additional information or datum of application.

Pieterson E.A.: J Clin Pharmacol, 32, 2002 s. 889