# PHYTOTHERAPHY

## Chapter 2

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# Central nervous system

- **Anxiety**, a depressed mood and sleeping disorders may be part of the normal life, but **if these symptoms become permanent** and affect the quality of life, psychotherapy and/or pharmacotherapy is indispensable.
- Some of these diseases (e.g. depression) were first described and defined in the 20$^{th}$ century.

# Central nervous system

- Synthetic antidepressants, antianxiety drugs and sleeping pills have some **undesirable effects** and **side-effects**.
- The most important undesirable effects of sleeping pills and antianxiety drugs are **dependence** and **increasing tolerance.**
- Antidepressants may have a wide range of side-effects, including obesity and a deterioration in the quality of life.

# Central nervous system

- **Herbal remedies** usually have fewer undesirable effects, although their efficacy is inferior to that of synthetics. However, in well-defined stages of the above-mentioned states, phytotherapeutics may be harmless equal alternatives to synthetic medicines and in efficacy.

# Central nervous system

## «*Anxiety, sleeping disorders*»

- The symptoms of anxiety include **uneasiness**, **nervous tension** and **apprehension**, and a **sleeping disorder** may also occur.
- Patients may additionally experience physical symptoms, e.g. **gastrointestinal disturbances**, **headache** or **excessive perspiration**.
- If the symptoms become **exaggerated**, **treatment is needed**

# Central nervous system
## «*Anxiety, sleeping disorders*»

- **Insomnia** may also be a consequence of normal life events, but the most common causes are related to an inadequate lifestyle (the **lack of physical activity**, **obesity**, or **alcohol** or **caffeine** consumption) or psychiatric diseases.
- The primary goal is the elimination of identified causes of insomnia (in cases of **secondary insomnia**), though in some cases, and especially in **primary insomnia**, pharmacotherapy (including phytotherapy) is inevitable.

# Central nervous system
## «*Anxiety, sleeping disorders*»

- Medicines used in the treatment of **anxiety and insomnia** usually act by enhancing the effects of **GABA** (gamma-aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system.
- The mechanisms of action involve **direct action on the GABA** receptor, **increasing the affinity** of the receptor for GABA or **increasing the concentration** of GABA in the synaptic cleft by decreasing its breakdown **or increasing its synthesis**.

# Central nervous system

## «*Anxiety, sleeping disorders*»

- Similarly to synthetic drugs, **herbal medicines** act through the above-mentioned mechanisms.
- However the mechanism of action in certain plants **has not been fully elucidated** so far.

# Central nervous system

## «*Anxiety, sleeping disorders*»

- Synthetic medicines are effective in more severe cases, while herbal remedies are effective in mild or moderate insomnia or anxiety.
- Herbal hypnotics are more effective if applied for a long time, in contrast with the straight-acting synthetics.

# Valerian
## «*Valeriana officinalis*»

**Used part:** standardized extract of root part

**Used type:** coated tablets, capsules, decoction, tenture

**Drog properties:** very odorous

**Combinations:** hops (*Humulus lupulus*) or lemon balm (*Melissa officinalis*)

# Valerian

## «*Valeriana officinalis*»

**Chemical composition and mechanism of action:**

**Essential oil .....** sesquiterpene «**valerenic acid**»

**Valerenic acid** allosterically modulates GABA-A receptors and induces anxiolytic activity.

The **monoterpene valepotriates** may have an important role in the effect.

**Valepotriates are UNSTABLE**

# Valerian

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**Valepotriates are UNSTABLE**

# Valerian
## «*Valeriana officinalis*»

**Efficacy and indications:**

- Valerian root improved sleep rather than exerting a general sedating effect (clinically).
- In a comparative study, valerian was as effective as oxazepam for the treatment of insomnia.

# Valerian
## «*Valeriana officinalis*»

**Efficacy and indications:**

The **EMA** has published monographs relating to the well-established and the traditional uses of valerian root (40-70% ethanol extract). It is used for;

- ✓ for the relief of **mild nervous tension and sleep disorders**.
- ✓ for the relief of **mild symptoms of mental stress and to aid sleep.**

# Valerian
## «*Valeriana officinalis*»

**Doses:**

- ✓ In well-established use a **single dose is equivalent to 2 to 3 g of the herbal substance**.
- ✓ In the treatment of anxiety, the **maximal dose is 4 times daily**.
- ✓ It can be administered to adolescents over 12 years of age, adults and the elderly.

Valerian root **is not appropriate for the acute treatment of mild nervous tension or sleep disorders**. To achieve an optimal treatment effect, administration for **2-4 weeks** is recommended.

# Valerian
# «*Valeriana officinalis*»

## Side effects, interactions & contraindications:

With the exceptions of hypersensitivity, lactation and pregnancy, **no contraindications are known**.

**Gastrointestinal symptoms** (e.g. nausea or abdominal cramps) may occur.

Clinically relevant **drug interactions have not been observed**.

Valerian **may increase the effect of sedatives**.

In contrast with benzodiazepines, valerian root does not reduce the level of vigilance during the morning after it has been taken to relieve insomnia.

An overdosage results in benign and reversible symptoms.

# Hop
## «*Humulus lupulus*»

**Used part:** dried female inflorescence

**Used type:** extract in combination products

**Drog properties:** bitter taste

**Combinations:** valerian (*Valeriana officinalis*)

# Hop

## «*Humulus lupulus*»

## Chemical composition and mechanism of action:

**Prenylated phloroglucinols .....** alpha-acids or «**humulones**» and beta-acids or «**lupulones**»

**Essential oils**

**Flavonoids ....** Xanthohumol and its derivatives

contains **isovaleric acid** in low concentration

# Hop
## «*Humulus lupulus*»

**Chemical composition and mechanism of action:**

- The mode of action of this plant **is not fully understood**.
- **Isovaleric acid** may contribute to the action, but **2-methyl-3-buten-2-ol** is of greater importance.
- The sedative effect of hop extracts has been confirmed in multiple animal experiments.
- A hop extract may also have an **agonistic effect on melatonin receptors.**

# Hop
## «*Humulus lupulus*»

**Chemical composition and mechanism of action:**

- The **spasmolytic effect** of the hop has been demonstrated preclinically.
- Hop also have an **estrogenic activity**.
- The **agonist effect on estrogen receptors** has been confirmed and the most active component has been identified as **8-prenylnaringenin**.

(**Xanthohumol derivatives** can be transformed to **8-prenylnaringenin** in the liver)

# Hop
## «*Humulus lupulus*»

## Efficacy and indications:

- **No clinical studies** are available in which the hop featured as single component.
- According to the **EMA**, hops can be used as a traditional herbal medicinal product in the form of **tea, dry herbal substance, liquid or dry extracts** (prepared with a mixture of water and ethanol or methanol). The approved indication is
  - ✓ **relief of mild symptoms of mental stress and to aid sleep.**

# Hop
## «*Humulus lupulus*»

**Side-effects, interactions & contraindications:**

- The possibility of the use during pregnancy and lactation and in children under 12 years of age has not been established due to the lack of adequate data.
- **No contraindications** (except for hypersensitivity) and special side-effects are known.

# Lavender

## «*Lavandula angustifolia*»

**Used part:** flowers and essential oil

**Used type:** extract in combination products

**Drog properties:** lavender taste and smell

# Lavender
## «*Lavandula angustifolia*»

## Chemical composition and mechanism of action:

**Essential oil .....** «**linalool**» and «**linalyl acetate**»

- lavender extracts and oil proved to exert a **spasmolytic effect**.
- other application in the treatment of **gastrointestinal symptoms**.
- The **antimicrobial effect** of the oil has been demonstrated against several strains.

# Lavender

## «*Lavandula angustifolia*»

### Chemical composition and mechanism of action:

- Sedative (a prolongation of the **sleeping time** and a **decrease in locomotor activity**) effects of various extracts and oils has been demonstrated in animals.
- **Linalool derivatives** reach a pharmacologically active concentration in the blood plasma even **after inhalation**.
- These compounds act by **increasing the effect of GABA**.

# Lavender

## «*Lavandula angustifolia*»

## Efficacy and indications:

- The **anxiolytic activity** of lavender oil has been studied in certain conditions (anxiety and depression).
- **Lavender oil** has been administered orally or as aromatherapy. Lavender oil positively influences anxiety and stress-related restlessness.

# Lavender
## «*Lavandula angustifolia*»

## Efficacy and indications:

- Lavender **essential oil** may be marketed as traditional herbal medicinal products for;
  - ✓ relief of **mild symptoms of mental stress and exhaustion and to aid sleep**.
- Its **oral daily dose is 20-80 mg**, though it can also be applied as a bath additive (with a proposed dose of 1-3 g).

# Lavender
## «*Lavandula angustifolia*»

### Side-effects, interactions & contraindications:

- ✓ Its use in children under 12 years of age is not recommended.
- ✓ Safety during pregnancy and lactation has not been established.
- ✓ **A full bath is contraindicated** in cases of open wounds, large skin injuries, acute skin diseases and when a warm bath may be dangerous (circulatory diseases).
- ✓ No cases of an overdosage, **no adverse effects and no drug interactions** have been reported. The **only known contraindication is hypersensitivity to the oil**.

# Lemon balm

## «*Melissa officinalis*»

**Used part:** dried leaves

**Used type:** herbal tea or alcoholic extracts

**Drog properties:** lemon type taste and smell

# Lemon balm
# «*Melissa officinalis*»

## Chemical composition and mechanism of action:

**Phenylpropanoids .... «caffeic, chlorogenic and rosmarinic acids»**

**Essential oil .....** Low amount and substituted with *Cymbopogon* oil.

- lemon balm **extracts proved to inhibit GABA transaminase** activity, resulting in elevated GABA levels (*in vitro* and *in vivo*).
- the **essential oil** does not seem to have a role in the effects on the central nervous system, its confirmed **spasmolytic activity** may be crucial in the **relief of gastrointestinal problems**.

# Lemon balm
## «*Melissa officinalis*»

**Chemical composition and mechanism of action:**

- The **effects on cognitive functions** may be explained by the fact that lemon balm **has acetylcholine receptor activity** in the central nervous system and had the ability to **inhibit acetylcholinesterase enzyme**.
- dry aqueous extract (70:1) of the leaves is used for the treatment of **herpes infections**.

# Lemon balm
## «*Melissa officinalis*»

**Efficacy and indications:**

- An **improvement of the cognitive functions** has been confirmed in clinical studies in healthy volunteers. In a population of Alzheimer patients, similar effects have been observed.
- An open study on volunteers suffering from mild to moderate anxiety disorders and sleep disturbances resulted in **improvements in the anxiety symptoms and insomnia**.

# Lemon balm
## «*Melissa officinalis*»

## Efficacy and indications:

- According to the **EMA**, lemon balm tea and preparations may be applied as traditional herbal medicinal products;

  for the **relief of mild symptoms of mental stress and to aid sleep for adolescents over 12 years of age, adults and the elderly**.

- The **dose as herbal tea** is 1.5-4.5 g of the comminuted herbal substance as a herbal infusion, 1-3 times daily.
- The posology of the **powdered herbal substance** is 0.19-0.55 g, 2-3 times daily.

# Lemon balm
## «*Melissa officinalis*»

**Side-effects, interactions & contraindications:**

- There is no data for under 12 years of age, lactating and pregnant women.
- **No contraindications except hypersensitivity**, and no undesirable effects are known.
- There have been no reports on the consequences of an overdosage.
- Preclinical data indicate that lemon balm **may inhibit the activity of the thyroid stimulating hormone**, but the clinical relevance of this finding is not known.

# Passion flower

## «*Passiflora incarnata*»

**Used part:** aerial parts (including the stems, leaves, flowers and fruit)

**Used type:** extract

# Passion flower
# «*Passiflora incarnata*»

## Chemical composition and mechanism of action:

**C-glycoside flavonoids .... «apigenin and luteolin glycosides»**

**Beta-carboline alkaloids ..... «harman, harmol»** *(undedectable)*

- extracts have **affinity for the GABA receptors and inhibit GABA uptake** to the neurons (in vitro).
- **Anxiolytic and sedative effects**, including the reduction of spontaneous locomotor activity and a prolongation of the sleeping time has been confirmed in animals.
- The available data suggest that the effects on the central nervous system may be mediated via modulation of the GABA system, but the doses employed in animal experiments are rather high relative to the human therapeutic dose.

# Passion flower
## «*Passiflora incarnata*»

### Efficacy and indications:

- There are only limited data to support the well-established use of passion flower.
- Passion flower showed a significant effect on **anxiety, tenseness and irritation** among the major neurotic symptoms.
- The effects of *Passiflora incarnata* tea on the quality of sleep were investigated. The treatment **improved the sleep-onset latency and the sleep efficiency.**

# Passion flower
# «*Passiflora incarnata*»

## Efficacy and indications:

- As a traditional herbal medicinal product, passionflower may be used

  **for relief of mild symptoms of mental stress and to aid sleep.**

- The dose as **herbal tea is 1-2 g** of the comminuted herbal substance as herbal infusion, **1-4 times daily** or as **powdered herbal substance: 0.5-2 g, 1-4 times daily.** Herbal extracts with similar posology may also be applied.

# Passion flower
## «*Passiflora incarnata*»

### Side-effects, interactions & contraindications:

- The use in children **under 12 years of age is not recommended**.
- Safety during **pregnancy and lactation has not been established**.
- **No drug interactions, no contraindications** (except hypersensitivity) and no special undesirable effects are known.
- No case of overdosage has been reported.

# Central nervous system

## «*Depression*»

- Depression is an **emotional disorder**, characterized by **sadness**, a **feeling of helplessness**, a **loss of interest or pleasure**, **poor concentration**, and **feelings of guilt or low self-worth**.
- It may be accompanied by **disturbed sleep** or an **altered appetite** and a **feeling of tiredness**.
- Depression **may impair a person's ability** to function at work and **in social functioning**.
- Severe **depression poses a severe risk of suicide**.

# Central nervous system

## «*Depression*»

- Depression often **starts at a young age**.
- **Stress and tragic life** events can provoke the development of the disease.
- **In females, the prevalence of depression (20%) is almost double that in males.**
- Depression **may be permanent or recurrent**.
- In all stages of the disease, **psychotherapy is a useful tool** in the treatment.

# Central nervous system

## «*Depression*»

- **Mild to moderate depression can be treated with phytotherapeutic preparations, but in more severe cases synthetics are needed.**
- The etiology of depression is not fully understood.

# Central nervous system
## *«Depression»*

- Apart from provoking life events (**stress and traumatic experiences**), it is widely accepted that the underlying cause is the dysregulation of certain **neurotransmitters**.
- The original assumption that depression results from a functional deficit of **noradrenaline and serotonine** (5-HT) has been refined and **today it is accepted** that the dysregulation of further neurotransmitters (**GABA and dopamine**) and some neuropeptides (**endogenous opioids**) also have a role.

# Central nervous system

## «*Depression*»

- Pharmacological treatment usually aims at;
  - **inhibition of the reuptake of serotonine or noradrenaline [selective serotonin reuptake inhibitors (SSRIs),**
  - **serotonin-norepinephrine reuptake inhibitors (SNRIs) and**
  - **norepinephrine reuptake inhibitors (NRIs)] or the breakdown of noradrenaline, serotonin and dopamine [monoamine oxidase inhibitors (MAOIs)].**

# Central nervous system

## «*Depression*»

- The modern phytotherapy of depression is limited to a single plant, ***Hypericum perforatum***.
- Although some other plants, primarily with anxiolytic and sedative effects, have also been used in folk medicine for this purpose, it must be made clear that **depression as a disease was defined only in the 20th century**, and it is therefore not possible to identify antidepressant herbs from the foregoing tradition.

# St. John’s wort

## «*Hypericum perforatum*»

**Used part:** dried flowering tops

**Used type:** extract and powder

**Drog properties:** yellow flowers

# St. John's wort

## «*Hypericum perforatum*»

**Chemical composition and mechanism of action:**

**phloroglucinol derivates ..... «hyperforin»**

**naphthodianthrones ..... «hypericin and its derivatives»**

**flavonoids «glycosides, quercetin and also biflavones, e.g. amentoflavone».**

# St. John's wort
# «*Hypericum perforatum*»

**Chemical composition and mechanism of action:**

- The mechanisms of action are still under discussion.
- The confirmed bioactivities relating to the clinical effect include inhibition of the **reuptake of serotonin** (5-HT), noradrenaline and dopamine, the **upregulation of dopaminergic receptors** and **post synaptic 5-HT1 and 5-HT2 receptors** and the **downregulation of beta-adrenergic receptors**.
- The extract also has an **effect on GABA receptors** (increasing the affinity).

# St. John's wort
## «*Hypericum perforatum*»

**Chemical composition and mechanism of action:**

- The effect of Hypericum was originally explained by its **inhibitory effect on MAO**.
- Hypericin **inhibits the dopamine beta-hydroxylase**, and **increases the level of serotonin** in the brain after 2 months of treatment in a comparable manner to imipramine.
- The **anxiolytic and antidepressant** effects of various extracts have been confirmed in animal experiments

# St. John's wort
## «*Hypericum perforatum*»

**Efficacy and indications:**

- The standardized extract has been assessed in several clinical trials lasting for 4-12 weeks on patients with mild to moderate major **depression**.
- There have been several sporadic studies with different *Hypericum* extracts, and these usually **confirmed the efficacy of St. John's wort in mild to moderate depression**.

# St. John's wort
## «*Hypericum perforatum*»

**Efficacy and indications:**

- Data published on the efficacy of *Hypericum* in the treatment of **premenstrual syndrome and menopause** indicate its favorable effect in **decreasing the psychological and psychosomatic symptoms**.

# St. John's wort
## «*Hypericum perforatum*»

**Efficacy and indications:**

- In the **EMA monograph** for well-established use, three dry extracts are to be found.
- The extract can be registered as herbal medicinal products for the;
  - **treatment of mild to moderate depressive episodes,**
  - **short-term treatment of symptoms in mild depressive disorders.**

# St. John's wort

## «*Hypericum perforatum*»

**Efficacy and indications:**

- The **daily doses** range between **600 and 1800 mg**.

# St. John's wort
## «*Hypericum perforatum*»

**Side-effects, interactions & contraindications:**

- In comparison with synthetic antidepressants, the **safety profile of St John's wort is more favorable and it is better tolerated.**
- The **extracts are less phototoxic than pure hypericin**.
- After the oral application of **1800 mg daily for 2 weeks**, the **skin sensitivity to UVA was increased**, but **no signs of phototoxicity were observed.**

# St. John's wort

## «*Hypericum perforatum*»

**Side-effects, interactions & contraindications:**

- *Hypericum* participates in clinically **important interactions with conventional drugs**.
- *Hypericum* affect the **CYP3A4, CYP2C9 and CYP2C19 enzymes** and **permeability glycoprotein (Pgp)**.

# St. John's wort

## «*Hypericum perforatum*»

## Side-effects, interactions & contraindications:

| Most significant drug interactions of St. John's wort | | |
|---|---|---|
| Mechanism:<br>1. CYP induction<br>2. Induction of permeability glycoprotein<br>3. Increase of serotonin activity | | |
| **Medicine** | **Mechanism** | **Sequel** |
| HIV protease inhibitors | 1, 2 | Decreased antiviral efficacy |
| HIV reverse transcriptase inhibitors | 1 | |
| Coumarin-type oral anticoagulants | 1 | Decreased anticoagulant effect |
| Cyclosporine, tacrolimus | 1, 2 | Rejection of a transplanted organ |
| Oral anticoncipients | 1 | Breakthrough bleeding, unwanted pregnancy |
| Antiepileptics | 1 | Epileptic seizure |
| Digoxin | 2 | Heart failure, arrhythmia |
| Theophylline | 1 | Asthmatic attack |
| Triptans | 3 | Serotonin syndrome |
| SSRIs | 3 | |

# St. John's wort
## «*Hypericum perforatum*»

**Side-effects, interactions & contraindications:**

- As adverse effects, **mild gastrointestinal disorders**, **allergic skin reactions**, **fatigue and restlessness** may occur.
- **Mild photosensitivity** may occur in sensitive patients.
- Administration to children, or during pregnancy and lactation is not recommended.
- There is **no known absolute contraindication** except hypersensitivity to St. John's wort.