



THE CENTRAL NERVOUS SYSTEM

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The Central Nervous System

- Drugs acting on CNS are analgesics (mainly opioid), anti-epileptics, anti-Parkinson agents and those for psychiatric disorders.
- Drugs of plant origin are important in all these areas, and of historical interest. For example, the anti-psychotic **reserpine**, from *Rauwolfia* spp. Played a great role in treatment of schizophrenic patients making them avoid hospitalization, before the introduction of the novel drugs such as phenothiazines. Unfortunately, it depletes neurotransmitter levels in the brain leading to depression. As a result, it is used in neuroscience to study the effect of other drugs (**study or experiment model**).
- For **milder** psychiatric conditions, phytotherapy can provide useful support, as it is the case in the mild cases of depression and anxiety. Serious cases should be under medical supervision.

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Hypnotics and sedatives:

- The difference between hypnotic and sedative is generally a question of dose.
- Plant products, used in this respect, are not as potent as synthetic drugs. Both are intended for short-term use.

Hops (*Humulus lupulus*) الجنجل الشائع = عشبة الدينار

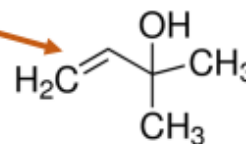
- Belonging to the family Cannabaceae, it is often referred to by the common name hops.
- Has been used traditionally for insomnia, neuralgia and excitability.
- Cultivated in European countries.
- Has a distinctive odor.
- The part of the plant pharmaceutically used is the female flower.



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Constituents:

- Its oleo-resin contain bitter principles such as α -acid humulone, β -acid lupulone and their degradation products such as 2-methy-3-buten-2-ol.
- Flavonoids, tannins and volatile oils.



Therapeutic uses:

- Sleep disturbances and restlessness; sedative and hypnotic activities have been proved *in vivo* in mice for both hop extract and the degradation product **2-methyl-3-buten-2-ol**. In combination with valerian, clinical studies also gave an evidence of this hypnotic effect.
- Antibacterial and antifungal.
- Hops is non-toxic; used in beers.

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Lemon Balm (*Melissa officinalis*) Lamiaceae:

- Has been traditionally used for its sedative effect, as well as for gastrointestinal disorders.
- The part of the plant used is the leaves.

Constituents:

- Its volatile oils contain **monoterpenes** (e.g. citronellal, geranial, ...) – **sesquiterpenes** (e.g. β -caryophyllene) – **flavonoids** (e.g. apigenin, quercetin and kaempferol) – **polyphenols**.

Therapeutic effects:

- ❖ **Sedative** and **antispasmodic** effects (*in vivo* trials in mice). It is used for nervous or sleeping disturbances and GIT complaints. **The hypnotic effect was not documented for *Melissa* alone, but in combination with other plants (hops and valerian).**
- ❖ **Anti-hormonal** effect (antithyroid).
- ❖ **Cholinergic** effect in human cerebral cells.
- ☐ Usually, taken in form of herbal tea 3 times a day (2-4 g).
- ❖ **Anti-infective:** for *Herpes simplex labialis* (HSV-1). 



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- Usually, for HSV-1, *Melissa* extracts are applied topically.
- It is regarded non-toxic, although it should NOT be used in excess owing to the reputed antithyroid effect.



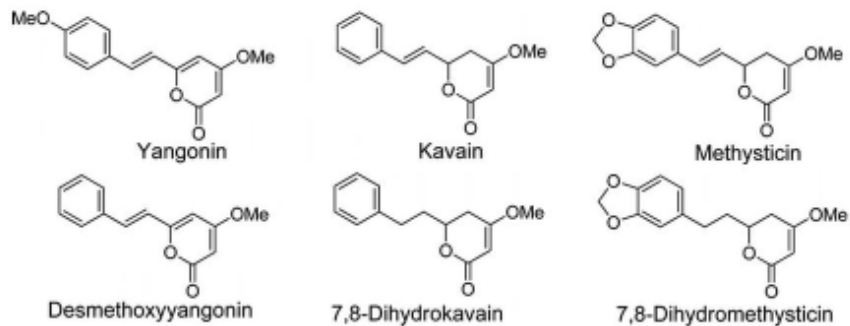
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Kava (*Piper methysticum*) Piperaceae:

- Also, it is known as kava-kava or kawa, and it has been used for hundreds of years by the Pacific islanders. Roots or rhizomes are fermented into a drink that is served in ceremonies as in the visits of the Pope and Queen of England.
- Used for its tranquilizing properties.

Constituents:

- **Kavalactones** (kavapyrones) including kavin, dihydrokavin, methysticin, yangonin and desmethoxyyangonin.



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Therapeutic effects:

- Current belief is that Kavalactones potentiate GABA_A receptor activity.
- **Anti-anxiety** effect: has been documented in several placebo-controlled, clinical trials.
- Overall, trials documented reduction in anxiety after 4-12 weeks of treatment with kava extracts (kavalactones).
- They are well-tolerated when used in recommended doses. However, liver injury has been documented in several patients worldwide, and this was ascribed to the inappropriate quality of raw material. A recent study in hepatocytes revealed that **kavin** has minimal cytotoxicity, **methysticin** has moderate concentration-dependent toxicity, whereas **yangonin** displayed marked toxicity.



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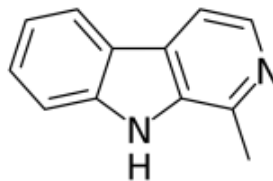
Passion Flower (*Passiflora incarnata*) Passifloraceae - زهرة العاطفة الحمراء

- It is also known as passion vine.
- It is a climbing vine.

Constituents:

- ❖ Not established till now, but **flavonoids** seem to be the principal ones, particularly, chrysin and the related compounds such as: schaftoside, isoschaftoside, vitexin, isovitexin, luteolin, quercetin, kaempferol, rutin, ... etc.
- ❖ **Alkaloids of the harman** (harmane) type exist in low amounts such as harmine, harmaline, harmol, ...etc.
- ❖ *Passiflora edulis* contains **triterpenoids** such as cyclopassifloric acids and cyclopassiflorisides.

Harmane is a heterocyclic amine found in a variety of foods including coffee, sauces, and cooked meat.



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Passiflora edulis

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Therapeutic effects:

- The historical uses of passion flower include treatment of insomnia, hysteria {**behavior exhibiting overwhelming or unmanageable fear or emotional excess**}, nervous tachycardia and neuralgia.
- Modern pharmaceutical uses comprise **nervous restlessness** and **insomnia** due to nervous tension, temporary relief of symptoms associated with **stress** and relief of **mild anxiety**. Anxiolytic effect has been confirmed in mice owing to a **sedative effect** which resulted in reduction in motility with ethanolic extracts.
- **Modulation of GABA system** was suggested to be one of the mechanism of actions.
- ❑ There are few clinical trials documenting passion flower effects. A randomized, double-blinded clinical trial including 36 patients with generalized anxiety showed the extract to be as effective as oxazepam, **but with lower incidence of impairment of job performance**.
- ❑ Generally, passion flower is well-tolerated with few side effects like nausea.

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Valerian (*Valeriana officinalis*): الناردين المخزني أو الناردين الطبي

- Valerian is one of the well-documented medicinal plants, particularly in Northern Europe.
- Is a herbaceous plant cultivated in most European countries, North America and Japan. It has an odor that is usually described to be unpleasant.
- It has a long history of traditional use for cases of nervous excitability such as hysterical and insomnia.
- The part of plant used is the root, rhizome and stolon {a horizontal branch from the base of a plant that produces new plants from buds at its tip or nodes}.



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Constituents:

- **Volatile oil: monoterpenes and sesquiterpenes:** (e.g. valerenic acid, valerenal, β -bisabolene, caryophyllene, valerionol, valeranone, valerenol, ... etc.).
- **Valepotriate compounds** (e.g. valtrate, isovaltrate, didrvaltrate).
- **Alkaloids** (e.g. valerianine and valerine).
- **Amino acids** (e.g. arginine, γ -aminobutyric acid (GABA), glutamine and tyrosine).

Therapeutic uses:

- ❖ European valerian possesses a well-documented **sedative** effect, hence, it is traditionally used for the temporary relief of mild anxiety and to aid sleep.
- ❖ The sedative effect as a result of CNS depression is thought to be due to valerian **volatile oil** (particularly, **valerenic acid** and **valerenal**) and **valepotriate compounds**, accordingly, the profile of these contents in valerian preparations will determine their activities.

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Mechanism of action:

Some biochemical studies hypothesize that the mechanism of action of valerian root is due to increased concentrations of the inhibitory neurotransmitter GABA in the brain by:

- a) Inhibiting GABA catabolism, or/and
- b) Inhibiting GABA reuptake, or/and
- c) Inducing GABA release.

- ❖ It is not known clear whether valerian have any effect on the binding of benzodiazepines to receptors.
- ❖ Valerian preparations should be taken, at least, 2 hours before driving a car or operating a dangerous machinery.
- ❖ Its effect may be potentiated by alcohol consumption.
- ❖ There are some reports talking about **hepatotoxicity** following consumption of valerian-containing preparations, although sure relation of this toxicity to valerian has NOT been established.

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Antidepressants

St. John wort (*Hypericum perforatum*)

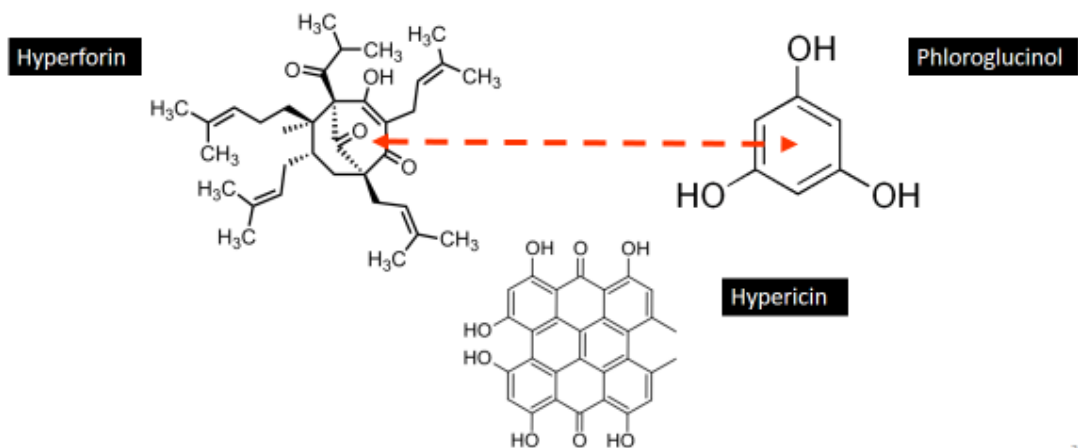
- Has a history of use as “nerve tonic” and for nervous disorders.
- Commonly used for mild to moderate depression, and is registered in UK for low mode and mild anxiety.
- A herbaceous perennial plant native to Europe and Asia.
- The preparations containing St. John wort were among the top-selling preparation in the developed countries recently.
- The used part of the plant is the dried aerial parts including the flowering tops, leaves, flowers and unopened buds.
- The name may have arisen as the plant bloom late in John around St. John’s day (24 John).

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Constituents:

- **Naphthodianthrones** such as **hypericin** and **pseudohypericin**, and prenylated **phloroglucinols** such as **hyperforin** and **adhyperforin**.
- **Prenylation:** is the addition of hydrophobic molecules to a protein or chemical compound.



- Initially, it was thought that only hypericin is responsible for the antidepressant activity of the plant, whereas, it has been revealed that hyperforin also participates. However, more research is needed to know if there are any other constituents that contribute to the activity.
- Most products containing St. John wort are standardized on hypericin content rather than hyperforin that is **unstable**.
- European Pharmacopeia requires that any preparation containing the plant should not contain less than **0.08 %** of total hypericin expressed as hypericin.
- Leaves and flowers also contain volatile oil including β -caryophyllene, α -pinene and β -pinene.

Therapeutic uses:

❖ **Antidepressant**, where the mechanism of action is proposed to include:

1. Inhibition of the reuptake of the synaptic neurotransmitters, serotonin (5-hydroxytryptamine, 5-HT), dopamine, norepinephrine and GABA.
2. **Clinical studies:** extracts of the plant may have a dopaminergic activity and effects on cortisol, which may influence the concentrations of certain neurotransmitters.
3. Some *in vitro* studies claim that the plant inhibited monoamine oxidase,,,,,,,,, 33

,,, where others fail to prove this.

- There is a clear evidence of the antidepressant activity of the plant from several trials performed on animal models.
- Randomized controlled trials indicate that the wort possesses an antidepressant effect and appeared more effective than placebo, and possibly as effective as conventional antidepressants in the treatment of mild to moderate depression.
- Generally, treatment should last for few weeks before improvement is seen,
- St. John wort is not indicated for **major depression**.
- A constant sense of hopelessness and despair is a sign you may have major depression.
- With major depression, it may be difficult to work, study, sleep, eat, and enjoy friends and activities.
- Standardized extracts are well tolerated when used in proper doses for 12 weeks.
- Adverse side effects reported are generally **mild**, and include gastrointestinal symptoms, dizziness, confusion and tiredness, and rarely, photosensitivity due to the hypericin content.

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- Clinical trials generally indicate that the herb is safer than some conventional antidepressants.
- However, concern has been raised concerning the interactions especially with preparations containing anticonvulsants, cyclosporine, digoxin, HIV protease inhibitors, oral contraceptives, serotonin reuptake inhibitors, theophylline, warfarin and triptans (for migraine, serotonin agonist; they constrict blood vessels).
- It should not be used during pregnancy and lactation.