Plant-based DIETARY SUPPLEMENTS (Botanicals/herbs)

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Approximately 40 % of the recently used drugs are originated from plants or other living systems,

e.g. many anticancer drugs, aspirine, digitalis, antibiotics, opioids, atropine, physostigmine e.t.c.

After isolation of active ingredients many of them are used as a synthetic drug today.

Screening for the new active ingredients, potential drug molecules in the nature is important even today.

Advantages of the purified chemicals and drugs:

1. the reproducible quality and
2. controlled dose with a dose-depending controlled effects

Quality and strengths of plant extracts and herbal dietary supplements are very variable !!

Standard plant extracts in European Pharmacopoeia have better quality and the content of only the main active ingredient much less variable.

Factors which influence the amount of the active ingredients:

- Culturing conditions, soil, sunshine, water
- Seasonal or daily rhythms of the plant's life cycle
- Which part of the plant was used
- Storage conditions
- Technology
- Pollutants e.g. agricultural chemicals
- Delivery conditions

Many ingredients of the herbal supplements saturate biotransformation in the liver !

→ **Drug interactions !!**

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Pollutants e.g. agricultural chemicals
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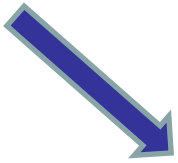
Many ingredients of the plant extracts saturate active transport molecules in absorption, distribution and excretion and enzymes in biotransformation in the liver !



Hepatotoxicity

Drug interactions !!

DIETARY SUPPLEMENTS with PLANT ORIGIN

Plant extracts have long been used to stay healthy or treat illnesses in any continents. Traditional Chinese Medicine has early written documents which make it well-known all over the world, but plant extracts have been used in any continents and regions.

The Food and Drug Administration (FDA) classifies herbals as dietary supplements, not drugs (2004).

Dietary supplements are made up of processed or unprocessed plant parts (bark, leaves, flowers, fruits and stems), extracts and essential oils. They may come in the form of tablets and capsules or teas and powders. Herbals may be sold as single substances or combined with other materials, such as vitamins and minerals.

The FDA does not regulate dietary supplements as it does the registered drugs:

1. **Herbal products do not have to be pure**
2. **Labelling of such products is under the purview of the FDA**
3. **Safety does not have to be demonstrated**

This means that the quality and strength of herbals can vary greatly among brands

The major problem with a lack of federal oversight on plant-based dietary supplements is the public perception of herbs. Pharmaceuticals, especially registered drugs, tend to be perceived as potent chemicals. What is more, because they are naturally occurring, the chemicals found in herbs may be perceived by the public as less harmful than a drug produced by chemists in labs.

Everybody should be able to appreciate that

these substances are marketed without review of efficacy and safety by authorities.

By law, dietary supplements can be sold legally as long as they do not make any health claims or say they cure a condition.

In many cases the medical value of these substances has not been demonstrated in controlled clinical studies.

Remember, just because it is “natural” does not mean it is gentler or more beneficial !

Many dietary supplements contain active ingredients that have strong biological effects and their safety is not assured.

Although herbal supplemenst are not synthetic, herbs contain powerful chemical commpounds as well. Monkshood, for example, can stop the heart and it is very toxic to CNS, killing a human within a couple of hours of even handling it.

It can be mistaken with horse-radish.

Monkshood

Aconitum variegatum

aconitine is a very toxic compound

Poison used for arrows in Asia

Horseradish

Toxic amanitine- containing mushrooms:

Amanita phalloides

Amanita muscarina contains muscarine

Some herbal medicines were evaluated for their therapeutical and toxic, side effects and they become registered drugs in some countries:

Sylimarine an extract of milk thistle (*Silybum marianum*)

is used in hepatic disorders even in hepatic failure or in poisoning with Amanita mushrooms

active ingredients: flavonoids

silybin (also known as silybinin or silibinin),
silychristin (silichristin)
and silydianin (silidianin).

Milk Thistle

Side effects:
laxative because of increased bile flow

Pharmacological effects of sylimarine:

in vitro: **reduces lipid peroxidation**

free radical scavenger

enhances superoxide dysmutase activity

inhibits lipoxygenase and formation leukotrienes

increases RNA polymerase I activity , protein synthesis and regeneration

in animal models:

It protects against liver injury caused by CCl_4 , alcohol or acetaminophene (=paracetamol) and prevent fibrosis

In clinical trials:

It has favorable effect on liver injury caused by poisoning with Amanita mushrooms. It was useful in viral hepatitis.

Echinacea extract from *Echinacea purpurea*

or E. pallida and E. angustifolia

most popular herbal dietary supplement
with the highest selling in USA.

active ingredients:
echinacoside,cichoric acid,
alkamides, water soluble polysacharides

water soluble extract has effect on cytokine release

THERAPEUTICAL EFFECTS:

1. immunmodulatory effect by release of cytokines:TNFalpha, interleukines, IFNgamma
2. increased phagocytosis, total circulating monocytes, neutrophils,
   and natural killer cells
3. immunosuppressive through cannabinoid receptors of immune cells
4. inhibition on lipoxigenase, COX enzimes, hyaluronidase - antiinflammatory effects
5. Virucidal activity against influenza and herpes simplex viruses
   and bactericidal activity against *Streptococcus pyogenes*, *Haemophilus influenzae,* and *Legionella pneumophila*

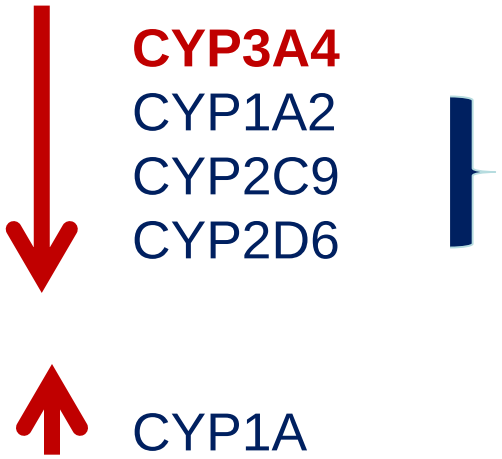
CLINICAL INDICATIONS: antiviral effects especially in the early phase of infections

Name	Popular Use (not proven in many cases)	Adverse Reactions
Echinacea / purple coneflower 	**To prevent and remedy colds and flu** **Mode of action:** **Increases cytokine deliberation (TNFalpha, ILs)** **Anti-inflammatory effect by inhibition of lipoxigenase and COX enzymes**	**Upset stomach and diarrhea; skin rash if used topically. Using regularly may suppress the immune system.** **Taking echinacea for eight weeks or more increases risk of hepatotoxicity.** **Flu-like syndrome after i.v. administration** Immunosuppression in long treatments **Contraindicated in immune disorders !!**

Echinacea extract on CYP enzimes

Echinacea alkamide compounds inhibit several CYP enzimes.

Effect of Echinacea extract:



CYP3A4
CYP1A2
CYP2C9
CYP2D6

E.purpurea dicreases by 40 % !

less inhibitory effect

CYP1A

inductory effect by 80 % !

Planta Med 2012; 78: 1490–1514

Hydrastis canadiensis

Hydrastis canadiensis = goldenseal (tabletta, extract)

active ingredients: hydrastin, berberin

antimicrobial effects, choleretic

Toxicity: hepatotoxicity in higher doses
carcinogenic in rats,
hepatocellular adenoma,hepatoblastoma

National Toxicology Program, USA, NTP TR 562, NIH Publication No. 10-5903 Planta Med 2012; 78: 1490–1514

Echinacea + *Hydrastis canadensis* combination on CYP enzimes

In USA Echinacea extract often contains *Hydrastis canadensis*

Hydrastis canadensis has izokinolin alkaloids: hydrastin and berberin with strong inhibitory effect on CYP enzymes.

Potentiated inhibitory effects of the two extract ↓ on CYP3A4 + CYP2D6 — **The most of the drugs are metabolized by these 2 enzymes**

eg. beta hydroxylation of testosteron is reduced by 88 %

14 -day -long administration increases significantly AUC of midazolam and cyclosporinA .

INCREASED HEPATOTOXICITY (both extract has hepatotoxicity)

Planta Med 2012; 78: 1490–1514

ginseng

Panax ginseng *P. quinquefolium*, the American variety Siberian ginseng (*Eleutherococcus senticosus*) and Brazilian ginseng (*Pfaffia paniculata*)	**Popular Use (not proven in many cases)**	**Adverse Reactions**
 	**Nootropic, to improve mental and physical performance ?** **Ginsenosids** **+** **Panaxosides** **Steroid glikozides** **Modulatory effect on :** **Ca, Na, K ion channels.** **GABA-A, 5HT-3, nicotin, Ach, NMDA receptors**	**Weak oestrogenic effect** **Insomnia, nervousness, hypertension** **CYP3A4 interactions** **Interaction with:** **warfarin** **Increased bleeding, increased INR** **The same risk with Thr aggregatory inhibitors** **With sympathomimetic drugs - Hypertension, sleepness** **Contraindication in Mania –depressíve disease**

	Beneficial effects	Adverse effects
Garlic / Allium sativum 	**To prevent stroke, atherosclerosis, high blood pressure and lower cholesterol** **Allicin** **Organosulfur compounds (***S*-allylcysteine) **inhibit HMG-CoA reductase, Improve vessel elasticity, Antiplatelete and fibrinolytic effect, relaxes smooth muscle,** **Antimicrobial effect**	**Upset stomach, intestinal problems, heartburn, bad breath and body odor.** nausea (6%), hypotension (1.3%), allergy (1.1%), and bleeding (rare).
St. John's Wort / Hypericum perforatum Blooming is in June at St. **John's feast** 	**To treat mild depression** **hypericin,** **Hyperforin has inhibitory effecton reuptake of biogen amines**	**Sensitivity to sunlight if taken for long spells, itching, headache, fatigue, bloating, weight gain and constipation. Hypomania, mania, autonomic arousal** **Cautions!** **With other antidepressants may result in serotonin syndrome (life-threatening sympathetic outflow)**

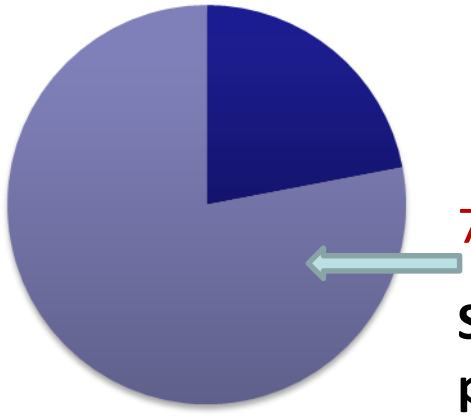
Importance of interactions of St John's Wort extracts

Hypericum perforatum is the most frequently used plant extract because of antidepressive effect of its active ingredient, hyperforin.

OTC product !!

15 % of plant dietary supplements to be selling for therapy of depression, especially **St John's Wort extracts are used** .

Drug- dietary supplement interactions



78 % are the interactions induced by

St John's Wort extracts in the cases published in scientific literature !!

Br J Clin Pharmacol. 2006 Jun;61(6):677-81.

Pharmacodynamic interactions in CNS

St. John's Wort / *Hypericum perforatum*

Warnings for patients:

With any antidepressant drugs

St. John's Wort extracts are NOT RECOMMENDED!!

As plant extract the concentrations of active ingredient are changing in wide range !!

Ingredients of Herbs brought in as dietary supplements are not controled by authorities → high amplitudes in amounts

Unpredictable amounts and effects és hatás miatt ⇨ Unpredictable serious toxicity in CNS/agitation, convulsion

or

malignant serotonin sy !

Pharmacodynamic interactions in CNS

St. John's Wort / *Hypericum perforatum*

Mode of action: hyperforin inhibits serotonin reuptake mechanism

It increases the effects of selective serotonin reuptake inhibitors
Toxicity – serotonin sy !!

Serotonin sy ⟷ amfetamin caused disco fever ?

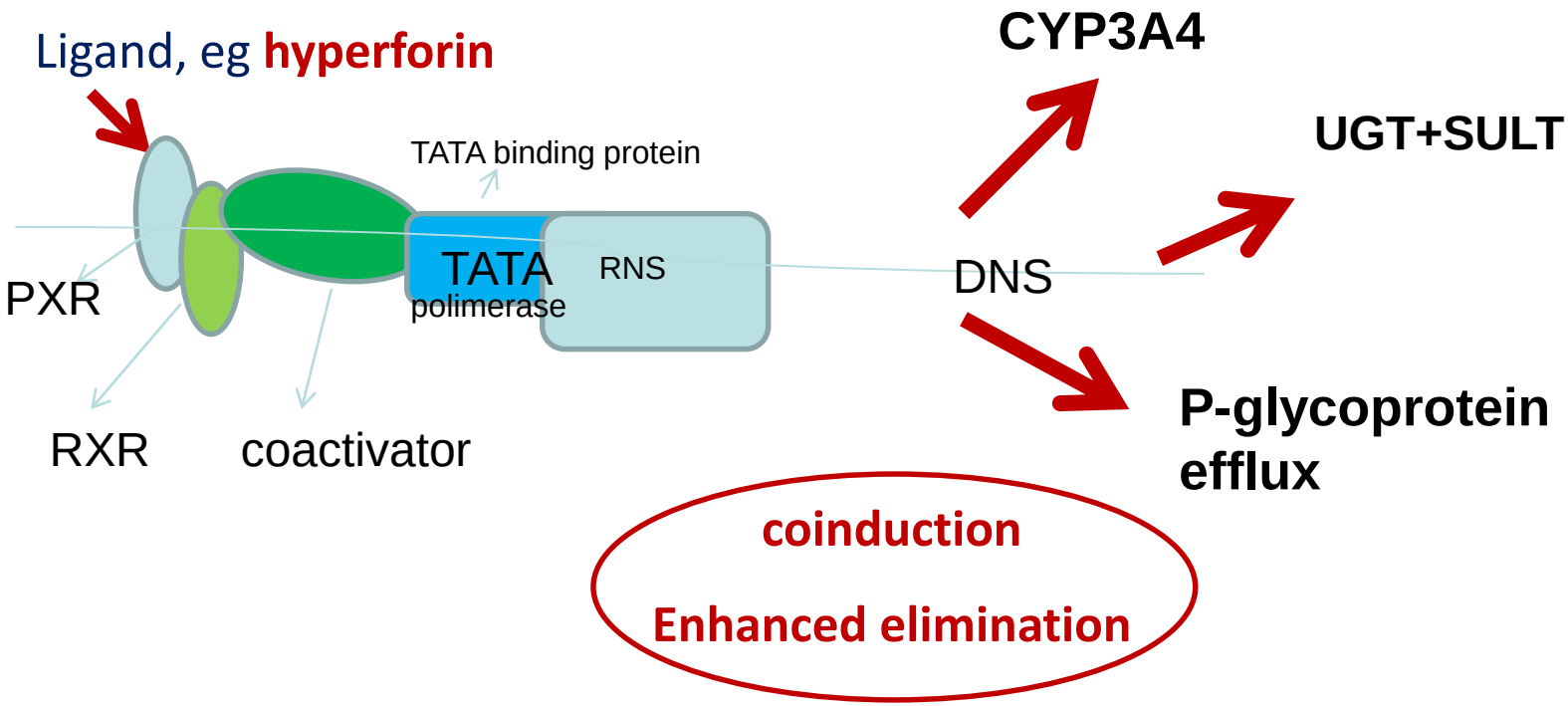
Common leading symptomes:

- malignant hyperthermia
- Malignant hypertension
- Muscle rigidity

→ Life-threatening !
DEATH WITHOUT TREATMENT

Pregnan X receptor - nuclear interactions

The strongest induction of CYP3A4 is through Pregnan X receptor (PXR =steroid XR nuclear receptor)



St. John's Wort extract results in inefficiency of many drugs e.g. anticoncipients, 5-HT1D agonists in migraine attacks, AIDS therapy, warfarin

Life-threatening interactions with St John's Wort extract + warfarin

St John's Wort extract may lay off effect of anticoagulant therapy

reason: enhanced elimination of warfarin

due to induction of CYP2C9 enzime which metabolizes warfarin

↓

trombosis, AMI, stroke

St John's Wort extract induced CYP enzimes: **CYP3A4, 2C9, 2C19,1A2**

↓

These all together influence metabolism, elimination and bioavailability of the 80 % of drugs!!

↓

It would be desirable to warn patients for the risk of the use on labels of packages of **St. John's Wort extract !!**

Br J Clin Pharmacol. 2006 Jun;61(6):677-81.

Ephedra sinica

Ephedra sinica: about 0,5 m in height, Northeast-China

Active ingredient:

ephedrin and pseudoephedrin alkaloids.

Ephedra distachya L.

Mode of action of Ephedrin :

Indirect + direct mixed type sympatomimetics
Effects in CNS+ perifery.

Indirect : neurotransmitter release from Adrenerg neurons – amfetamin-like effect

CNS sympathetic overflow sy – stimulatory amfetamin-like effect - euphoria

Direct effect:

	alfa1	beta1	beta2
adrenalin	+++	++++	+++
efedrin	+	+++	++

Ephedra sinical Ma Huang

ephedra is one of the most infamous dietary supplement

use: body building, sportmen, obesity,
for weight reducing, enhancement of performance

effects: weight reducing effect within 1-12 months
synergistic effect in combination with caffeine

Acute sympathomimetic effects in CNS+periferally

Reduced sensation of fatigue, enhance breath volume + cardiac output

Adrenergic effects , e.g. enhanced blood sugar ⇒ excess energy

⇓

Enhancement of performance

Ephedra sinica withdrawal

Ephedrin therapeutic use:

as a drug, the synthetic ephedrin is the component of
Mixtura pectoralis FoNo

Bronchodilatation in obstructive bronchitis, asthma bronchiale

Ephedrin-containing dietary supplements: are PROHIBITED to sell

2004.U . S . Food and Drug Administration (FDA) banned dietary supplements, herbs containing *ephedra sinica*

2005. in Utahban tried to delibarate, but several months later it was banned again.

Many DEATH of young men due to the uncontrolled use of *ephedra sinica*

Ephedra sinica toxic interactions

Ephedrin-containing dietary supplements became forbidden products because of unsafety

It was impossible to control their use

hypertension, tachycardia, sympathetic overflow in CNS , arrythmias, myocardial infarction, stroke even in healthy young men!

Interaction:

With any drugs and energy drinks which may result in

sympathetic stimulation or overflow in CNS

Synergistic effect with caffeine

Even physical activity enhances the risk!!

Biloba- prophylaxis of dementia ?

Name	Popular Use (not proven in many cases)	Adverse Reactions
Ginkgo Biloba  Ginkgo leaves	**To treat headache, tinnitus,** prophylactic agent to prevent progression to dementia **Flavone glycosides and terpenoids** including ginkgolides A, B, C, J, and bilobalide Increased blood flow : **PAF antagonist** **Inhibits erythrocyte and thr aggregation** **Decrease capillary permeability and edema** **Antioxidant**	**Muscle spasms, anxiety, allergic skin reactions, cramps, and mild digestive problems.** **Bleeding ! (overdose)** Or in interactions with other thr. aggregation inhibitors as aspirine

Remarkable Ginkgo biloba in Tournai, (Belgium).

Name	Popular Use (not proven in many cases)	Adverse Reactions
Feverfew / Tanacetum parthenium	To treat headache, migraine, rheumatoid arthritis Parthenolide and other antiinflammatory agents	Mouth ulcers, gastrointestinal upset,contact dermatitis Rebound: nervousness, tension-type headache, insomnia

Name	Popular Use (not proven in many cases)	Adverse Reactions
Aloe vera There are more than 300 species of the aloe plant, but *Aloe barbadensis* (aloe vera) is the best known. grows naturally in dry, tropical climates in Africa, Asia, Europe, and the southern and western parts of the United States and also known as “burn plant,” “lily of the desert,” and “elephant’s gall” .	Popular herbal remedy that was used to help treat wounds, hair loss, hemorrhoids, and digestive issues or prevent sunburn. Heartburn (GER) relief and lowering blood glucose are also hoped. From leaves bright **green gel** or juice, capsules The yellow pulp that’s found just under the outer part of the plant leaf. **Aloe latex** has been shown to have laxative properties, and it’s usually taken orally to treat constipation. Drinks, juice, aloe vera water contain aloe latex. **Aloin**, which is an anthraquinone is the active ingredient.	Aloe latex, however, can be dangerous. Taking aloe latex orally can lead to **cramps and bloody diarrhea**, haemorrhoids. Renal toxicity: Taking even just 1 gram orally per day for several days could end up causing kidney damage and may even be fatal ! Pregnants are very sensitive to aloe vera !! – haemorrhages, even **abortus** may develop. whole-leaf aloe vera extract created cancerous tumors within the large intestines of rats

Name	Popular Use (not proven in many cases)	Adverse Reactions
Datura stramonium **jimsonweed** or **devil's snare** Dose dependent toxicity of atropine	Hiosciamine and atropin especially in seeds Scopolamine especially in leaves It was used in neuralgia, pain killer in rheumatic arthritis. Smoke or cigarette against asthma bronchiale.	Atropin intoxication or scopolamine intoxication. OPPOSITE EFFECTS on CNS ! Atropin is sympathomimetics both centrally and peripherally. Excitation, involuntary movements, epileptiform convulsions, hallucinations, coma Scopolamine is sedatohypnotics. Somnolence, coma, respiratory distress

Atropa belladonna

HIGH Atropin containing plant ! Only the standard belladonna leaf extracts are good to use as medicine

Name	Popular Use (not proven in many cases)	Adverse Reactions
Viscum album L. commonly known as **European mistletoe**, **common mistletoe** or simply as **mistletoe.** It is native to Europe and Western and Southern Asia.	Active ingredient: Viscotoxin - vasodilation Cold dipping of leaves to obtain tea was used. Mistletoe leaves and young twigs are used by herbalists.	Very dangerous- contraindication in children The toxic lectin viscumin has been isolated from *Viscum album.* Viscumin is a cytotoxic protein (ribosome inactivating protein, or RIP) that binds to galactose residues of cell surface glycoproteins and may be internalised by endocytosis Viscumin strongly inhibits protein synthesis by inactivating the 60 S ribosomal subunit. The structure of this protein is very similar to other RIPs, showing the most resemblance to ricin and abrin.

Table 63–2. Potential toxicity of selected botanicals.

Name	Intended Use	Potential Toxicity
Aconite (monkshood, wolfsbane)	Analgesic (topical and oral)	Cardiac and CNS toxicity with oral use
Borage (beebread, burrage)	Anti-inflammatory, diuretic	Oral use causes gastrointestinal distress and possible hepatotoxicity
Chaparral (creosote bush, greasewood)	Anti-infective, antioxidant	Hepatotoxicity and renal dysfunction
Coltsfoot (coughwort)	Respiratory tract and oral infections	Allergic reactions, phototoxicity, liver dysfunction
Ephedra (ma huang, sea grape, yellow horse)	Bronchodilator, diet aid, CNS stimulant	Hypertension, cardiac arrhythmias, stroke, seizures
Germander	Diet aid, digestive aid, gastrointestinal dysfunction	Multiple cases of hepatitis and death. (Still used as flavoring agent in United States)
Jimsonweed (*Datura*, devil's apple, stinkweed)	Respiratory tract diseases, hallucinogen	Marked adverse effects due to atropine and related M-blockers
Pennyroyal	Abortifacient, digestive aid, induction of menstrual flow	Gastrointestinal distress (hematemesis), CNS dysfunction, hepatotoxicity, renal dysfunction, disseminated intravascular coagulation
Pokeweed berries and root (American nightshade)	Berries used as food coloring; root extracts for emesis, rheumatism	Oral use highly toxic: bloody diarrhea, hypotension, coma, blindness, respiratory failure
Royal jelly	Tonic, immune potentiation, hyperlipidemia	Allergic reactions including anaphylaxis and death
Sassafras	Blood thinner, urinary tract disorders; oil used topically as antiseptic	Diaphoresis, hot flushes with oral use of bark; ingestion of sassafas oil may be lethal (coma, cardiovascular collapse and respiratory paralysis)

Katzung et al Basic and clinical Pharmacology textbook