

Convegno

L'uso di piante e preparati vegetali per il benessere animale

Bologna, 6 maggio 2019

Piante medicinali e oli essenziali nella salute animale

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Piante medicinali e oli essenziali nella salute animale

Introduzione generale

Posizione dei botanicals (integratori, farmaci)

Claims dei botanicals ed esempi:

- Antimicrobici
- Antiossidanti
- Altre Indicazioni

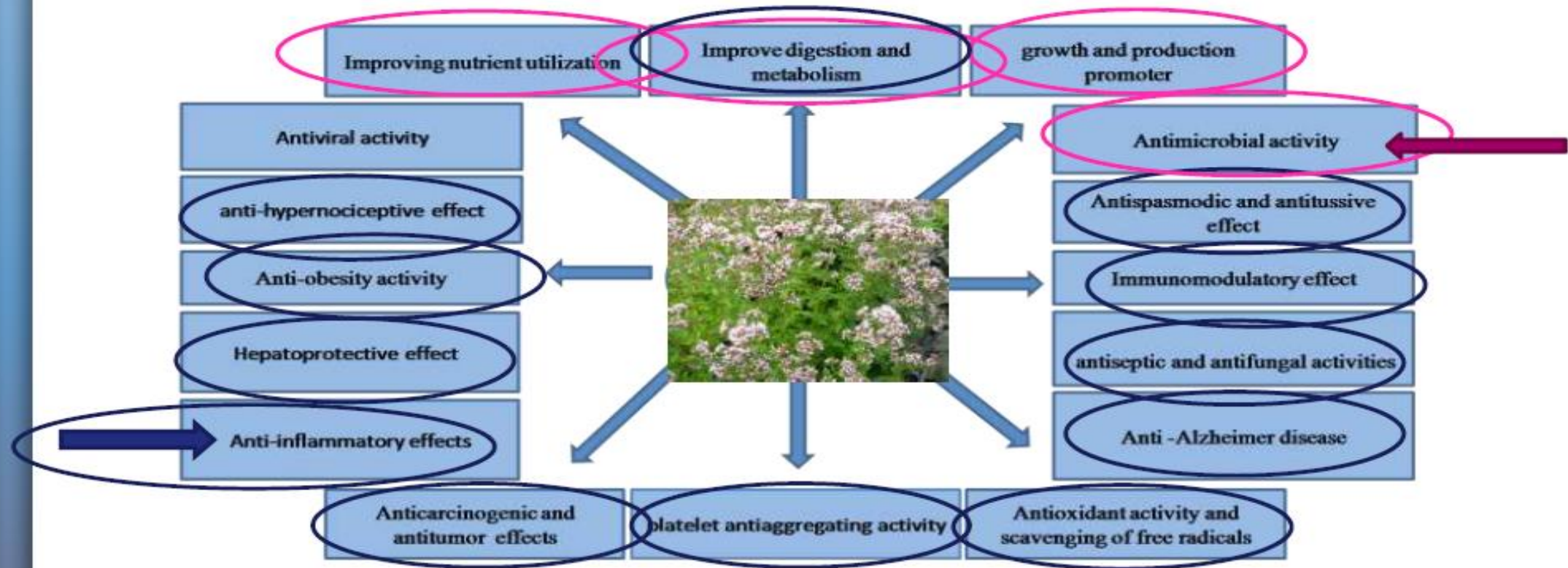




Tantissime piante officinali ed aromatiche usate in veterinaria e nutrizione animale in Europa



Medicinal plants – multi talented!



...a key to understand Systems Biology...

Functional Plant Products / Secondary Metabolites

Pharmaceutical
use: **EFFICACY!**

Herbal
Medicinal
Products

Medical
Devices
etc.

Food / Feed Use:
SAFETY first!

Food
Supplements
Dietary
Products,...

Feed
Additives

Additivi / Integratori per l'alimentazione animale

Regolamento (EU) 1831/2003

Direttiva (EU) 834/2007, 889/2008

Linea Guida (EU) 429/2008 (docu)

Animali da allevamento

Dir. (EU) 2377/90 (MRL-Values)

Dir. (EU) 834/2007 e 889/2008

(Organic Production)

Prodotti Medicinali

Linee Guida 2004/28/EU (Community Codex Veterinary Drugs)

Direttiva (EU) 726/2004 (Human- & Veterinary Medicinal Products)

Direttiva (EU) 834/2007, 889/2008
(Organic Production)

Cavalli e

Animali da compagnia

Integratori: anche EFSA responsabile!



Austria-Codex 2015/2016 - Vet-Phyto Spezialitäten Österreich

Produktbezeichnung	Produktart	Tierart	Arzneimittelform	Pflanze/Pflanzenteile	Pharmafirma
Colosan	Tierarzneimittel	Großtier, Pferd, Kleintier	Lösung zum Eingeben für Tiere	Sternanisöl, Bitterfenchelöl, Kümmelöl, Kassaöl, Leinsamenöl	Vans, Wien
EucaComp	Tierarzneimittel	Großtier, Pferd, Kleintier	Suspension zur intravaginalen Anwendung und intrauterinen Instillation für Tiere	Eukalyptusöl, Ringelblume, Majoran, Melissenblätter	PlantaVet, Bad Waldsee, DE
Phlegmone - Salbe	Tierarzneimittel	Großtier, Pferd	Salbe für Tiere	Campher, Phenol, Terpentin	Jacoby Pharmazeutika, Hallein
Phlegmovet - Salbe	Tierarzneimittel	Großtier, Pferd, Kleintier	Salbe für Tiere	Campher	Richter Pharma, Wels
Sporyl - Salbe für Rinder	Tierarzneimittel	Rind	Salbe für Tiere	Nelkenöl, Eugenöl	Richter Pharma, Wels
Stullmisan	Tierarzneimittel	Großtier, Pferd, Kleintier	Pulver für Tiere	Fichtenspitzen, Kamillenblüten, Melissenblätter, Wermutkraut	Richter Pharma, Wels

Prodotti Fitoterapici per uso veterinario in Austria, Germania e Svizzera

(I. Hahn-Rammsl, 2016)

Germania:

7 topici (appl. esterna), **tutti oli essenziali**
 18 orale (uso interna) di questi **7 oli ess.**
 1 parenterale (iniez.) : Echinacea

Tierarzneimittel - Kompendium der Schweiz 2016

Produktbezeichnung	Produktart	Tierart	Arzneimittelform	Pflanze/Pflanzenteile	Pharmafirma
Api Life Var	Tierarzneimittel	Bienen	Evaporationsplättchen	Thymol, Eukalyptusöl, Campher, Levomenthol	Bienen Meier AG
Bismutal	Tierarzneimittel	Großtier, Kleintier	Pulver für Tiere	Johannisbrot	Dr. E. Gräub AG
Embrocation Stricker	Tierarzneimittel	Großtier, Pferd	Emulsion für Tiere	Campher, Rosmarinöl, Terpentinöl	Werner Stricker AG
Globus-Spezial	Tierarzneimittel	Großtier	Emulsion für Tiere	Terpentinöl	Werner Stricker AG
Koi Med Tincture	Tierarzneimittel	Zierfische	Flüssigkeit	Rhabarber	Fishmed GmbH
Koi Med Wound Spray	Tierarzneimittel	Zierfische	Spray	Aloe, Kamille, Mariendistel, Propolis	Fishmed GmbH
Lacolyset	Tierarzneimittel	Großtier	Pulver für Tiere	Banane, Johannisbrot, Karotte, Molkenproteine, Reis, Sojamehl	Dr. E. Gräub AG
Laxatone	Tierarzneimittel	Kleintier	Paste für Tiere	Sojaöl	Provet AG
Omasin	Tierarzneimittel	Großtier	Pulver für Tiere	Fenchel, Enzian, Johannisbrot	Dr. E. Gräub AG
Phlogal	Tierarzneimittel	Großtier	Salbe für Tiere	Arnika, Campher, Hammelis-Extrakt	Dr. E. Gräub AG
Reinigungstrank Natürlich	Tierarzneimittel	Großtier	Pulver für Tiere	Lindenrinde	Fritz Suhner
Stullmisan S	Tierarzneimittel	Großtier, Pferd, Kleintier	Pulver für Tiere	Fichtenspitzen	MSD Animal Health GmbH
Totalin	Tierarzneimittel	Großtier, Pferd	Pulver für Tiere	Algen, Fenchel	Werner Stricker AG
Ultrorale	Tierarzneimittel	Großtier	Emulsion für Tiere	Terpentinöl	Werner Stricker AG

Compilazione e confronto dei fitoterapici ed integratori/ supplementi / dietetici per uso animale in Austria

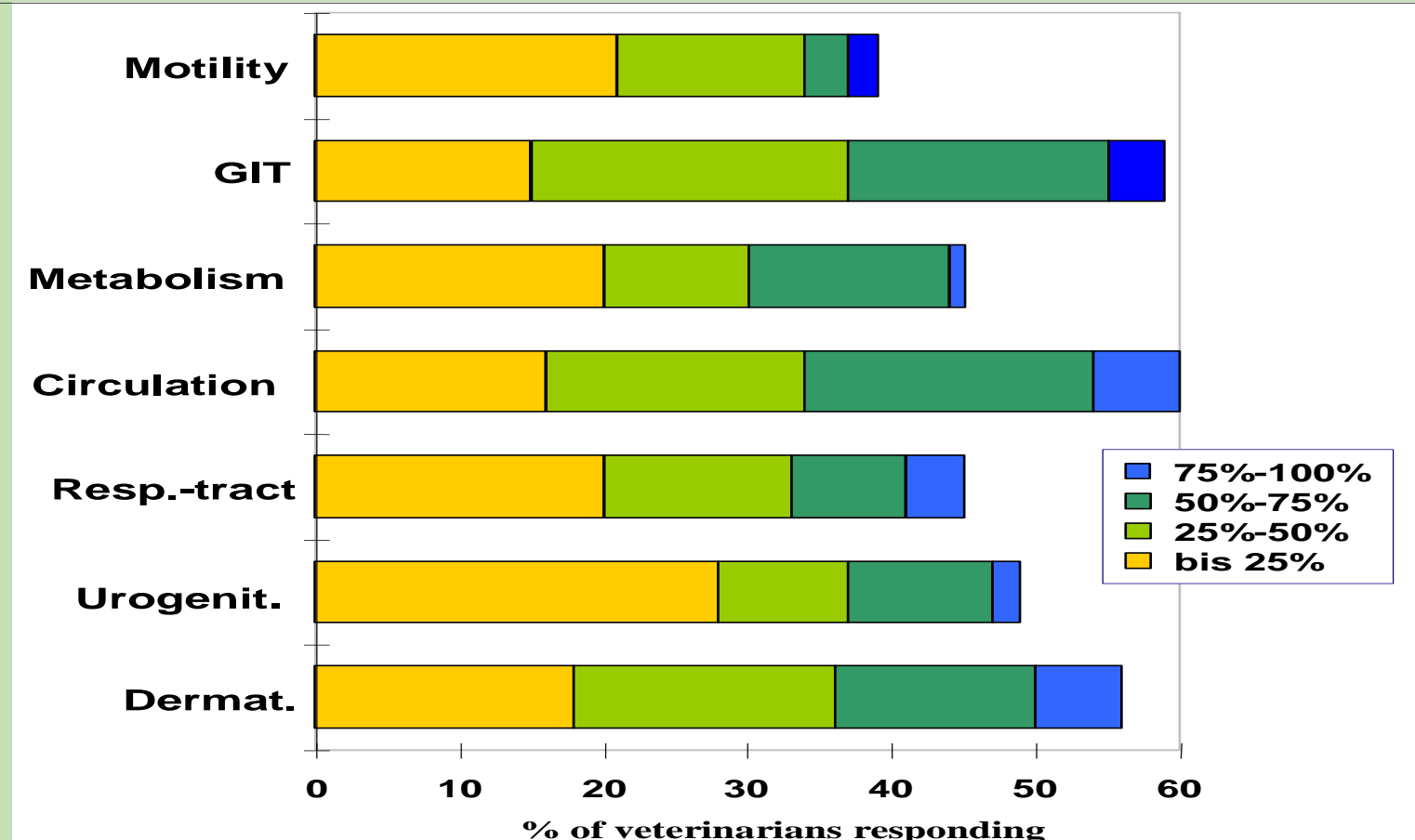
(MSc Tesi Vetmeduni Vienna 2012)

Species	Fitoterapici	Integratori
<i>Calendula officinalis</i>	3	-
<i>Crataegus oxyacantha</i>	- (!)	2
<i>Cynara scolymus/</i>	-	5
<i>Echinacea sp.</i>	3	3
<i>Harpagophytum procumbens</i>	- (!)	4
<i>Hypericum perforatum</i>	- (!)	4
<i>Matricaria recutita</i>	2	5
<i>Panax ginseng</i>	1	3
<i>Silybum marianum</i>	- (!)	4
<i>Thymus vulgare</i>	-	6
<i>Valeriana officinalis</i>	- (!)	4
<i>Zingiber officinale</i>	-	3

Prodotti Fitofarmaci in Veterinaria

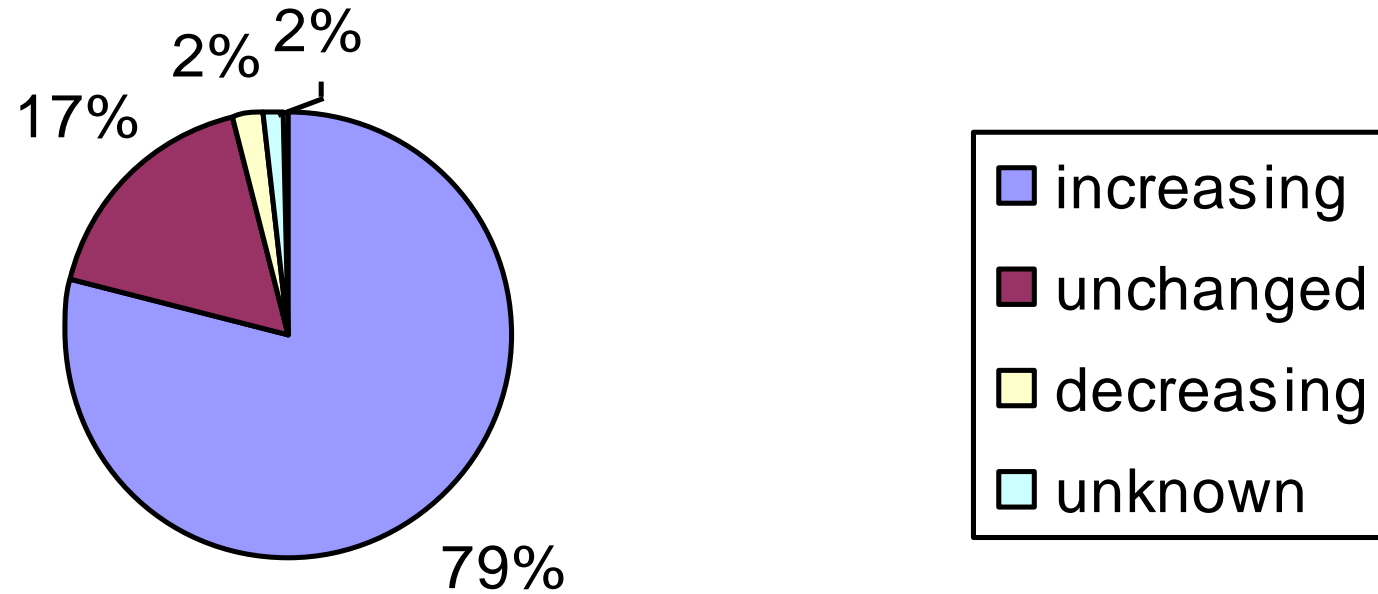
- pochi prodotti registrati in Austria, Svizzera e Germania
- ? *In Italia ?*
- Altri prodotti:
- dietetici, integratori, appetibilizzanti, „cosmetici“ ...per la cura del corpo animale, ecc. =„parafarmaceutici“
- „Prodotti per il benessere degli animali“ !

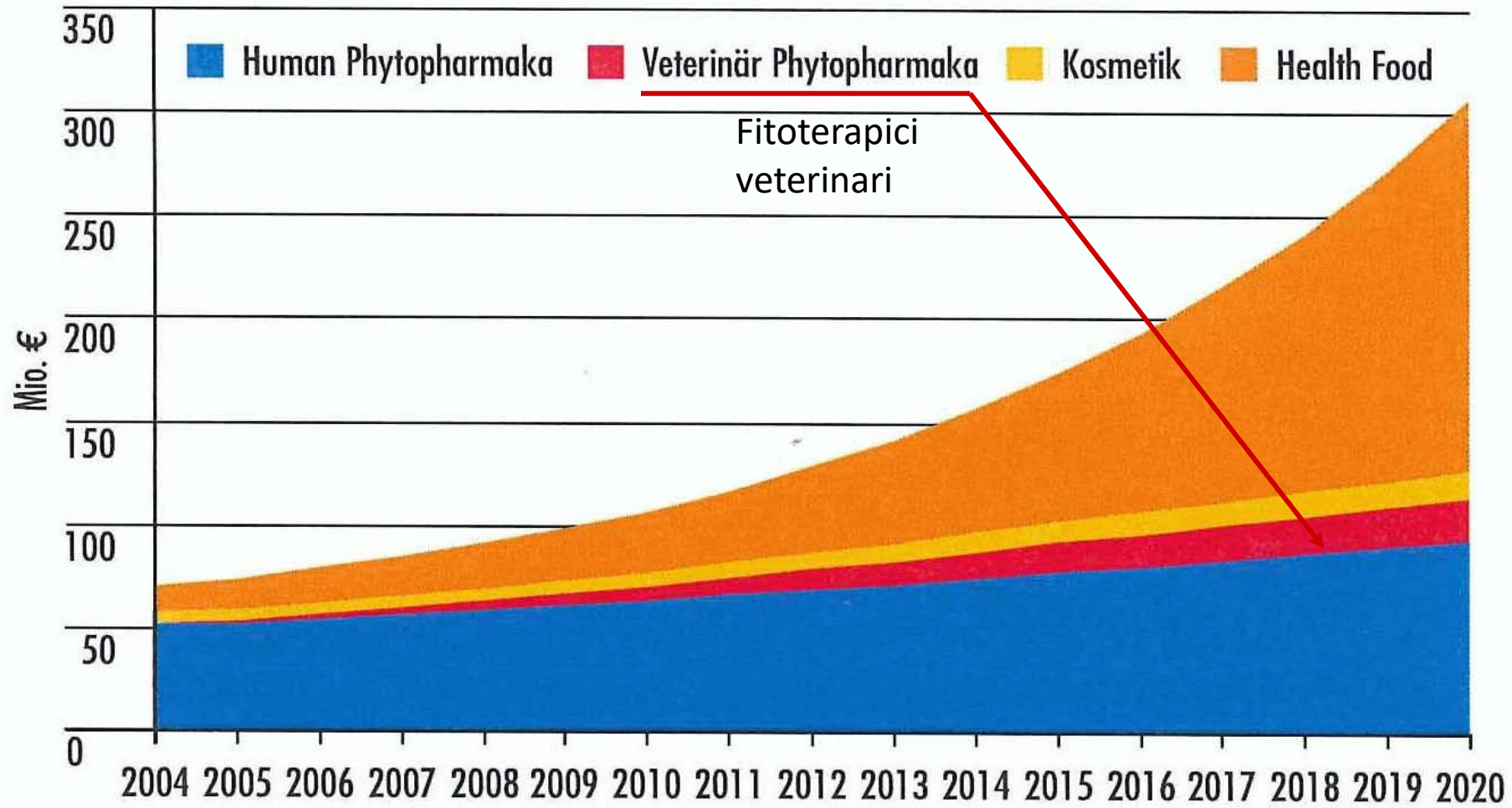
Percentage of treatments with HMPs for most important animal health problems



Companion Animals and Horses:

Tendency to use natural products and complementary medicine is increasing, documented by the interest of animal owners in phytoterapy





Previsione sviluppo prodotti a base di piante officinali in Germania fino a 2020

Fitoterapici e Fitointegratori in Medicina veterinaria e Nutrizione animale

Table 1. Most commonly used herbs and essential oils in traditional animal health care and livestock production in Austria and neighbouring countries

Latin name	Common name	Parts/products used
<i>Achillea millefolium</i> s.l.	Yarrow	Infusion
<i>Arnica montana</i>	Arnica	Extract
<i>Boswellia sacra</i>	Frankincense	Resin
<i>Carum carvi</i>	Caraway	Seed, essential oil
<i>Citrus</i> sp.	Citrus oil	Essential oil
<i>Curcuma longa</i>	Curcuma	Rhizome
<i>Foeniculum vulgare</i>	Fennel	Seed
<i>Matricaria recutita</i>	Camomile	Infusion, essential oil
<i>Mentha</i> sp.	Mint	Infusion, essential oil
<i>Pimpinella anisum</i>	Aniseed	Seed, essential oil
<i>Pinus</i> sp.	Turpentine	Essential oil, (oleo)resin
<i>Salvia officinalis</i>	Sage	Infusion, essential oil
<i>Syzygium aromaticum</i>	Cloves	Buds, essential oil
<i>Zingiber officinale</i>	Ginger	Rhizome

Franz et al. 2010, FFJ 25, 327

- ***Laudato M, Capasso R.:* Useful plants for animal therapy**
OA Alternative Medicine 2013, Feb. 01; 1(1)1. OA Publ. London
- „...in this paper we have reviewed the herbal drugs most commonly utilized in domestic animals.“
- Cardiovascular system; Skin; Helminthiasis; Digestive apparatus; Respiratory app.; Reproductive app.; Additional uses (mastitis, milk production; Dogs and Cats: antiinflamm., anxiety, immunostimulants,...)
- 45 plant species mentioned, from *Allium sativum* to *Zingiber officinale*,
- 29 literature citations

„Curriculum Fitoterapia Veterinaria“ in Austria (Svizzera, Germania)

1. **Tratto respiratorio**
2. **Pelle (cute), occhi, orecchi**
3. **Apparato digerente (disturbi intestinali)**
4. **Tratto cardiovascolare**
5. **Tratto urogenitale**
6. **Apparato di moto (agilità)**
7. **Condotta („stato psicologico“)**
8. **Invecchiamento („geriatria“)**

Pretese („Claims“) di „botanicals“ come integratori mangimistici (e fitoterapici)

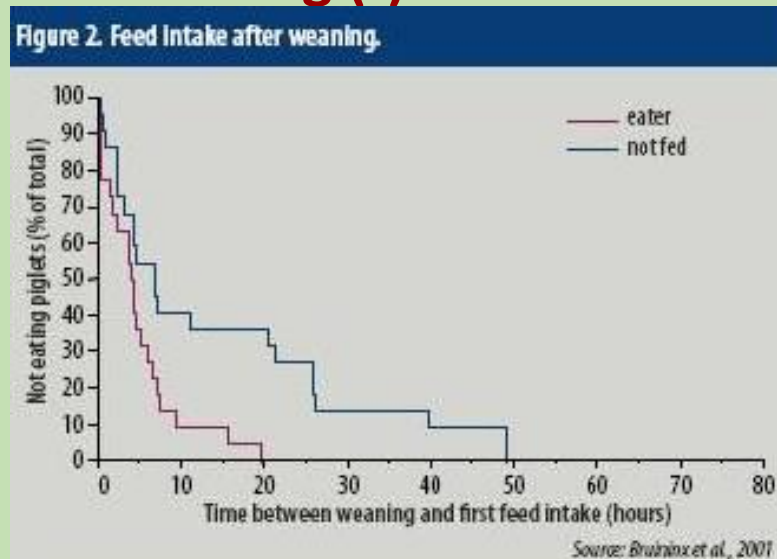
- **Claim 1: migliorare il sapore, palatabilità e „feed shelf life“**
- **Claim 2: migliorare il rendimento**
- **Claim 3: attività antimicrobica**
- **Claim 4: attività antiossidativa**
- **Claim 5: anti-metanogenico e riduzione della escrezione di azoto (N...) in ruminanti**
- **Claim 6: altri effetti positivi nella fisiologia animale, es.stato salutistico, benessere animale**

Flavourings

Zootechnicals...

Claim 1: Aroma / Flavouring / Sapore e Palatabilità

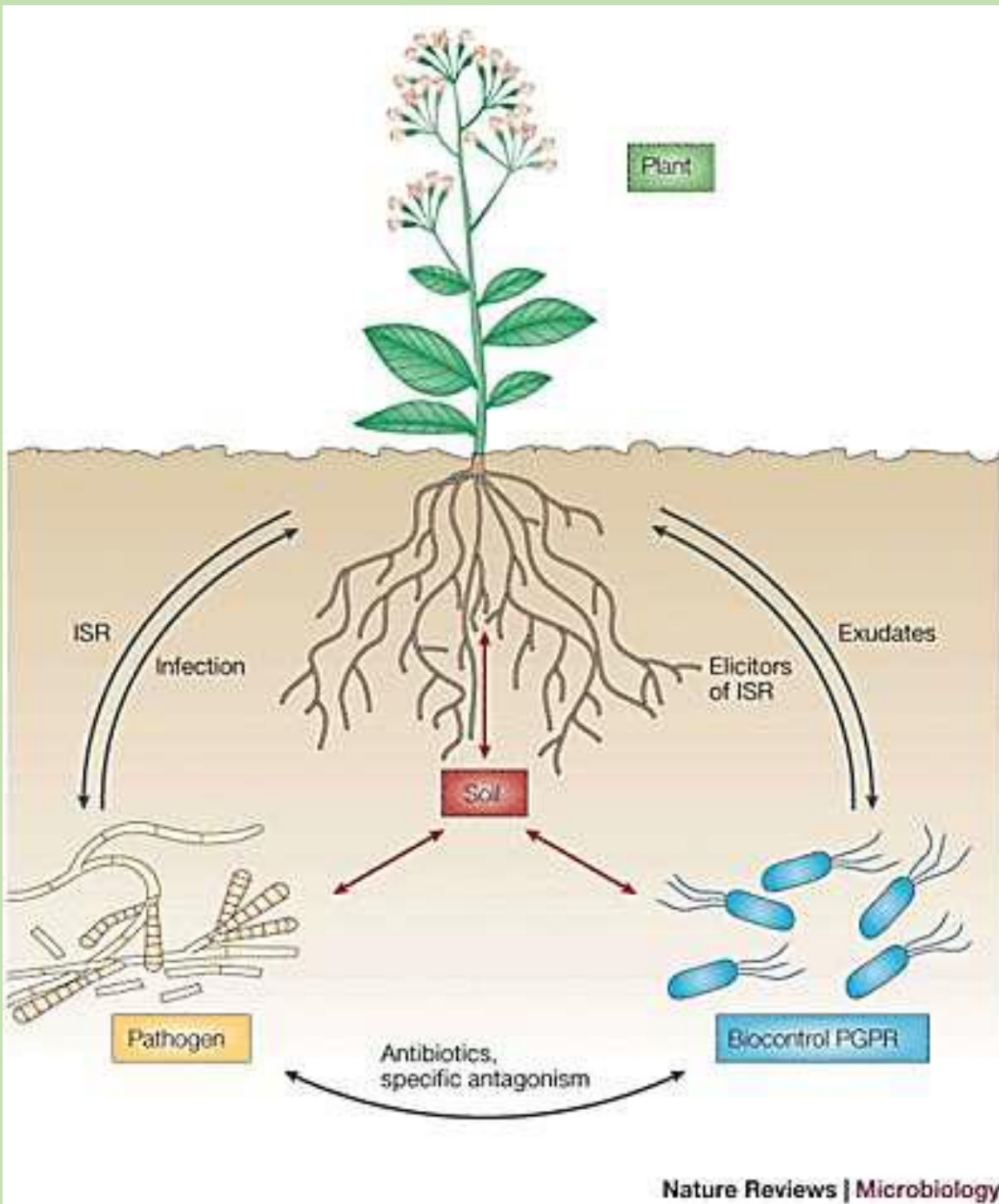
- Adding of flavourings in feeding stuffs improves feed smell/taste and/or palatability in order to:
 - Cover/mask variations in taste and smell caused by formulation changes
 - Mask the taste of unpalatable raw materials or additives
 - Improve early feed intake in young animals after weaning
 - **Brand differentiation of feeds, addiction effects, conditioning (!)**



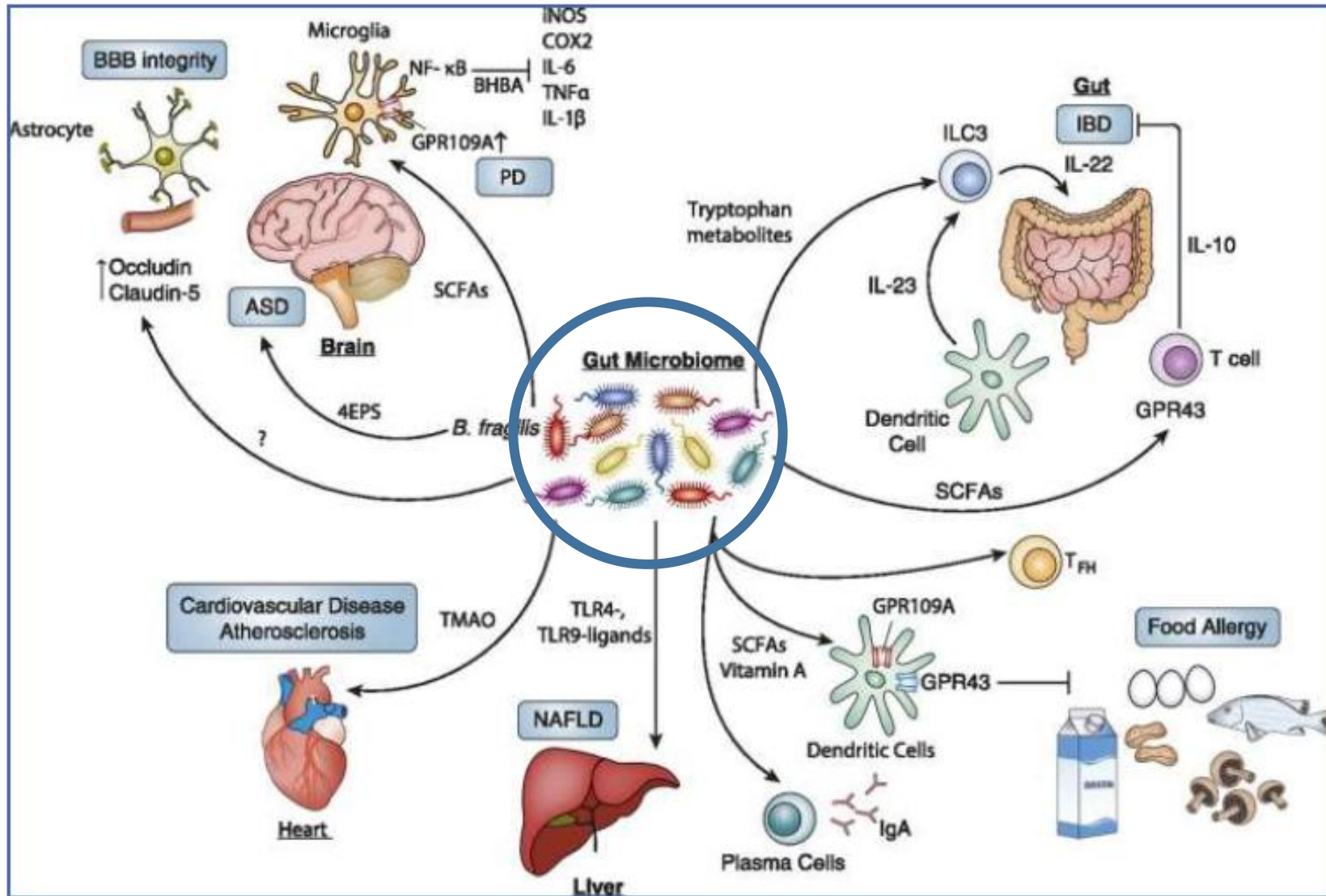
Claim 3: attività antimicrobica

**Plant metabolites:
Natural biocontrol of
microorganisms
– maintaining microbial
biodiversity**

***Metaboliti delle piante:
Controllo biologico dei
microrganismi mantenendo la
biodiversità microbica***

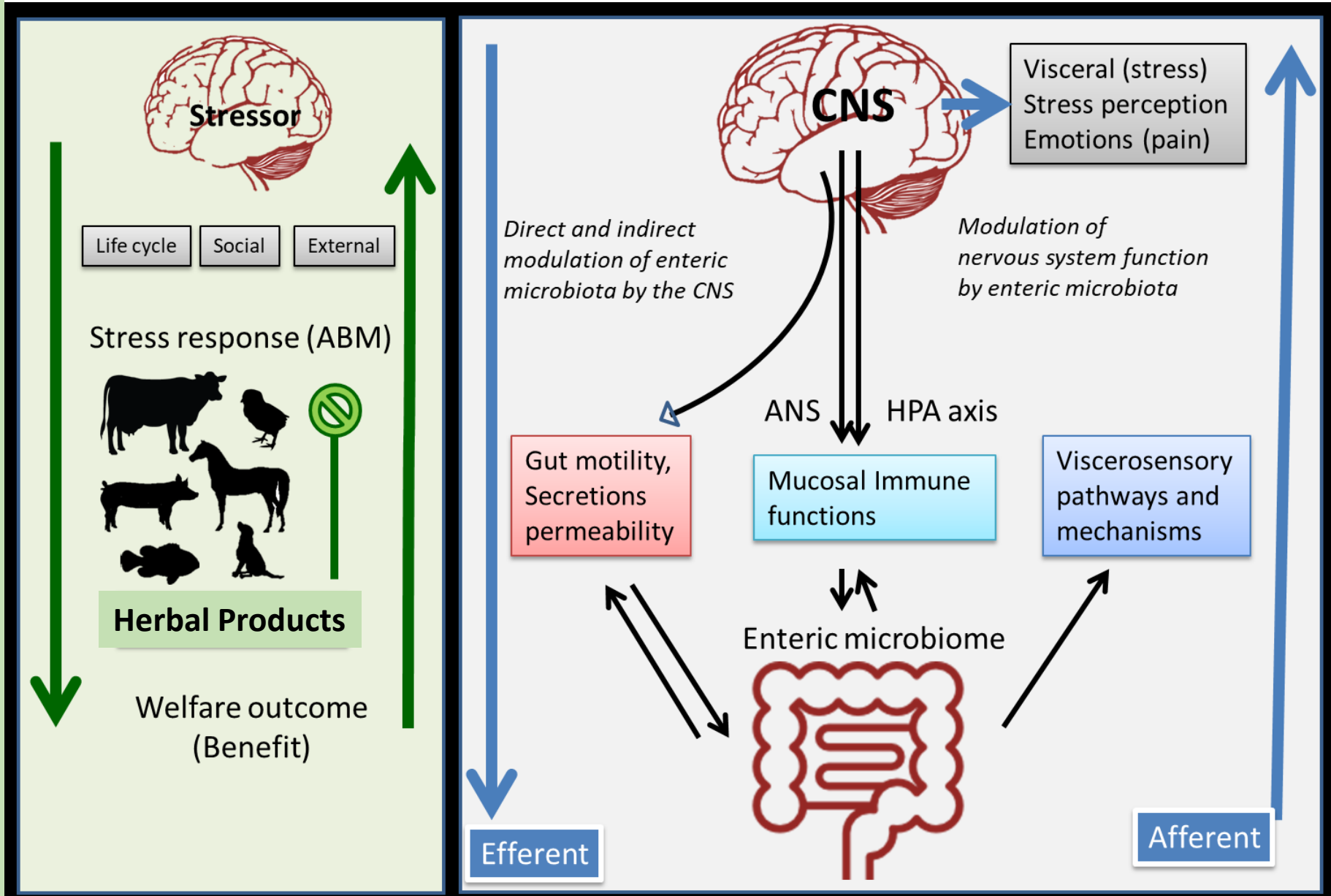


Gut – Microbiome:



The link between nutrition and health

Interactions between stress(factors) and intestinal functions: Where/how could herbal products / plant extracts act?

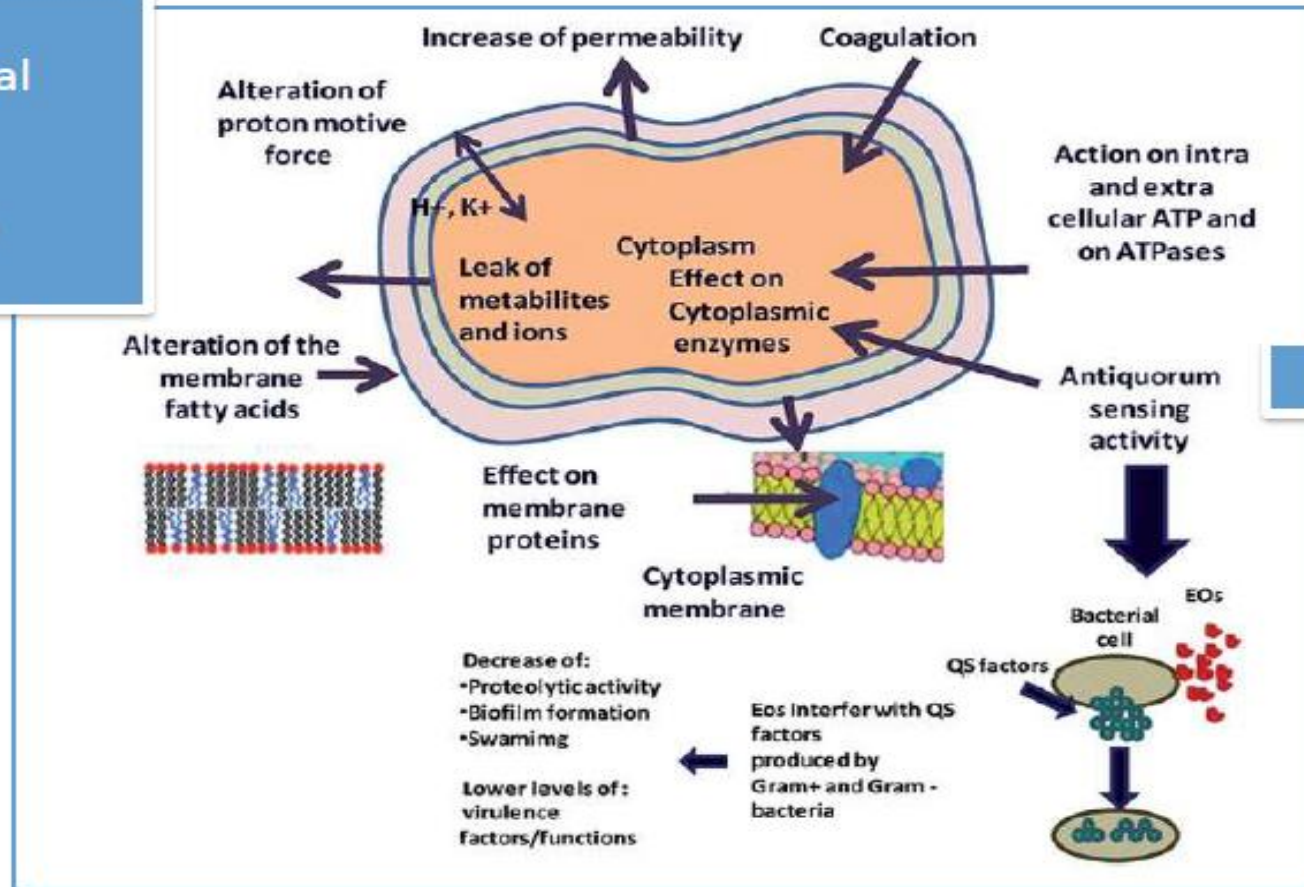


ABM: animal-based measures; ANS: autonomic nervous system; HPA – hypophysis-hypothalamus axis.

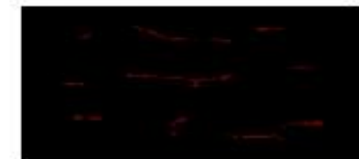
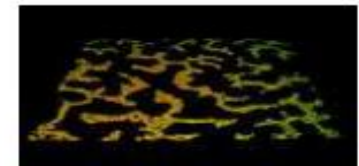
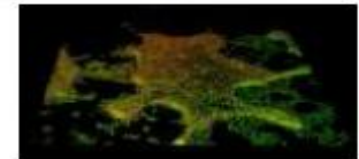
Phytobiotics – mild antibiotics with a multi-target mechanism of action



Mild antibacterial effects;
Antiadhesive
Anti-virulence factors



Anti-Biofilm



Minimum inhibitory concentration (MIC) of several essential oils and some compounds on selected microorganisms (in $\mu\text{L/mL}$)

(Pauli 1994, Deans 2000, Burt 2004, Penalver et al. 2005)

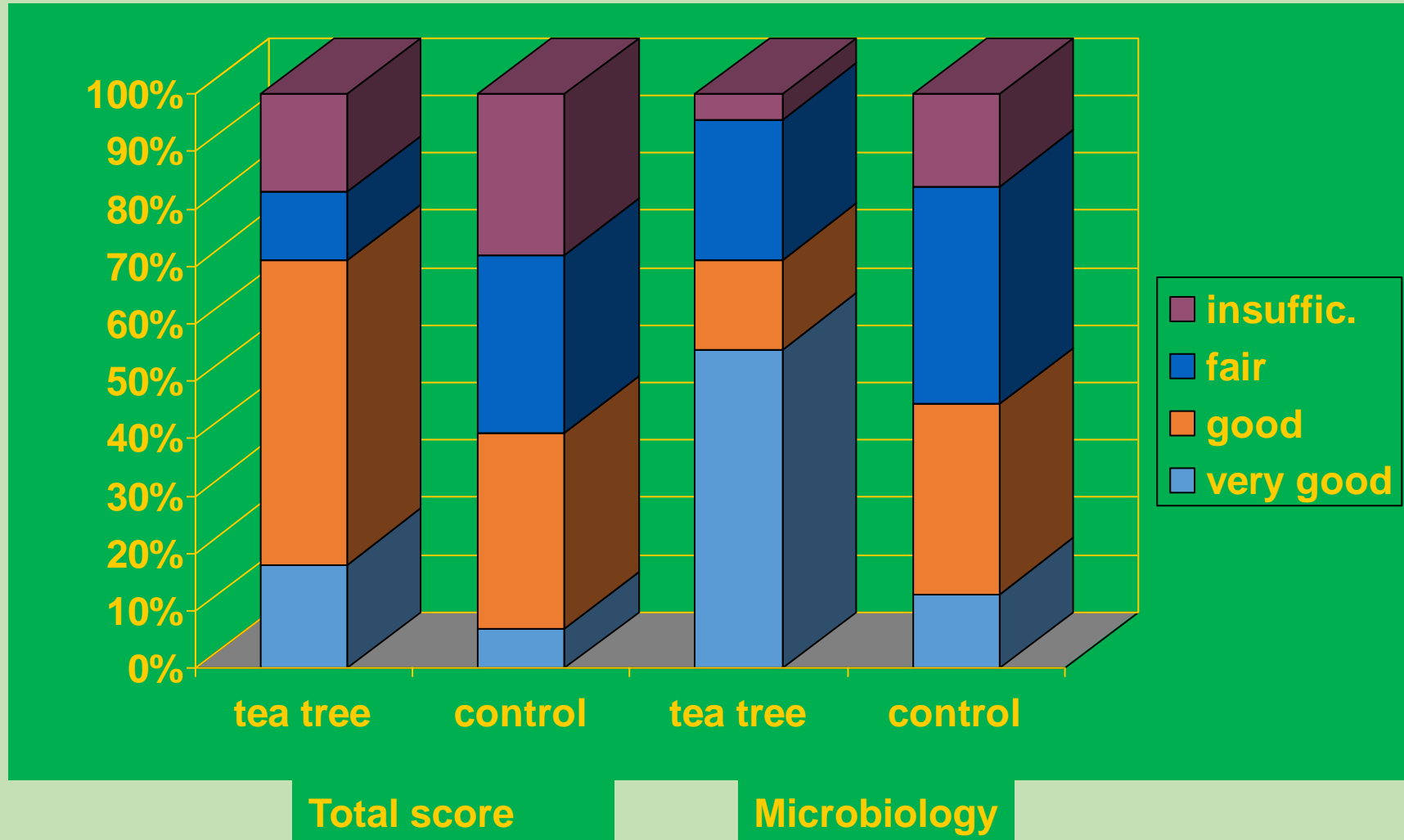
	<i>Escherichia coli</i>	<i>Salmonella typhimurium</i>	<i>Staphylococcus aureus</i>	<i>Listeria monocytogenes</i>	<i>Bacillus cereus</i>
Rosemary	4,5-10,0	>20,0	0,4-10,0	0,2	0,2
Sage	3,5-5	10-20	0,75-10	0,2	
Oregano	0,5-1,2	1,2	0,5-1,2		
Thyme	0,4-1,2	0,45-20	0,2-2,5	0,2-0,5	
Clove	0,4-2,5	>20,0	0,4-2,5	0,3	
Lemongrass	0,6	2,5	0,6		
Limonene	0,70				
Carvacrol	0,1-5,0	0,2-0,25	0,2-0,45	0,4-0,5	0,25
Thymol	0,10-0,45	0,06	0,17-0,25	0,20-0,45	0,35-0,45
Geraniol	0,15		0,35	1,25	0,35
Eugenol	0,55		0,75	0,55	0,30

Tea Tree Oil Treatment of Dermatitis – a randomised double blind study with dogs

(J. Reichling et al., Kleintiermed. 5/6, 145-149, 2004)

- 57 dogs with chronic dermatitis,
- Microbiology: *Staphylococcus aureus/intermed.* (30)
Malassezia pachydermatis (9)
- Randomised in race, age, sex
- Treatment: Tee tree oil ointment (10%) n=28
- Control: Standard hydroxybenzoate ointment n=29
- Duration: 20 d

Tea Tree Oil Treatment of Dogs Suffering from Chronical Dermatitis (Reichling et al. 2004)



Effect of *Thymus*- and *Origanum* Oil on *E. coli*-Isolates

(Jugl-Chizzola et al., 2003)

E.coli Isolates	O 147 K 89	O147 K 85	O 149 K 91	O139 K 81	O 147 K 91	O 138 K 81
Agar-diff.-test	mm inhib.					
<i>Thyme oil</i>	10	9	10	9	9	10
<i>Oreg.-oil</i>	11	10	11	9	10	10
MIC / MBC	conc. %					
<i>Thyme oil</i>	0,31	0,31	0,31	0,31	0,63	0,63
<i>Oreg.-oil</i>	0,16	0,16	0,16	0,16	0,31	0,31

Effetto di Pectine idrolizzate sullo Stato di Salute di Suinetti: la „Carrot Soup Story“ (Jugl et al. 2002)

**Alimentazione con pectine da carota (0,1% of the diet,
materiale: boiled dried carrot chips)**

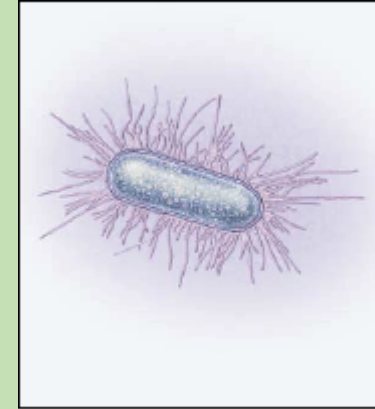
Suinetti: n = 183

	Diarrea	senza Diarrea
Controllo	50 %	50 %
Tylosinphospat	24.6 %	75.4 %
Pectine (gal.-ac.)	14.7 %	85.3 %

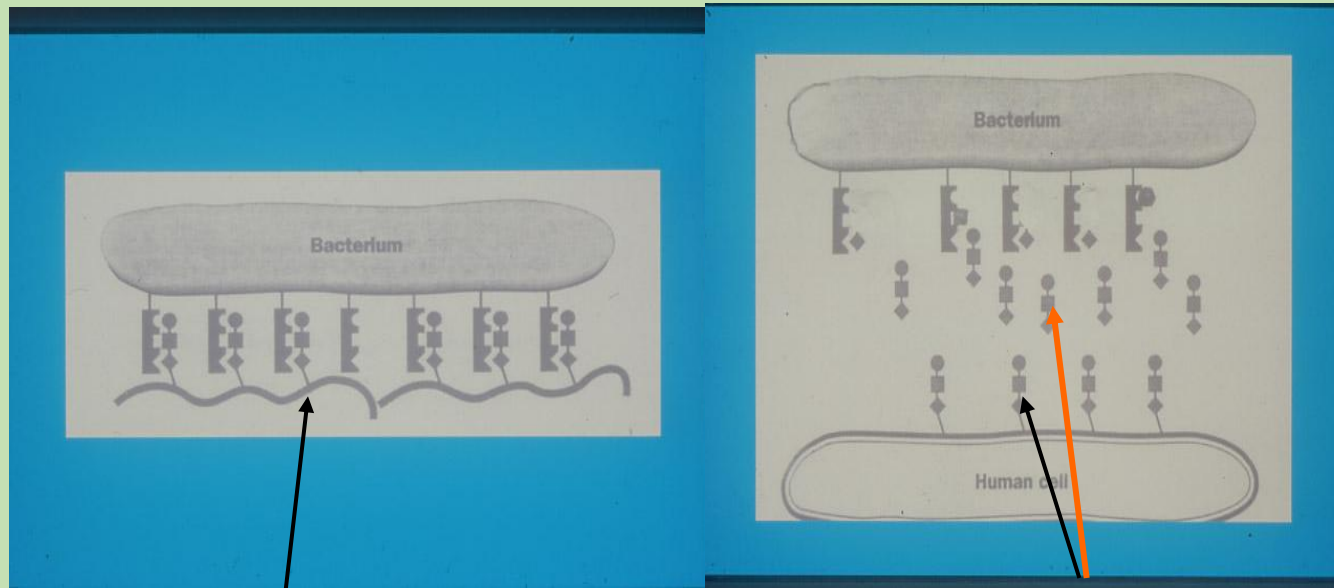


Microrganismi con potenziale adesivo ai carboidrati (Guggenbichler & Jurenitsch, 2004)

- *E. coli* (ETEC, EPEC, EHEC, fimbrious *E. coli*)
- *Salmonella* spp.
- *Klebsiella* spp.
- *Enterobacter* spp.
- *Aeromonas hydroph.*
- *Helicobacter*
- *H. influenzae*
- *S. pneumoniae*
- Meningokokki
- *B. pertussis*
- *C. albicans*
- Rotaviruses



E. coli

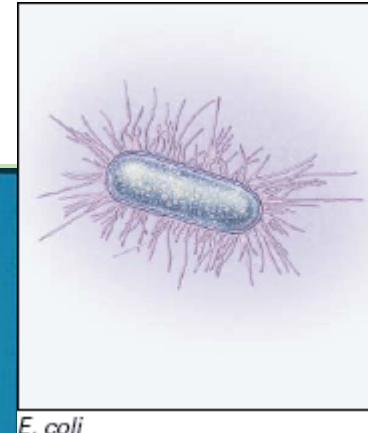


Receptor at epithelial cells: Glykolipid with 1 molecule Glucose and 3 molecules Galactose in Globoserie

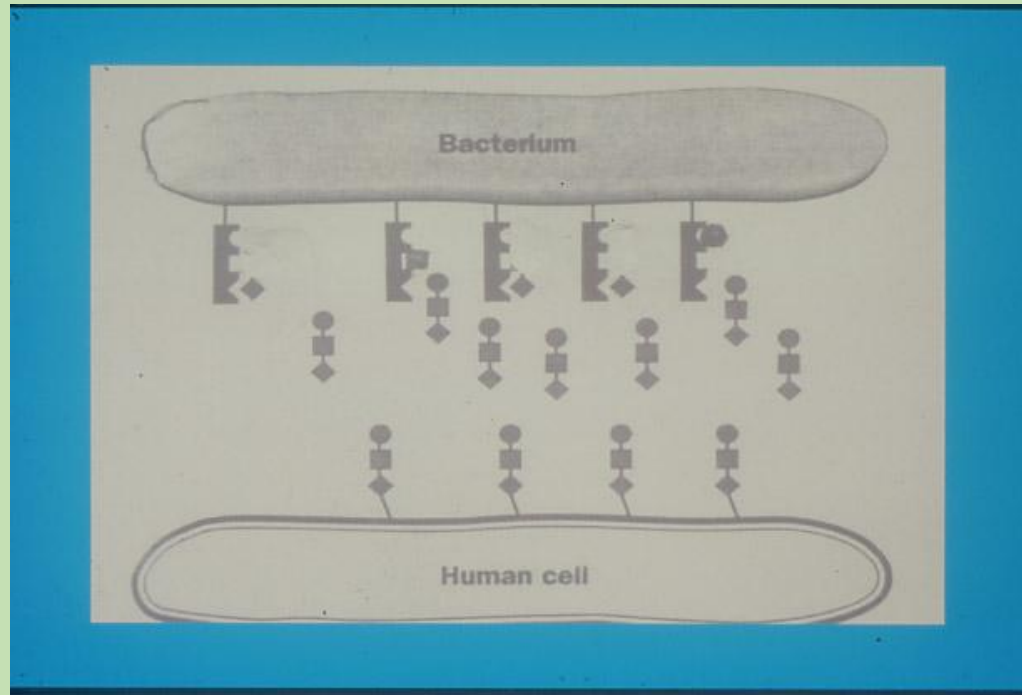
Da Moro's Zuppa di Carota a Immunonutrizione

Oligosaccaridi (acidi glucuronici, prodotti da idrolisi della parete cellulare di piante) sono capaci di impedire l'adesione dei batteri all'epitelio intestinale legandosi ai recettori presenti su flagelli/fimbrie

Guggenbichler 2002

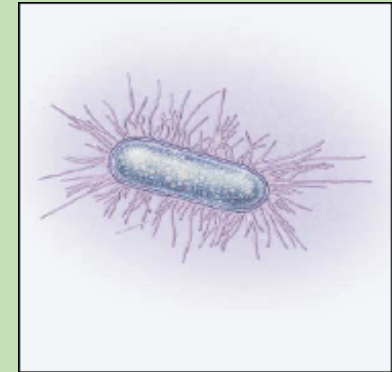


E. coli

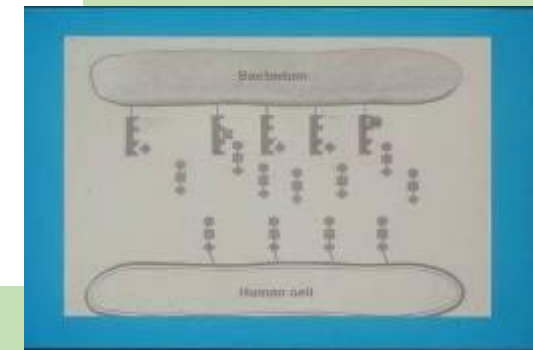
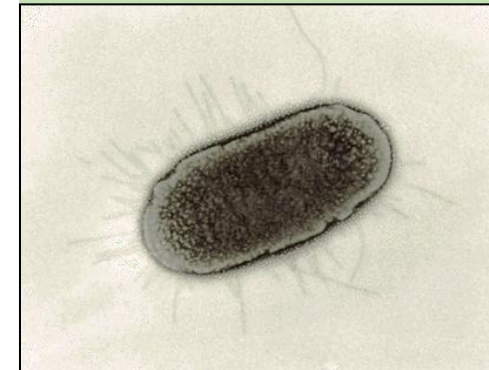


Ragioni per il legame/ distruzione dei microorganismi:

- Distruzione delle membrane delle cellule (oli ess. e altre sost. second.)
- **Interferenza di componenti degli oli ess.**
Nel processo di formazione delle fimbrie batteriche
- **Inibizione della adesione alla mucosa intestinale mediata da „competitive binding“**
- **Analogia all'effetto della zuppa di carota (pectine/acidi galatturonici)**



E. coli



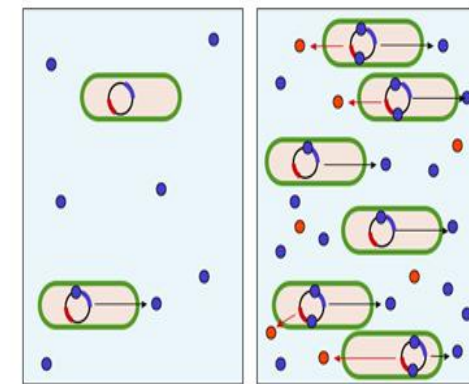
Quorum Sensing Inhibition (QSI)

- **Quorum Sensing:** capacità dei micorganismi di percepire la densità della popolazione batterica mediante comunicazione chimica. Alcuni geni sono attivati soltanto quando una certa densità cellulare è raggiunta (espressione del gene di virulenza come risposta a molecole segnale, risultati: e.g. motilità, adesione, sintesi delle tossine)
- **Quorum Sensing Inhibition:** Interferenza con QS e soppressione della virulenza batterica, e.g. tra oli essenziali/componenti (carvacrolo,...)

(Khan, M.S. et al., Lett. Appl. Microbiol. 2009;

Müller, A.S., Plan A – Performing Nature

Sympos. Bangkok 2014)



Cellule bassa densità:
solo molecole segnale

alta densità:
anche tossine

Quorum sensing inhibition (QSI): The domain of herbal medicines



Inhibition of major Autoinducers

Gram +

agr (RNAIII)- auto-inducing peptides (AIP)

Proto type: TP-1

Hamamelitannins = inhibitors of MRSA & MRSP

Gram –

Acyl-homoserine lactones (AHL) → LuxR

Proto type: **SAM-analogues, Cranberry!**



QS-inhibitors



ADHESION &

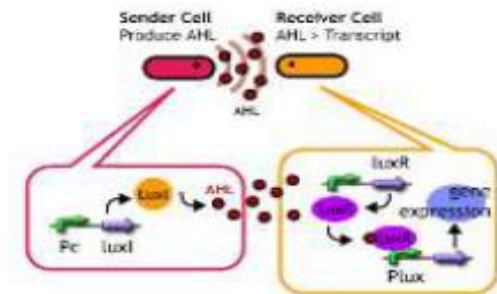
Expression of virulence factors inhibited



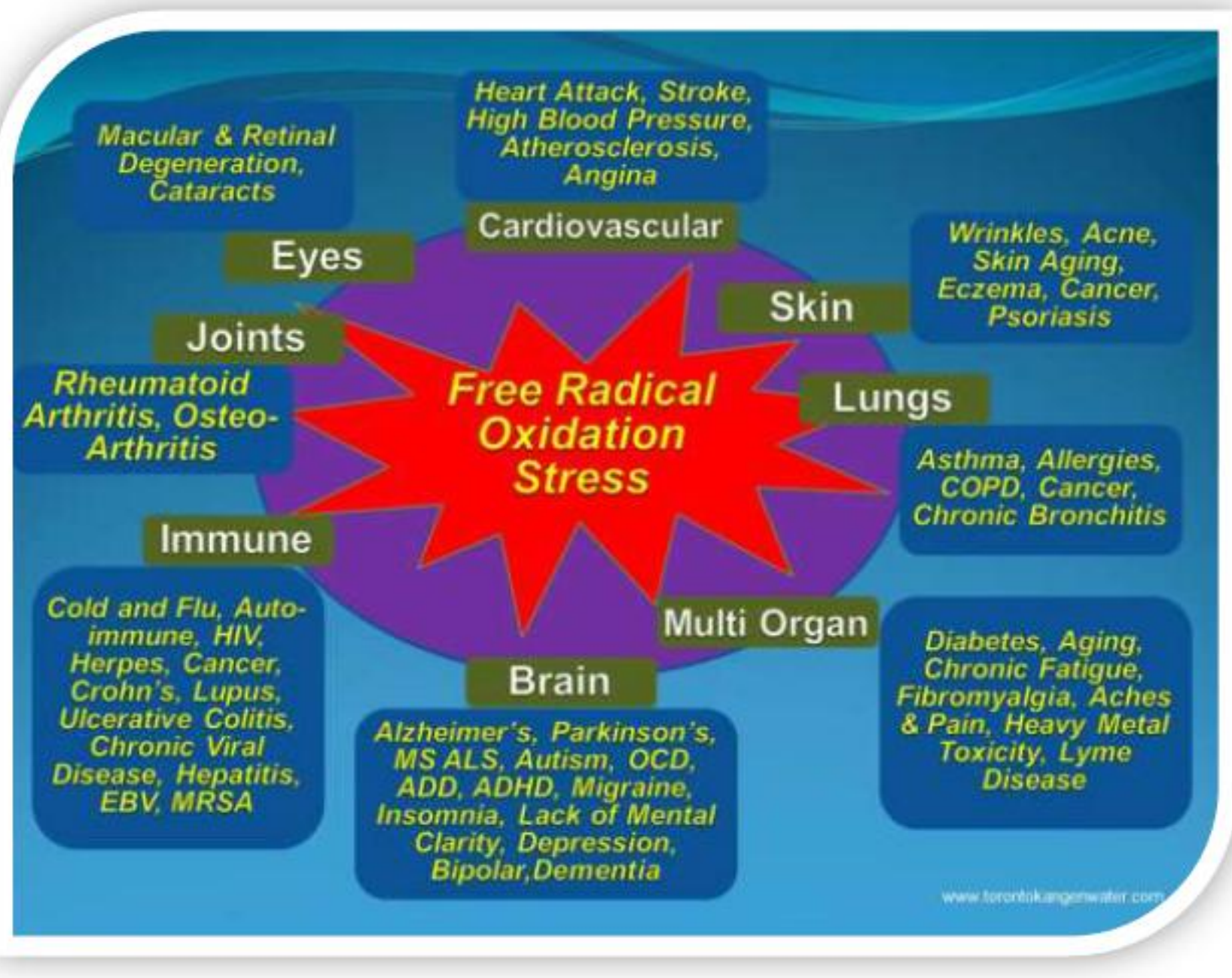
Interspecies communication: *LuxS/AI-2* signaling

Inter-kingdom signalling: AI-3/epinephrine/norepinephrine

i.e. Salmonella, E. coli, Shigella a.o.



Claim 4: attività antiossidativa



Reduction of oxidative stress – a typical benefit of many herbal Products

Riduzione dello stress ossidativo – Un effetto benefico tipico di molti preparati vegetali

Inflammation: first sign of oxidative stress, but not yet a sickness!



Influence of Bronchipret® on the pulmonar function of horses suffering from RAO (Recurrent Airway Obstruction)

(van den Hoven et al. ,
Vet. Record 2003)

- | Parameter | PRE treatment | AFTER treatment | P |
|--|---------------|-----------------|--------|
| • Max. Intrapleural pressure (cm H ₂ O) | 17,10 (7,80) | 11,70 (5,20) | < 0,01 |
| • Dynamic Compliance (cm H ₂ O/l) | 1,02 (0,36) | 1,53 (0,85) | < 0,01 |
| • Pulmonary resistance (cm H ₂ O/l/s) | 1,17 (0,57) | 0,72 (0,30) | < 0,01 |
- **Result:** >Thyme extract improves the lung function significantly <

Improvement of the pulmonary function of horses suffering RAO after treatment with Sinupret®

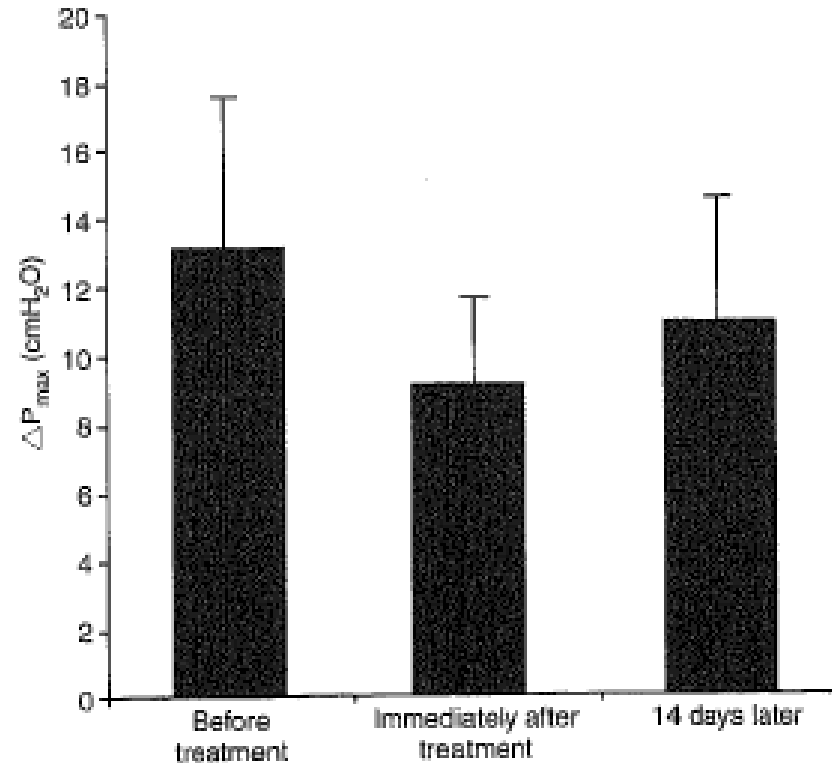


Figure 1: Mean (sd) maximal intrapleural pressure difference ΔP_{max} of five horses (group 1) before treatment with the botanical preparation, immediately after 14 days' treatment, and 14 days later

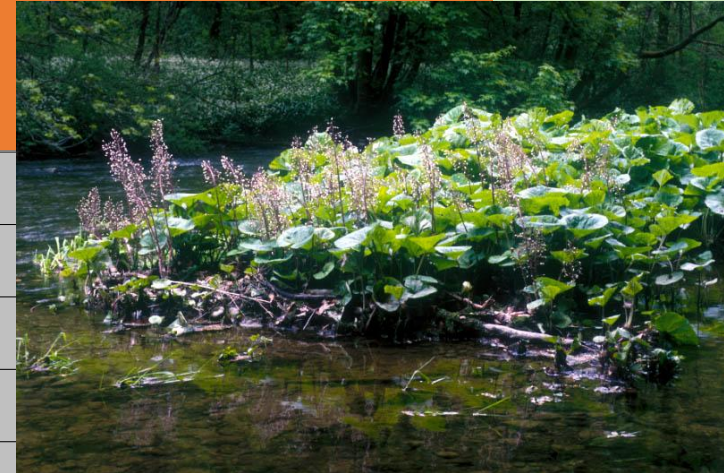
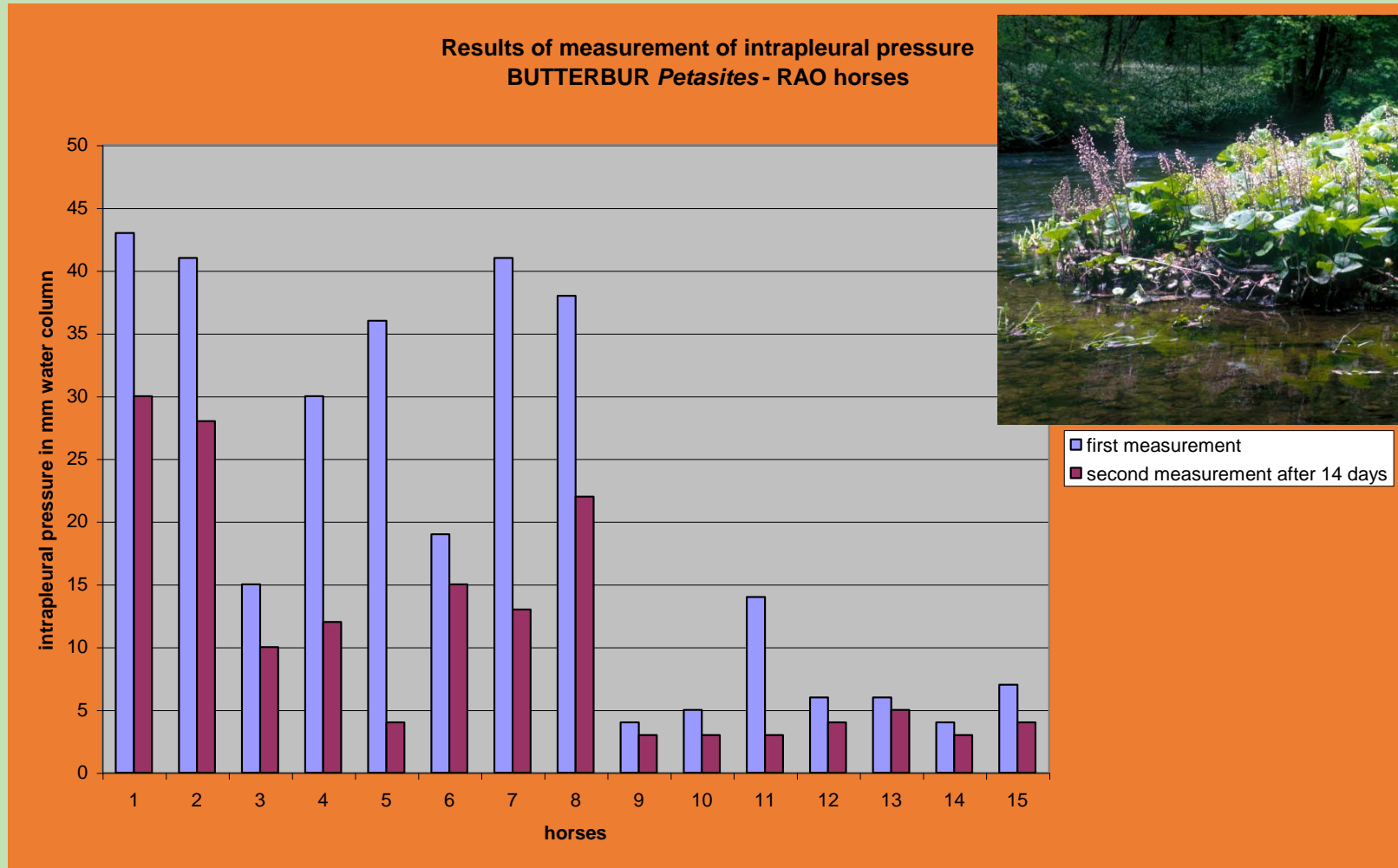
Treatment of horses suffering from RAO (COPD) with a *Petasites hybridus* extract (Ze 339)

(Pommer, E. et al.: WTM – Veterinary Medicine Austria 104 (2017))

- Orally administered extracts of butterbur are a popular treatment option for equine asthma syndrome in veterinary practice, despite the fact that none of these preparations are registered as phytopharmaceutical products for horses.
- The aim of the present study was to establish a sensitive LC/MS/MS method for measurement of petasin, isopetasin and neopetasin in plasma and urine as markers for the active constituents of a *Petasites hybridus* preparation.

Treatment of horses suffering from RAO (COPD) with a *Petasites hybridus* extract (Ze 339)

dosage: 25 tabl./d = 200 mg petasin/d



■ first measurement
■ second measurement after 14 days

Rhizomes:

Petasines,
antiallergic,
spasmolytic,
analgesic

Inhibition of Spontaneous Canine Benign Prostatic Hyperplasia by an *Urtica fissa* Polysaccharide Fraction

Chen X et al. Inhibition of Spontaneous... Planta Med 2015; 81: 10–14

Table 1 Dog prostatic volume change after three months *U. fissa* polysaccharide fraction treatments measured by CT scanning.

Groups	Age	Weight (kg)	Prostate volume (cm ³)		
			Before treatment	After treatment	Volume change (%)
Control	9.3 ± 2.1	14.5 ± 2.1	14.05 ± 1.73	14.41 ± 1.76	+ 0.36 ± 0.70 (102.69)
Finasteride (0.5 mg)	8.0 ± 1.1	13.7 ± 0.9	14.68 ± 2.73	10.34 ± 2.08 [#]	- 4.34 ± 1.12 ^{***} (70.47)
UFP (30 mg)	8.2 ± 2.0	14.0 ± 1.1	13.59 ± 2.90	12.79 ± 3.15	- 0.80 ± 0.58 [*] (93.54)
UFP (60 mg)	8.7 ± 1.8	14.9 ± 2.5	13.83 ± 1.53	12.45 ± 2.06	- 1.39 ± 0.62 ^{**} (89.52)
UFP (120 mg)	7.5 ± 1.4	14.0 ± 1.3	15.08 ± 2.74	11.45 ± 2.40 ^{*#}	- 3.63 ± 1.05 ^{***} (75.72)

Six dogs in each group; [#] p < 0.05: after 3 months treatment vs. before treatment. ^{*} p < 0.05, ^{**} p < 0.01, ^{***} p < 0.001: treatment groups vs. control group

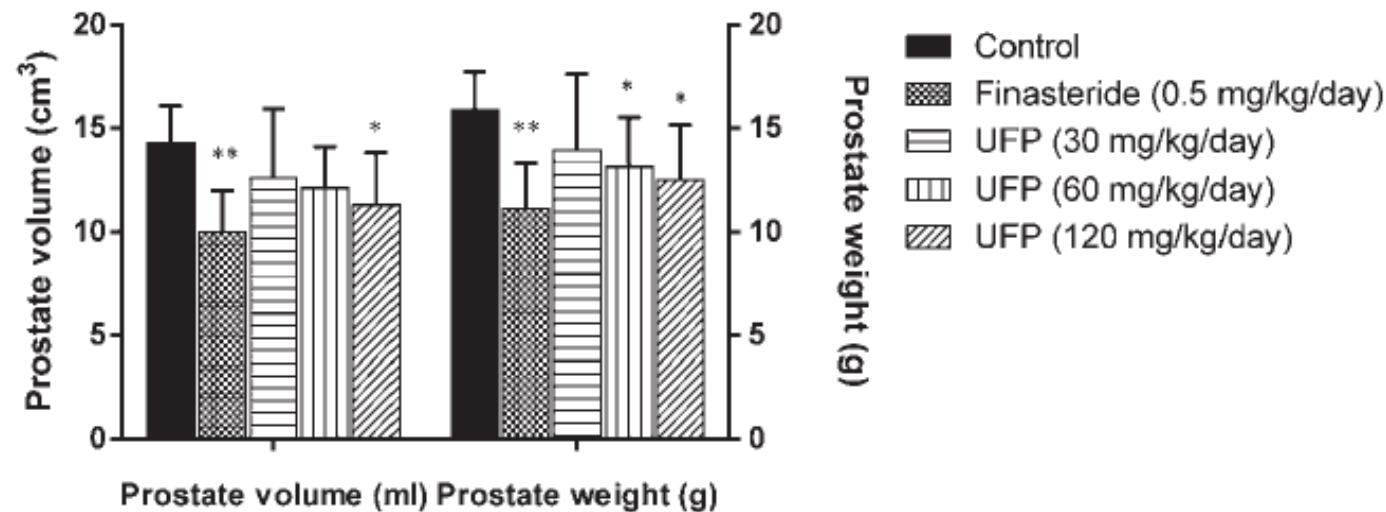


Fig. 1 UFP inhibition on dog prostatic volume and weight after three months treatment measured by water displacement. Six dogs in each group. ^{*} p < 0.05, ^{**} p < 0.01: treatment groups vs. control group.



***Cucurbita pepo* var. *styriaca*:**
Extracts of pumpkin seeds frequently used
for the treatment of BPH in humans
(due to the content of phytosterols)



Influsso dell'estratto di semi di zucca sulla iperplasia benigna della prostata in cani

<u>Dog-Race</u>	<u>Age</u> (years)	<u>Weight</u> (kg)	<u>Main symptoms</u>	<u>Start-dose</u> (x tabl./day)	<u>After x month</u> [dose]	<u>Improvement</u> after x weeks
Bernese mountain	5,5	45	blood in ejaculate	1	2 [1/week]	4
Bernese mountain	5,5	45	blood in ejaculate	1	2 [1/week]	4
Groenendal	3	25	micturition + defecation difficult	1	-	6
Bernese mountain	6,8	58	blood in urine	1	3 [2/day]	4
Basset	7	28	blood after ejaculation	1	1 [2/day]	12
Wire-haired dachshund	11,5	9,5	blood after ejaculation	1	5 [2/day]	4
Wire-haired dachshund	7,5	9,5	blood after ejaculation	1	5 [2/day]	4
Beagle	5	5	blood after ejaculation	2	-	12

High compliance since symptom improvement was noticed after 1 – 3(!) months

(Schäfer-Somi et al. 2004)

Joint Pain and Improvement of Motility

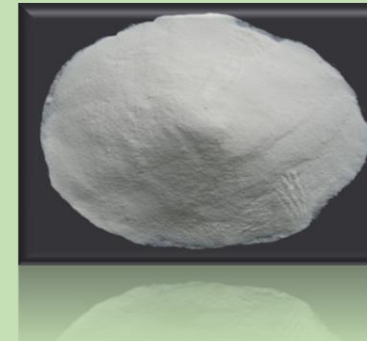
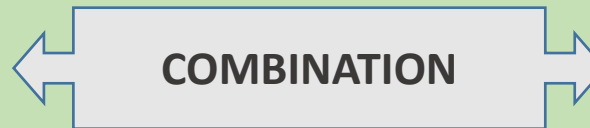
1. Rose Hip Special Extracts

2. Cannabis and CBD

A purified rose hip extract – effective in a new joint health concept



Rose Hip extract



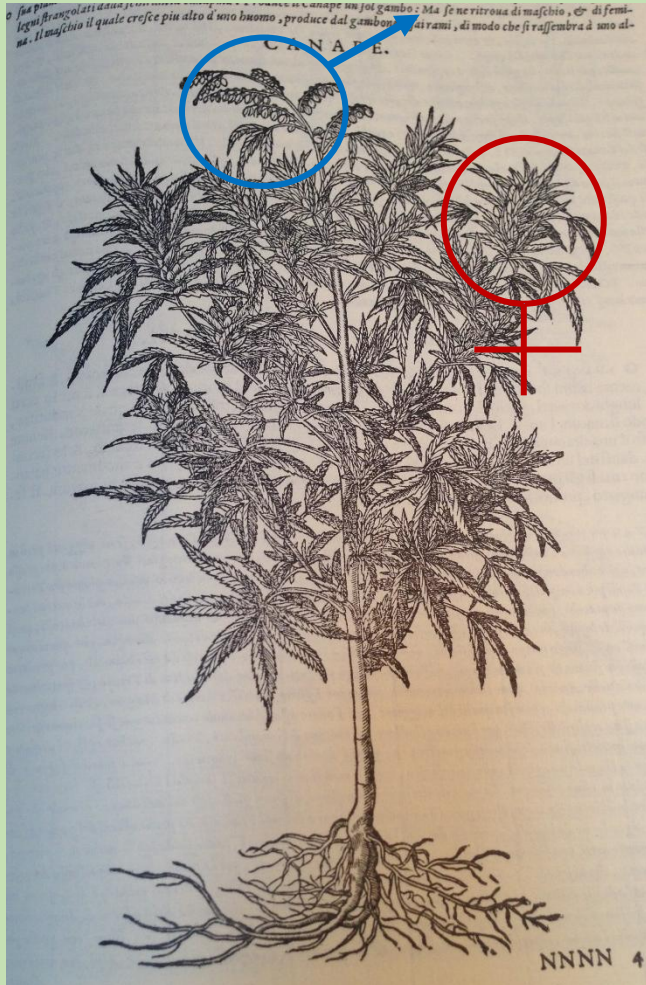
Collagen hydrolysate

Three different extracts:

- Water extract (A)
- Ethanol 70% v/v extract (B)
- Ethanol 35% v/v extract (C)

- Enzymatically hydrolyzed collagen
- Collagen specific amino acids: OH-proline, proline, OH-lysine, glycine
- Decreases joint pain and stimulates production of collagen

Cannabis sativa L. (Cannabaceae): Botany and specific characteristics



Cannabis sativa ssp. sativa

a) fiber hemp

b) drug hemp

Cannabis sativa ssp. spontanea

Cannabis indica ssp. indica

Cannabis indica ssp. kafiristanica

annual herb, dioecious **m/f**

„Short-day-plant“,

Easily propagated vegetatively!



Cultivation of fiber hemp (Westeurope)

***Cannabis sativa*: dioecious, i.e. female and male plants**



**Female flowers:
spike, with resin and
essential oils**

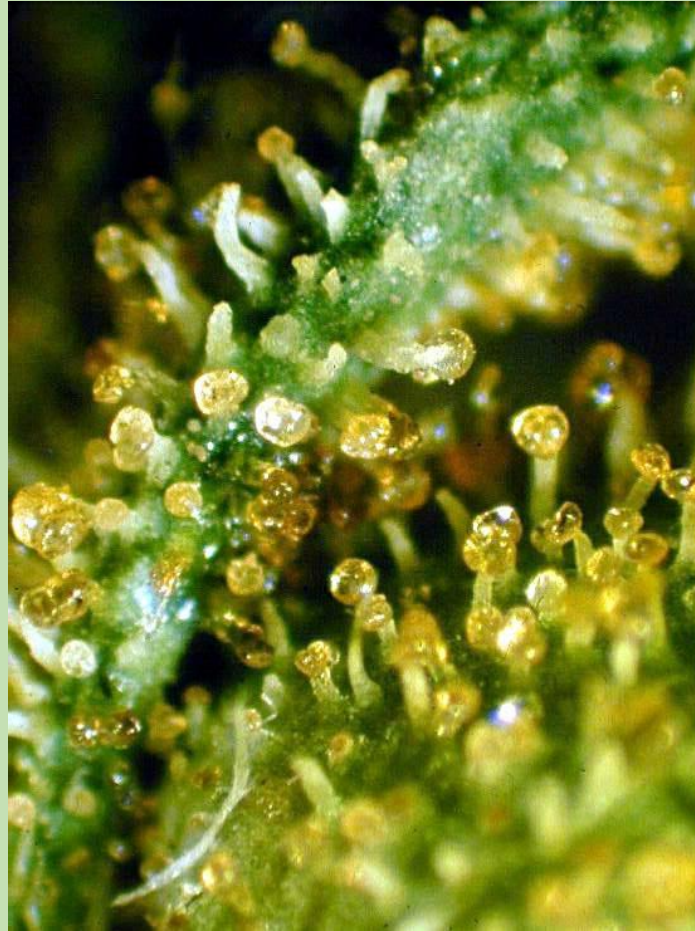
dry: „Marijuana“

**male flowers:
panicle with pending
anthers**

Hemp, *Cannabis sativa* L.: Secondary substances and activities



Cannabinoids and essential oil



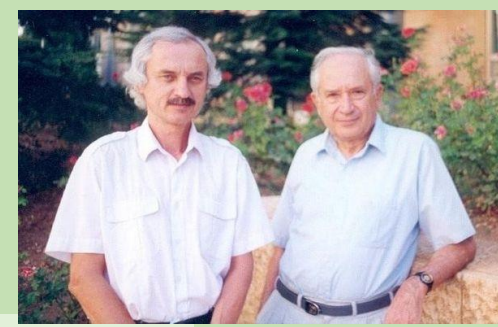
The essential oils of five different cultivars of *Cannabis sativa* contained as main compounds α -pinene, myrcene, trans- β -ocimene, α -terpinolene, trans-caryophyllene and α -humulene.

J. Novak et al., FFJ **16**, 259-262 (2001)

Up to date more than 110
Phytocannabinoids in *C. sativa* elucidated,
they belong to terpenphenolics

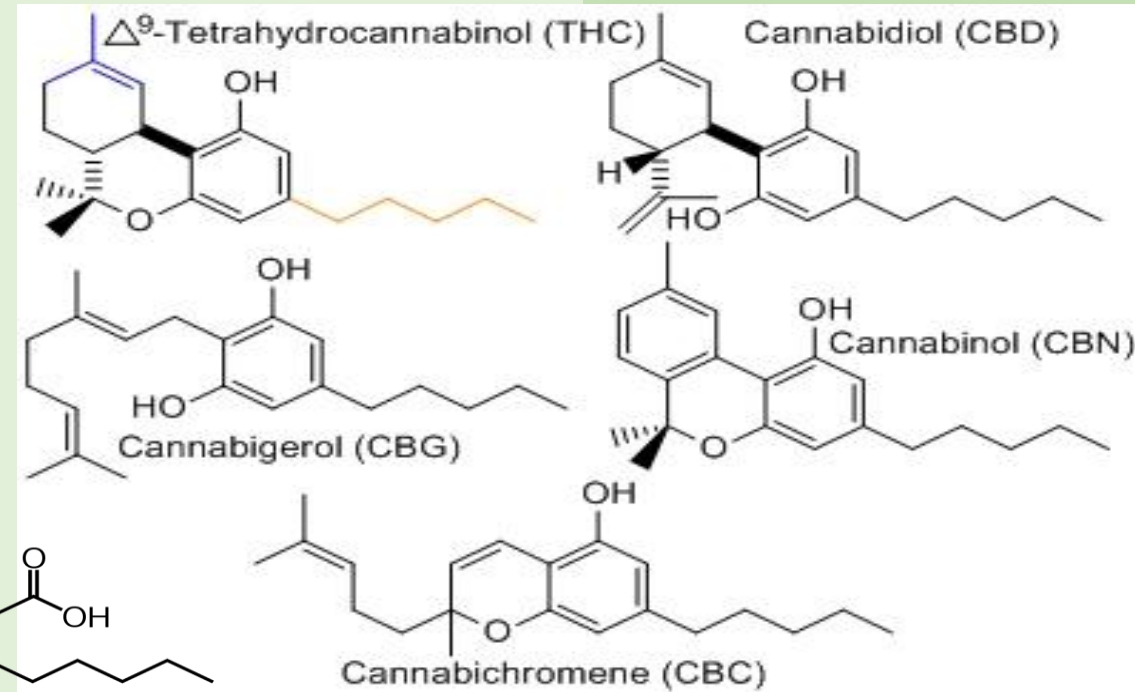
R. Bauer, HMPPA-Konf. (2018)

Cannabis sativa: Compounds

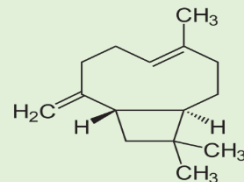


Yehiel Gaoni und Raphael Mechoulam (1965)

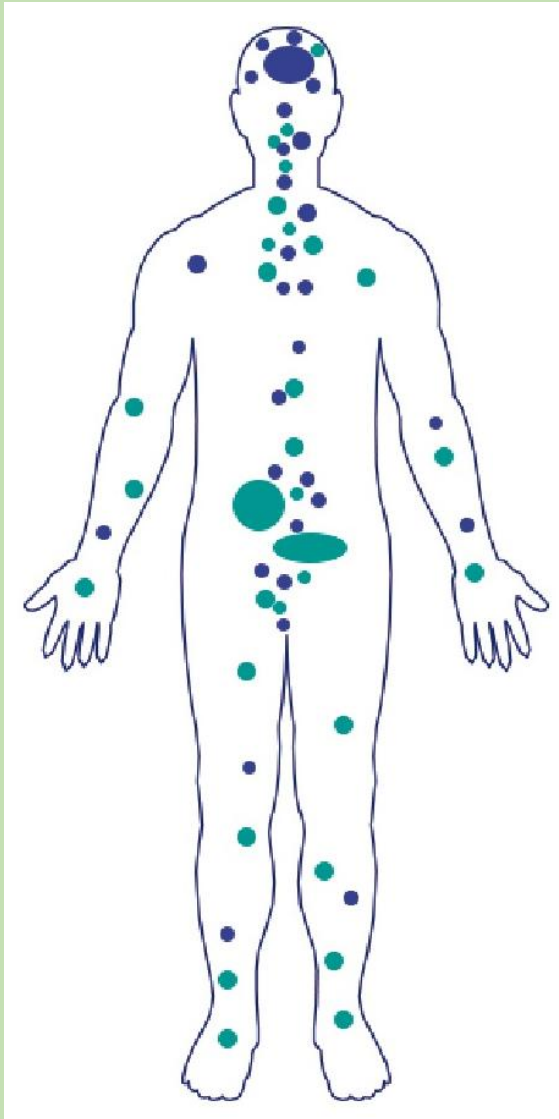
- 113 different **Cannabinoids** belonging to Terpenphenolics
- 0,1-25 % **Δ^9 -Tetrahydrocannabinol (THC)**
INN: Dronabinol
- **Δ^9 -Tetrahydrocannabinolacid (THCA)**
(= precursor; 90 % of total THC)
- 0,1-2,9 % **Cannabidiol (CBD)**
- 0-2,6 % **Cannabinol (CBN)**
- 0-0,65 % **Cannabichromene (CBC)**
- ca. 120 terpenes (essentil oil);
i.a. β -Caryophyllene
- Flavonoids, etc.



Δ^9 - tetrahydrocannabinol acid (THCA)



The Endocannabinoid-System



CB1

Receptors mainly in nerve cells of the brain, but also in the intestine

Hypothalamus: Appetizer

Amygdala: Memory and emotions

Nerve ends / neurons: pain (to be controlled by analgesics)

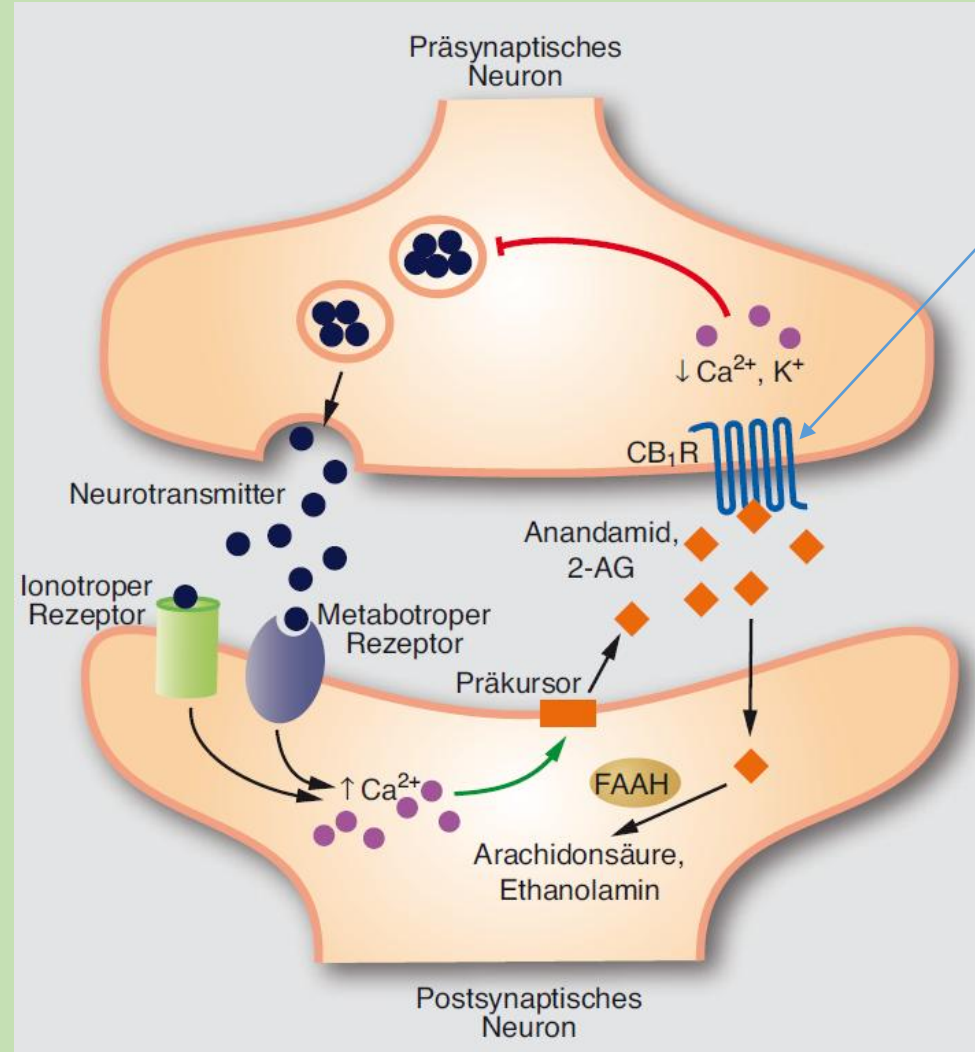
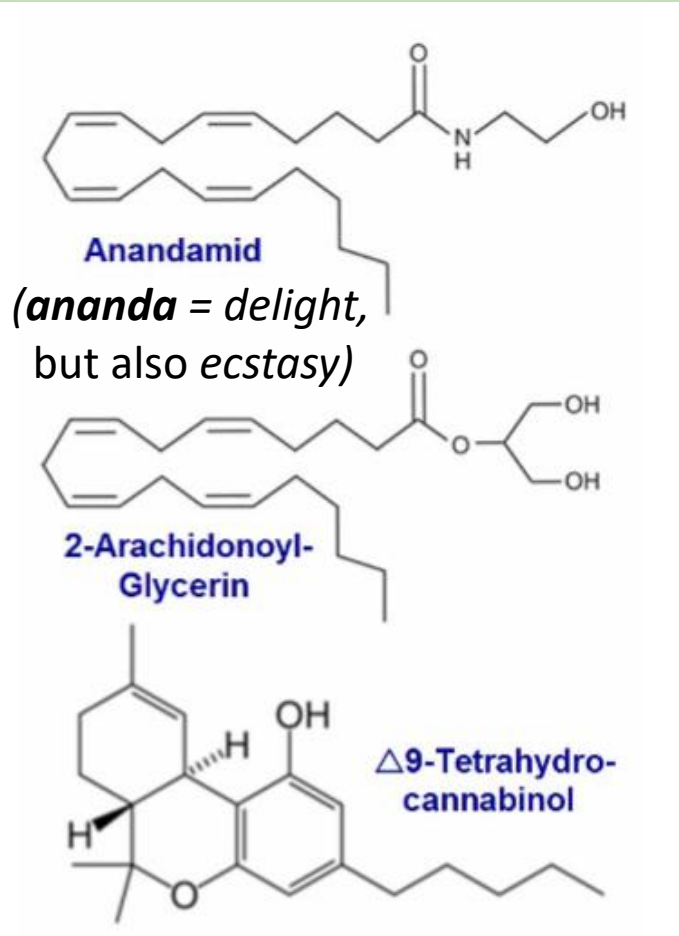
CB2

Receptors mainly in the immune system and peripheral cells

Endogenous Ligands:

- **2-AG** (2-Arachidonoyl glycerin): Highest concentration in the brain
- **Anandamid** (Arachidonylethanolamid): Higher Concentrations in peripheral parts of the body (distant from brain)

The Endocannabinoid-System



Activation of the CB₁-Receptor
 ↓
 Inhibition of potential depending Ca-channels (Voltage-gated calcium channels, VGCC) and inhibition of the adenylate cyclase
 ↓
 Blockade of the liberation of neurotransmitters (i.a. Glutamate)
 ↓
 Inhibition of the excitability of Post synaptic nerve cells
 ↓
e.g. analgetic activity

Effects of THC, THC acid and CBD on MPP+ or glutamate affected dissociated mesencephalic cultures of mice

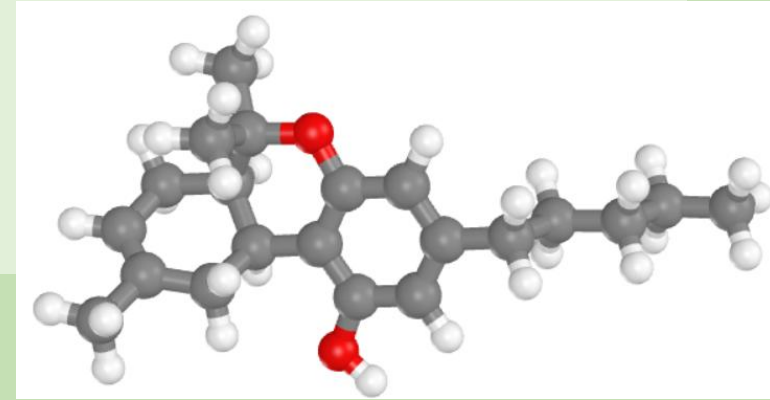
Moldzio, R; Krewenka, C; Kolmanz, C; Duvigneau JC; Pacher, T; Novak, J; Rausch, WD.: Planta med. (2012)

„Phytocannabinoids support the cell survival in glutamate treated cultures significantly already at low concentrations.

Cannabinoids might be candidates for neuroprotective agents in disorders in which excitotoxicity and oxidative stress occur.“

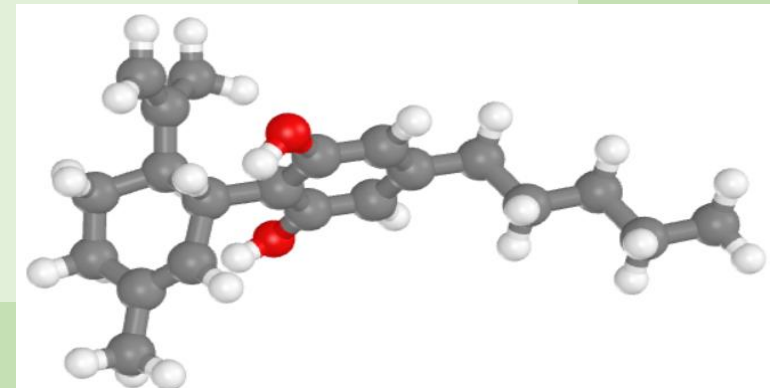
Activities of Δ 9-Tetrahydrocannabinol (THC)

- Binding on Cannabinoid-Receptors (partial agonist of CB1 and CB2)
- analgesic, antiinflammatory, muscle relaxant
- antiemetic, appetizing
- **Psychotropic!!**



Activities of Cannabidiol (CBD)

- **not psychoactive!** Antagonist of the Cannabinoidreceptor GPR55 (antiinflammatory and analgesic)
- Blocking the decay/metabolism of Anandamid
- Blocking Ca-channels
- anxiolytic



Hemp, *Cannabis sativa* L.: Actual situation and application



Cannabidiol:

**A new option
for pets in
pain?**



Functional Plant Products and Animal Nutrition

European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003

Annex I: List of additives

(Released date 15.11.2018)

Edition 19/03/2019

DIRECTORATE-GENERAL FOR HEALTH AND FOOD
SAFETY

Directorate E - Food and feed safety, innovation
Unit E5 - Animal nutrition, veterinary medicines



The image shows the cover of the 'Community Register of Feed Additives' document. At the top, there are logos for the European Commission, ToGethé (Since 1957), and the Health & Consumer Protection Directorate-General. The main title is 'Community Register of Feed Additives pursuant to Regulation (EC) No 1831/2003'. Below this, it specifies 'Appendixes 3 & 4. Annex : List of additives' and includes the status '(Status: Released 30 June 2009.)'. A yellow box on the right side of the cover contains the text: '2010: almost 300, 2019: less than 200 Notifications of plant extracts and ess. Oils (Abies ... Zingiber)'. At the bottom of the cover, there are several small images: a chicken, a pig, a sheep, a cow, and a bowl of feed. There are also some decorative icons at the very bottom of the page.

EU Feed Material Register: of **Cannabis...**

...are used the **inflorescences** and the **leaves** of this plant. The **CBD (cannabidiol)** is one of the three active ingredients, has no psychotropic effects and has anxiolytic effects, antipsychotic effects and analgesic effects. Scientific studies have shown that cannabis produces cannabinoids capable of interacting only with the human endocannabinoid system

(Eintrag Nr. 07518 v. 2018-05-04)

*...but this is the Product-Register of the EU-feed-/-additives-)
Industry only!*

Efficacy of Cannabidiol for the Treatment of Osteoarthritis and of Epilepsy in Dogs

- Dr. Stephanie McGrath, neurologist and assistant professor at Colorado State University's College of Veterinary Medicine & Biomedical Sciences



Pharmacokinetics, Safety and Clinical Efficacy of CBD- Treatment in Osteoarthritic Dogs

L.-J. Gamble et al.: Front. Vet. Sci. 23 July 2018, 15 p.

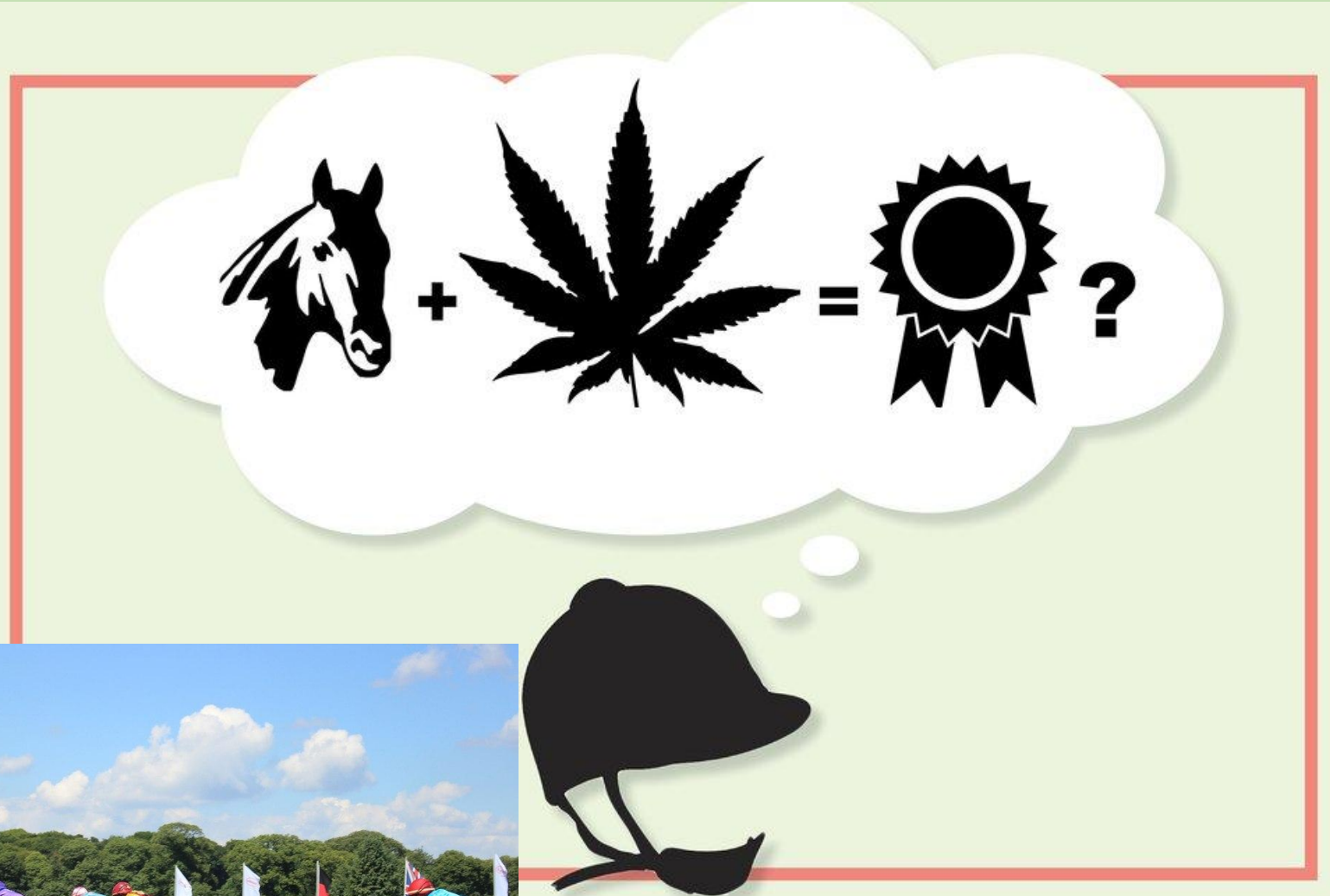
- 16 (22) dog patients of different races and age suffering from clinically manifest ***Osteoarthritis***
- 2 x daily 2 (resp. 8) mg/kg CBD-oil (10 mg/mL CBD/CBDs, 0,24 mg/mL THC, 0,27 mg/mL Cannabichromene, 0,11 mg/mL Cannabigerol)
- CBD metabolic half-life (analyt.): 4, . h
- Significant reduction of pain (CBPI)
- Significant increase of activity/motility
- Significant improvement of animal welfare (e.g. smooth, quiet sleep)

Resume of the limited number of veterinary medical-clinical data:


- CBD is primarily **antiinflammatory** and **pain reducing** (analgesic).
- Main target: **Vanilloid-Receptor Type 1 (VR1)** in the neural system (pain perception!)
- **CBD-Extracts** are interesting **pain killers** if pain is caused by **inflammation** (inflammation is a physiological, not a pathological process!)
- First results show also reduction of pain caused by **Arthritis** and **Rheuma** (*Cannabinoid-mediated antinociception is enhanced in rat osteoarthritic knees*)
- In completion of the above mentioned study on dogs suffering from osteoarthritis we perform actually a similar broader study in Austria. First results are promising!

Riding and Racing Horses:

- Only some anecdotic reports from Vets, Animal Owners, Jockeys... or
- – from Companies producing/selling Cannabis-Products
- But: ***DOPING??***



Cannabis and CBD: actual legal situation

- Hemp and hemp products with $\leq 0,2 / 0,3$ % THC (EU-registered fiber / industrial varieties) **legal!**
- 01.02.2019: EC reclassified CBD and hemp derived products as Novel Food and therefore **illegal...?!** (since not yet approved according to the Novel Food Directive)  decision legally questionable...!
- 28.03.2019: US-FDA censure: **CBD Unapproved New Animal Drug** *due to misleading, medical or unsubstantiated advertising claims*
- ***New regulations in EU and US expected within 2019 !***
- Liberation of CBD and hemp products $\leq 0,2 / 0,3$ % THC expected...

Cannabis and cannabis-related substances

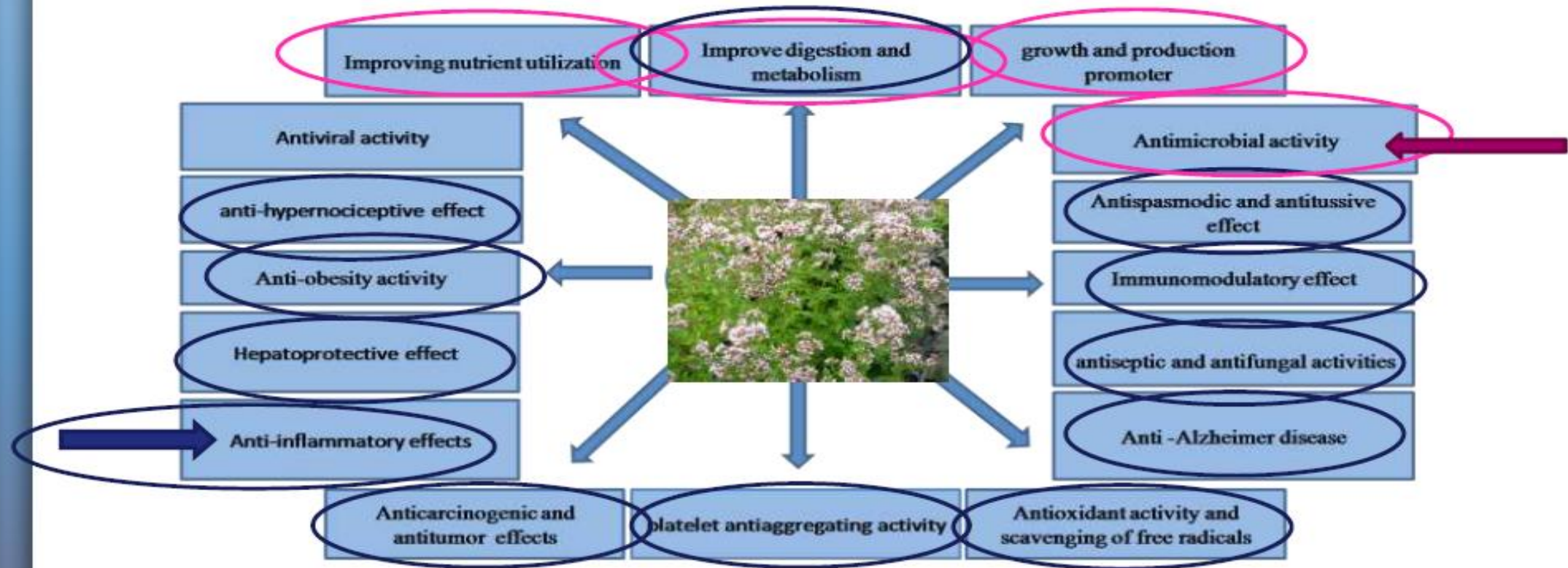
- **Cannabis and cannabis resin**
 - To be deleted from Schedule IV of the Single Convention on Narcotic Drugs (1961)
- **Dronabinol (*delta-9-tetrahydrocannabinol*)**
 - To be added to Schedule I of the Single Convention on Narcotic Drugs (1961)
 - To be deleted from Schedule II of the Convention on Psychotropic Substances (1971), subject to the CND's adoption of the recommendation to add dronabinol and its stereoisomers (*delta-9-tetrahydrocannabinol*) to Schedule I of the Single Convention on Narcotic Drugs (1961)
- **Tetrahydrocannabinol (Isomers of *delta-9-tetrahydrocannabinol*)**
 - To be added to Schedule I of the Single Convention on Narcotic Drugs (1961) subject to the CND's adoption of the recommendation to add dronabinol and its stereoisomers (*delta-9-tetrahydrocannabinol*) to Schedule I of the Single Convention on Narcotic Drugs (1961)
 - To be deleted from Schedule I of the Convention on Psychotropic Substances (1971), subject to the CND's adoption of the recommendation to add tetrahydrocannabinol to Schedule I of the Single Convention on Narcotic Drugs (1961)
- **Extracts and tinctures**
 - To be deleted from Schedule I of the Single Convention on Narcotic Drugs (1961)
- **Cannabidiol preparations**
 - To give effect to the recommendation of the fortieth meeting of the ECDD that preparations considered to be pure cannabidiol (CBD) should not be scheduled within the International Drug Control Conventions by adding a footnote to the entry for cannabis and cannabis resin in Schedule I of the Single Convention on Narcotic Drugs (1961) to read "*Preparations containing predominantly cannabidiol and not more than 0,2 percent of delta-9-tetrahydrocannabinol are not under international control*"
- **Preparations produced either by chemical synthesis or as preparation of cannabis, that are compounded as pharmaceutical preparations with one or more other ingredients and in such a way that delta-9-tetrahydrocannabinol (dronabinol) cannot be recovered by readily available means or in a yield which would constitute a risk to public health**
 - To be added to Schedule III of the Single Convention on Narcotic Drugs (1961)

**Letter of the
WHO Gen.-Dir. Dr. Ghebreyesus
to the
UN Secr. General Mr. Guterres**

dated 24.01.2019, regarding:

***Deletion of CBD from the
UN Single Convention on
Narcotic Drugs!***

Medicinal plants – multi talented!

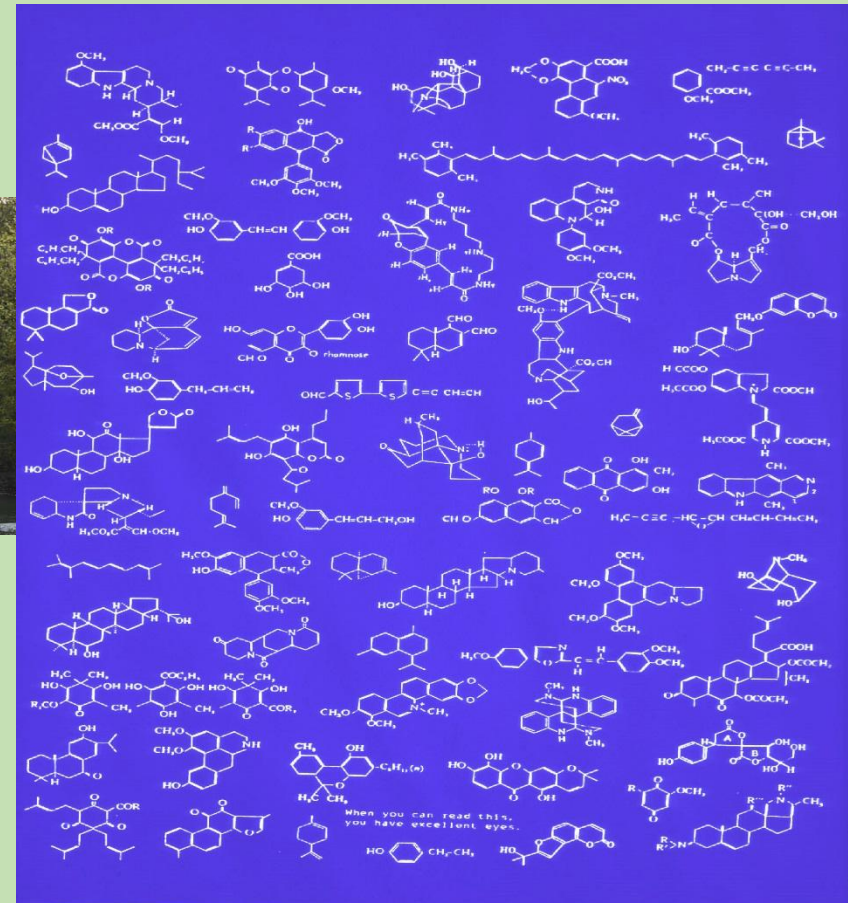
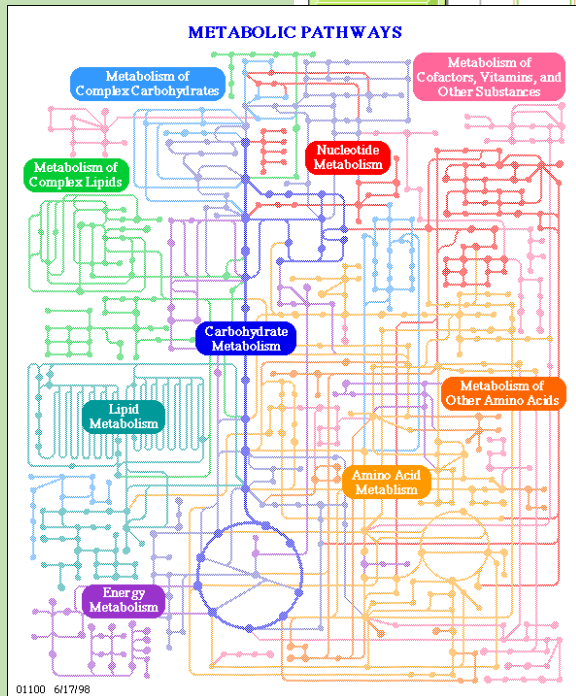
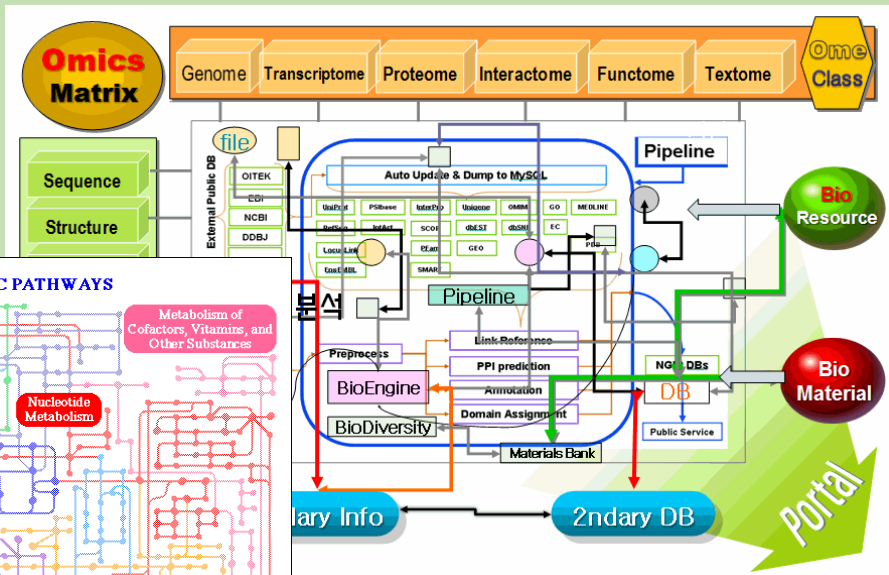


...a key to understand Systems Biology...

Learning from experienced-based (traditional) evidence!

Using the opportunities of systems biology & modern research tools

1 + 1 ≠ 2, Synergism, (antagonism), ...



Bioinformatics as tool!!

Quo vadis Vet-Phyto? („Take Home Message“)

Traditional Phyto- (Medicine)

Experienced-based
(empirical)

Directed to the individual symptoms

Considered as “natural AND safe”

Species differences often neglected

Variability of products high
□ variable efficacy

Often laborious preparation
conventional techniques

Modern approaches to Herbal remedies

Mechanism-based
(evidence-based)

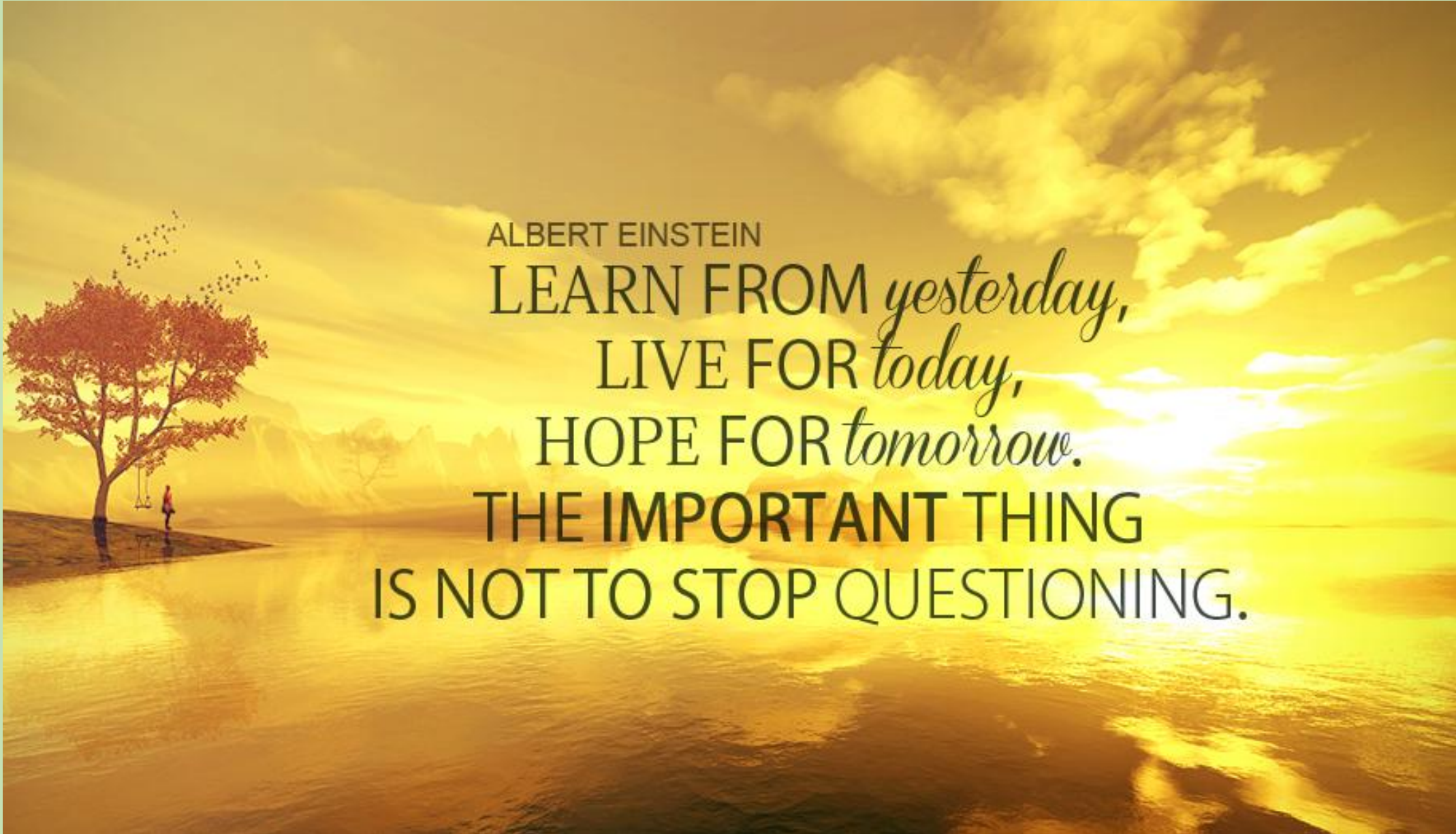
Appreciating the benefits of mixtures
of active compounds

Efficacy and safety to be evaluated

Species differences considered

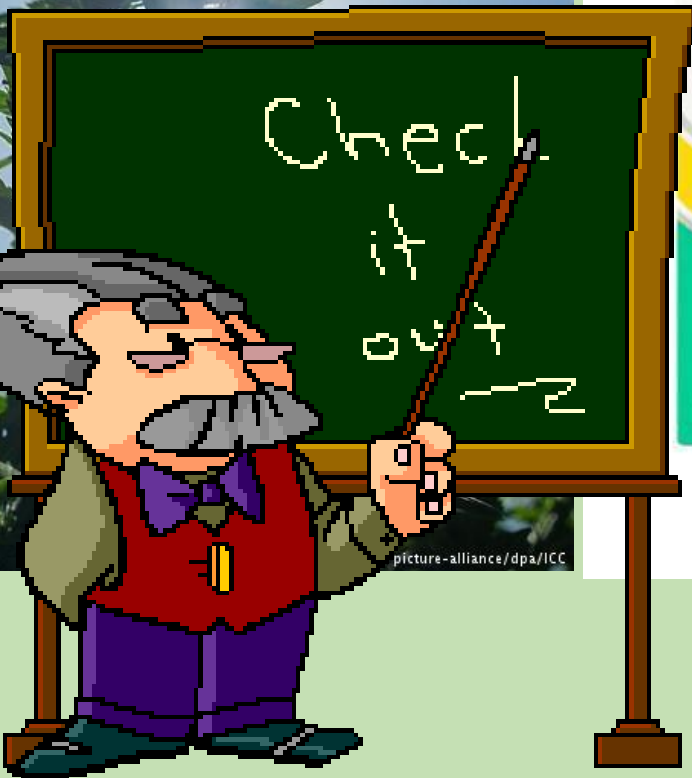
Standardized production &
medication protocols (target attainment)

Innovative technologies
(including nanotechnology,
drug targeting, prodrugs a.o.)

A serene sunset scene over a calm body of water. The sky is filled with golden light and soft, wispy clouds. On the left, a tree with vibrant autumn foliage stands on a small peninsula. A person is visible near the base of the tree, and a few birds are flying in the sky above. The water reflects the warm colors of the sunset.

ALBERT EINSTEIN
LEARN FROM *yesterday*,
LIVE FOR *today*,
HOPE FOR *tomorrow*.
THE IMPORTANT THING
IS NOT TO STOP QUESTIONING.

Grazie per l'Interesse!



picture-alliance/dpa/ICC

