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 Doctoral thesis about the bioavailability of curcumin (University of Hohenheim, Germany)

#### Disclaimer



All statements made in this presentation refer to scientific/medical studies as well as to procedures of the naturopathic empirical medicine, which do not belong to the generally accepted methods in the sense of a recognition by orthodox/conventional medicine.

The indications presented are not recognized by orthodox medicine and are based solely on the knowledge and experience of the author, alternative practitioners and doctors who use the therapies described here. The mechanisms of action of the presented micro-, macronutrients and secondary plant products refer to cell line experiments, animal studies, double-blind studies as well as laboratory documented practical cases.

Neither dietary supplements nor the therapies presented here replace the use of drugs or conventional medicine, scientifically recognized and necessary therapies. The food supplements presented in this script are not drugs (medicines) and do not replace them. Food supplements are food and therefore unsuitable for the treatment of diseases.

Image and sound recordings are not permitted.



## Turmeric: Natural healing power from the golden root



For more than thousands of years used in Ayurvedic medicine:

- Gastrointestinal disorders
- > Rheumatism
- Liver disease
- Infections
- Gynaecological problems
- Psoriasis
- > Dermatitis
- > Sinusitis
- Several more chronic diseases --> anti-inflammatory
- Gupta et.al. Curcumin, a component of turmeric: from farm to pharmacy. Biofactors **39**, 2-13, doi:10.1002/biof.1079 (2013).
- Goel et. al. Curcumin as "Curecumin": from kitchen to clinic. Biochem Pharmacol 75, 787-809, doi:10.1016/j.bcp.2007.08.016 (2008).
- Prasad & Aggarwal. Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. Herbal Medicine: Biomolecular and Clinical Aspects (2011).







#### **Turmeric, curcuminoids and curcumin**



- Curcuminoids: 3-5% of the rhizome:
  - Curcumin (75-85%)
  - Demethoxycurcumin (15-20%)
  - Bis-demethoxycurcumin (2-8%)
- Curcumin: Predominant curcuminoid and the most bioactive component.
  - Nelson et. al. The Essential Medicinal Chemistry of Curcumin. J Med Chem. 60(5), 1620–1637, doi:10.1021/acs.jmedchem.6b00975 (2017).





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Bis-demethoxycurcumin

#### **Research on curcumin? More than 18.384 publications**



11 Cognitive disorders

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#### **Positive effects of curcumin**





- Singh & Aggarwal. Activation of transcription factor NF-kappa B is suppressed by curcumin (diferuloylmethane) [corrected]. J Biol Chem 270, 24995-25000 (1995).
- Zhang et al. Curcumin attenuates skeletal muscle mitochondrial impairment in COPD rats: PGC-1alpha/SIRT3 pathway involved. Chem Biol Interact 277, 168-175, doi:10.1016/j.cbi.2017.09.018 (2017).
- Hu et al. Curcumin as therapeutics for the treatment of head and neck squamous cell carcinoma by activating SIRT1. Scientific Reports 5, 13429, doi:10.1038/srep13429 (2015).
- Trujillo et al., Mitochondria as a target in the therapeutic properties of curcumin. Arch Pharm (Weinheim) 347, 873-884, doi:10.1002/ardp.201400266 (2014).
- Gupta, Patchva & Aggarwal. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J 15, 195-218, doi:10.1208/s12248-012-9432-8 (2013).
   Eckert et al., Curcumin prevents mitochondrial dysfunction in the brain of the senescence-accelerated mouse-prone 8. Neurochem Int 62(5), 595-602, doi: https://doi.org/10.1016/j.neuint.2013.02.014 (2013).
- Jaruga, E., et al., Apoptosis-like, reversible changes in plasma membrane asymmetry and permeability, and remeability, and remeability and massient modifications in mitochondrial membrane potential induced by curcumin in rat thymocytes. FEBS Lett 433(3), 287-
- Jaruga, L., et al., Apoptosis-like, reversible changes in plasma memorane asymmetry and permeability, and transient modifications in mitochondrial memorane potential induced by curcumin in fat thymocytes. FEBS Lett 433(3), 2
  93 (1998).

#### **Effects of curcumin in clinical trials**





- He et al. Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin. Cancer Invest 29, 208-213, doi: 10.3109/07357907.2010.550592 (2011).
- Choi et. al. A randomized, double-blind, placebo-controlled trial to evaluate the role of curcumin in prostate cancer patients with intermittent and rogen deprivation. The Prostate 79, 614-621, doi:10.1002/pros.23766 (2019).
- Belcaro et al. Product-evaluation registry of Meriva(R), a curcumin-phosphatidylcholine complex, for the complementary management of osteoarthritis. Panminerva Med 52, 55-62 (2010).
- Holt, Katz & Kirshoff. Curcumin therapy in inflammatory bowel disease: a pilot study. Dig Dis Sci 50, 2191-2193 doi:10.1007/S10620-005-3032-8 (2005).
- Bundy et. al. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: a pilot study. J Altern Complement Med 10, 1015-1018, doi:10.1089/acm.2004.10.1015(2004).





## **Curcumin and arthritis**

#### **Risk factors for arthritis**

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Johnson & Hunter. The epidemiology of osteoarthritis. Best practice & research. Clinical rheumatology 28, 5-15, doi:10.1016/j.berh.2014.01.004 (2014)

#### NSAIDs (Nonsteroidal anti-inflammatory drugs)





- Handa et. al. The impact of non-steroidal anti-inflammatory drugs on the small intestinal epithelium. Journal of Clinical Biochemistry and Nutrition 54, 2-6, doi: 10.3164/jcbn.13-84 (2014)
- Mukherjee et. al. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 286, 954-959, doi: 10.1001/jama.286.8.954 (2001)
- Fleischmann et. al. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a prospective randomized 13-week study versus placebo and celecoxib. Clinical Rheumatology 25, 42-53, doi: 10.1007/s10067-005-1126-5 (2006)

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#### **Curcumin in arthritis**





- Shep et. al. Safety and efficiacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study. Trials 20:214, doi: 10.1186/s13063-019-3327-2 (2019).
- Daily et. al. Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Journal of Medicinal Food 19, doi: 10.1089/jmf.2016.3705 (2016)
- Kwiecien et. al. Curcumin: A Potent Protectant against Esophageal and Gastric Disorders 20, doi: 10.3390/ijms20061477 (2019).
- Gupta, Patchva & Aggarwal. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J 15, 195-218, doi:10.1208/s12248-012-9432-8 (2013).



139 patients with knee osteoarthritis

- > 3x 500 mg curcumin/day (70 patients)
- > 2x 50 mg diclofenac/day (69 patients)
- Reduction of pain and symptoms in daily living: curcumin = diclofenac
- > Side effects:

Curcumin 13%

Diclofenac 38%

#### > Abdominal pain:

Curcumin 0%

Diclofenac 27.5%

| Comparison of pain by visual analogue scale |                     |                        |                   |
|---|---------------------|------------------------|-------------------|
| Visit                                       | Curcumin $(N = 70)$ | Diclofenac<br>(N = 69) | P value           |
| Baseline                                    | 7.84 ± 0.63         | 7.81 ± 0.73            | 0.79              |
| Day 14                                      | 4.69 ± 0.79         | 4.58 ± 0.60            | 0.38              |
| Day 28                                      | 2.20 ± 0.81         | 2.20 ± 0.61            | 0.98              |
| Change at day 14                            | -3.16 ± 0.79        | $-3.23 \pm 0.91$       | 0.61 <sup>t</sup> |
| Change at day 28                            | $-5.93 \pm 0.99$    | $-5.61 \pm 0.88$       | 0.82 <sup>z</sup> |
| P value                                     | P <0.01 ₩C          | P <0.01 <sup>wc</sup>  |                   |
|   |                     |                        |                   |





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#### How does curcumin exactly work?

 $\succ$  Chemical injected into rats  $\rightarrow$  arthritis  $\uparrow$ 

6 rats per group were treated for 14 days daily with

- Curcumin (injected; 50 mg/kg body weight)
- Methotrexate (injected; 50 mg/kg body weight)
- NaCl (injected)

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Curcumin **reduced NF-\kappaB** expression and **TNF-** $\alpha$  levels in blood serum



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# **Challenge of curcumin bioavailability**

#### Low oral bioavailability of curcumin



- Low water solubility and digestive stability
- > Only small amounts are absorbed in the intestine







#### **Small systemic effects**

- Anand et. al. Bioavailability of curcumin: problems and promises. Mol Pharm 4, 807-818, doi:10.1021/mp700113r (2007).
- Sharma et. al. Pharmacokinetics and pharmacodynamics of curcumin. Adv Exp Med Biol 595, 453-470, doi:10.1007/978-0-387-46401-5\_20 (2007)
- Schiborr et al. The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes. *Mol Nutr Food Res*, **58(3)**, 516-27, doi: 10.1002/mnfr.201300724 (2014).



#### Native curcumin

- > Often administered in high doses in clinical trials
- No unmetabolized curcumin in blood detectable

## **Bioavailability improvement by**

- > Co-administration of curcumin with other substances
  - Fat
- Improvement of its water solubility and stability
  - Complexation

<sup>•</sup> Flory S et al. Increasing Post-Digestive Solubility of Curcumin Is the Most Successful Strategy to Improve its Oral Bioavailability: A Randomized Cross-Over Trial in Healthy Adults and In Vitro Bioaccessibility Experiments, Mol Nutr Food Res 65: 2100613 doi: 10.1002/mnfr.202100613 (2021)

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#### **Aim: Bioavailability improvement**



Different mechanistic approaches

Some ingredients are not natural

Safety? (Keyword: Intestine)

#### What is the most bioavailable formulation – and safe at the same time?



Wong et. al. Curcumin Nanoformulations for Colorectal Cancer: A Review. Front Pharmacol, 10:152, doi: 10.3389/fphar.2019.00152 (2019)

#### Human clinical trial on curcumin bioavailability



- > Crossover study with 12 healthy adults (6  $\[Gamma]$  and 6  $\[Gamma]$ )
- Direct comparison of different curcumin formulations
- Single oral administration of the formulations containing 207 mg curcumin
- Blood was taken after 1, 2, 4, 6, 8 and 24 hours



Flory S *et al.* Increasing Post-Digestive Solubility of Curcumin Is the Most Successful Strategy to Improve its Oral Bioavailability: A Randomized Cross-Over Trial in Healthy Adults and In Vitro Bioaccessibility Experiments, *Mol Nutr Food Res* **65**: 2100613 doi: 10.1002/mnfr.202100613 (2021)

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Flory et al. Increasing Post-Digestive Solubility of Curcumin Is the Most Successful Strategy to Improve its Oral Bioavailability: A Randomized Cross-Over Trial in Healthy Adults and In Vitro Bioaccessibility Experiments, Mol Nutr Food Res 65: 2100613 doi: 10.1002/mnfr.202100613 (2021)

#### Human clinical trial on curcumin bioavailability



- > 207 mg curcumin, oral administration
- Blood samples after 1, 2, 4, 6, 8 and 24 hours
- γ-Cyclodextrin and
- Polysorbate 80/ Tween 80 improve the bioavailability of curcumin

## Bioavailability of the formulations compared to native curcumin



Flory S et al. Increasing Post-Digestive Solubility of Curcumin Is the Most Successful Strategy to Improve its Oral Bioavailability: A Randomized Cross-Over Trial in Healthy Adults and In Vitro Bioaccessibility Experiments, Mol Nutr Food Res 65: 2100613 doi: 10.1002/mnfr.202100613 (2021)

#### **Polysorbate 80 – problematic emulsifier**



Polysorbate 80 (= Tween 80 = E433)
Defined acceptable daily intake of
25 mg/kg for food
(= 1.5 g for 60 kg body weight)

Study in mice published in **Nature** Administration of **1% polysorbate 80** (drinking water) for 12 weeks

- $\succ$  Microbiome diversity  $\checkmark$
- $\succ$  Intestinal inflammation  $\bigstar$
- ➢ Body weight ↑



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#### **Curcumin with polysorbate 80**

- > 60x better bioavailable
- Only 100 mg curcumin in form of the supplement deliver 1.5 g polysorbate 80

## Primum non nocere!

(First, do no no harm!)

- Chassaing, Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature, 519, 92-96 (2015).
- http://edubily.de/2015/09/vitamin-mangel-macht-fett

#### **Reduction of the intestinal barrier function by polysorbate 80**





• Roberts et. al. Hypothesis: Increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease. J Crohns Colitis 7, 338-341, doi:10.1016/j.crohns.2013.01.004 (2013).







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of E.coli





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#### Curcumin-y-cyclodextrin complex



γ-Cyclodextrin:

≻Ring of glucose subunits

≻Natural origin

≻Water soluble

≻Vegetarian







Curcumin-y-cyclodextrin

#### Transport and absorption of curcumin-γ-cyclodextrin





#### Curcumin-y-cyclodextrin improves the intestinal absorption





Graphics were provided by Wacker Chemie AG



With common curcuma extracts

#### With curcumin-γcyclodextrin





#### **Summary**

## **Curcumin-y-cyclodextrin complex**

#### <u>Bioavailability</u>

- > Water soluble
- > 30-fold better bioavailable

### <u>Safety</u>

- > Free from problematic polysorbate 80
- Cyclodextrin complex made of glucose molecules

#### Optimization of its anti-inflammatory activity

Combination with turmerosaccharides, theaflavines from black tea, ginger extract, quercetin and vitamin C





#### For all further inquiries

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