Theracurmin:

An Advanced Form of Curcumin

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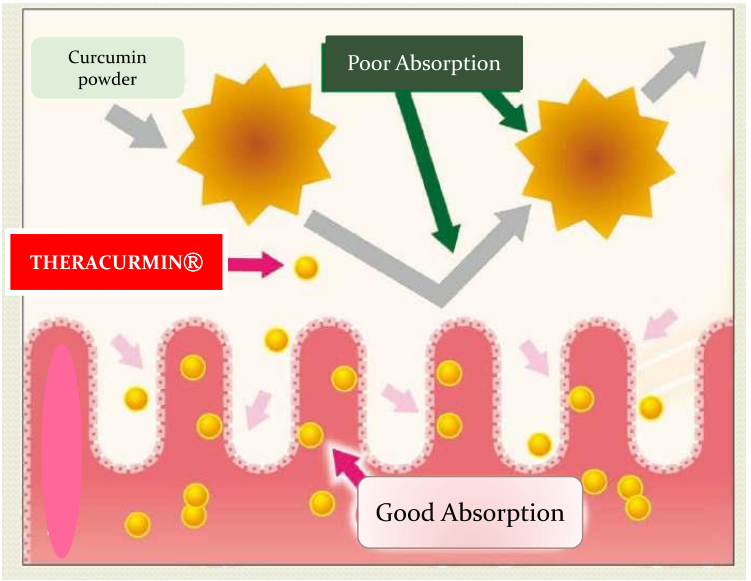
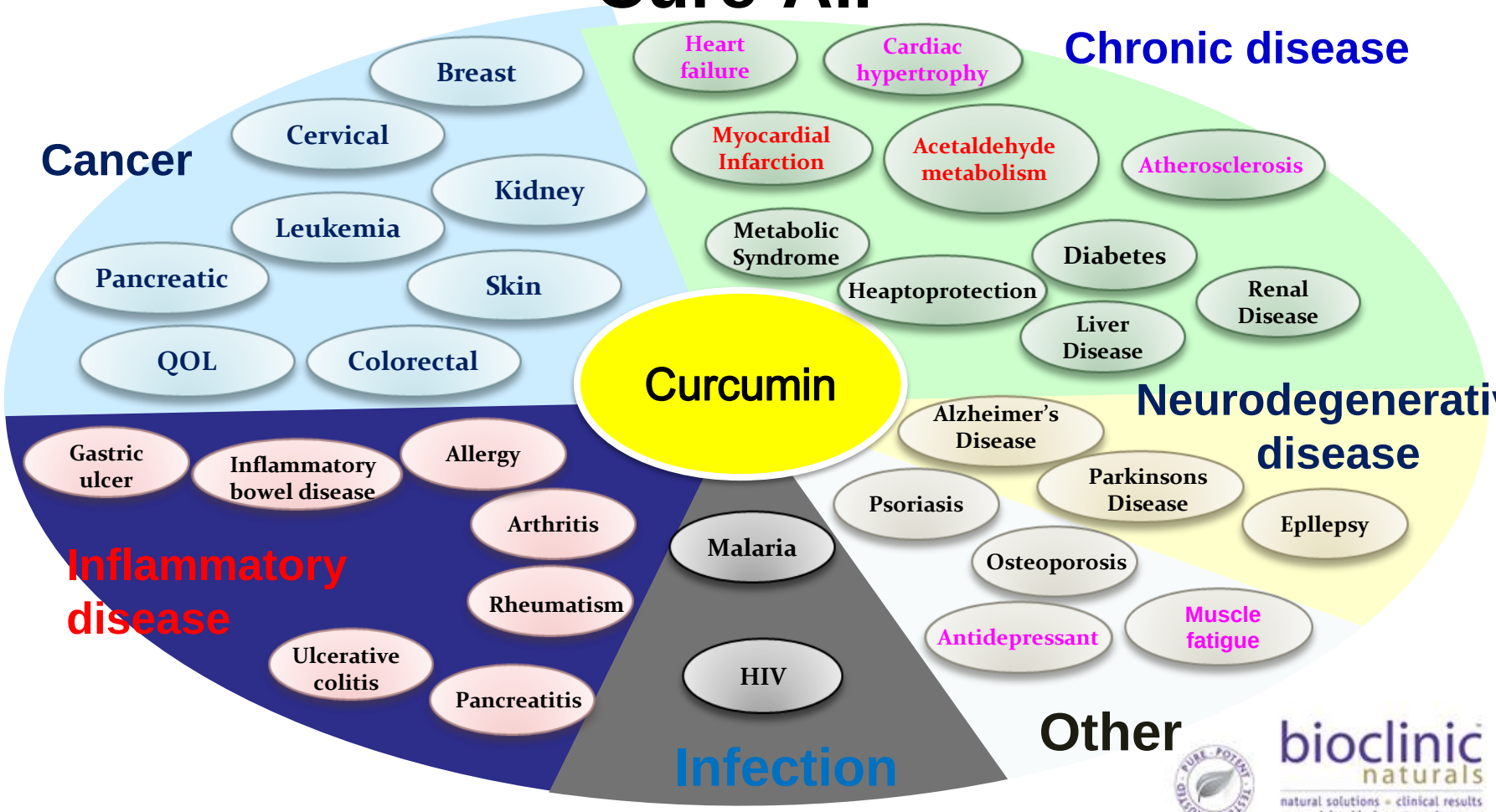
Major Breakthrough



SPICING UP MEDICINE:
what curry is to Indian cuisine, curcumin could be to medicine

- **Inflammation** (ostheoarthritis, rheumatoid arthritis)
- **Eye health** (cataract, uveitis)
- **Cancer** (chemoprevention)
- **Alzheimer's disease**
- **Gastrointestinal conditions** (IBD, CD, UC)
- **Diabetes and metabolic syndrome**

CURCUMIN: A Molecular and Preclinical Cure-All



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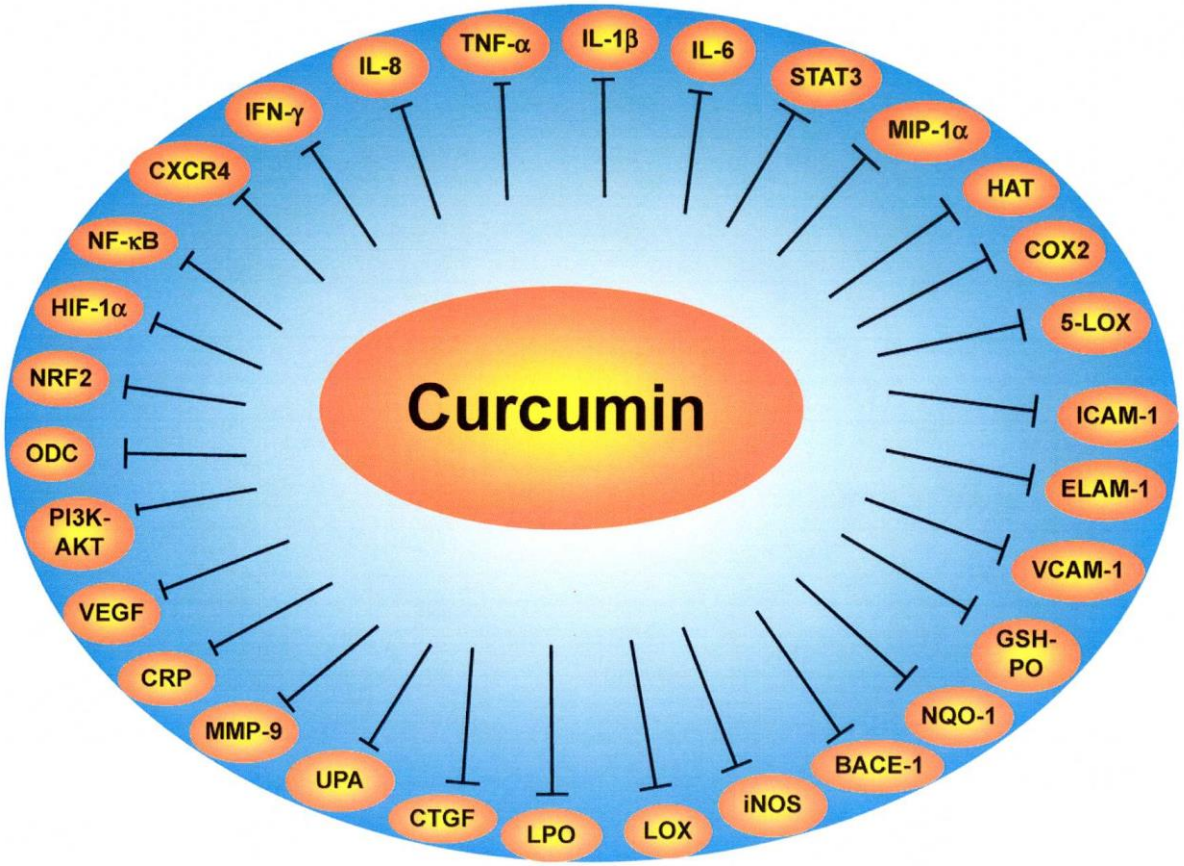
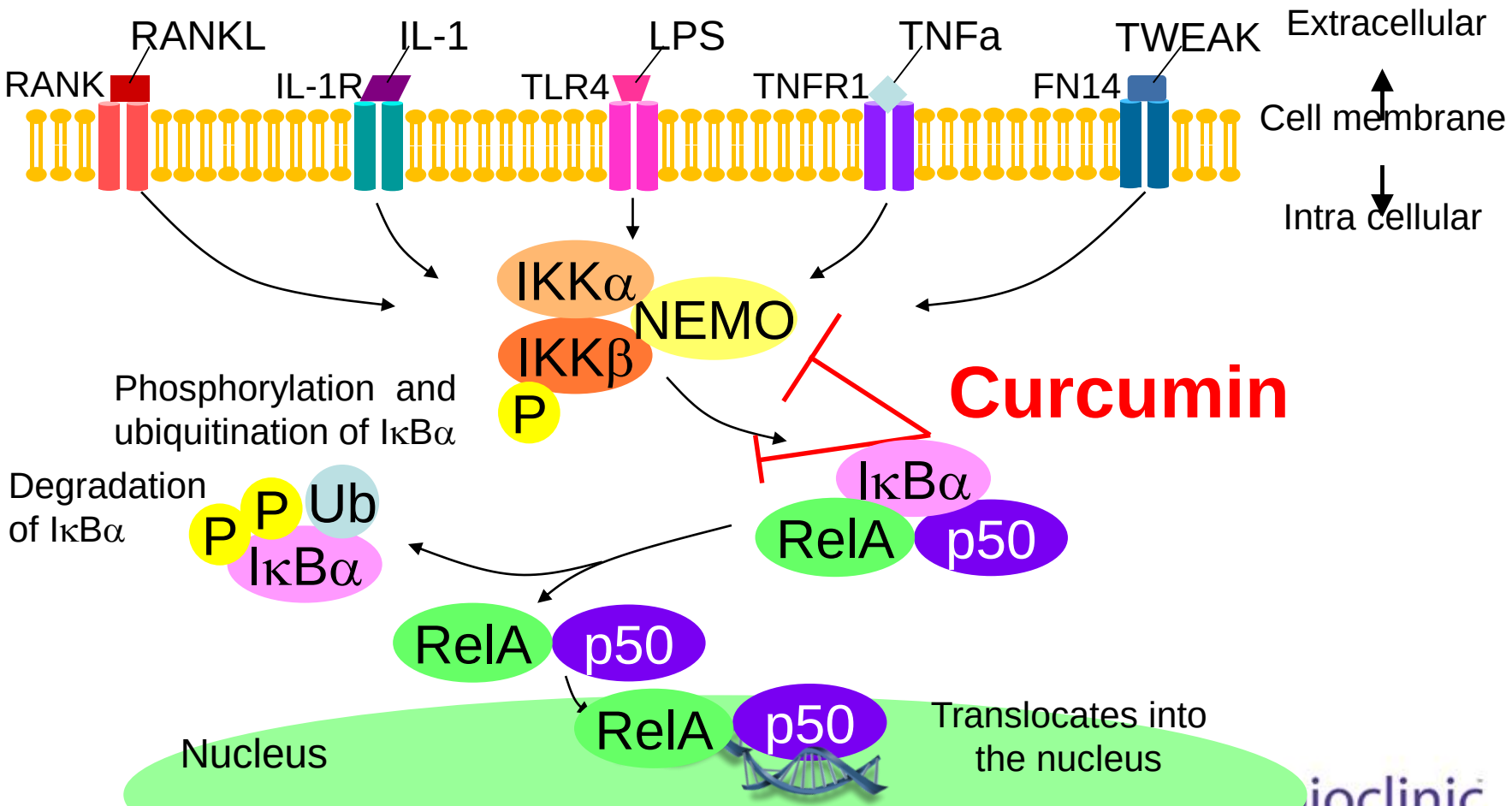
THE MASTER SWITCH OF INFLAMMATION*



*Blocks transcription factors involved in inflammation (AP-1/NF-kB /STAT3)

Suppression of NF-κB Activation by Curcumin



NF-κB activation: TNFα、IL-1、Proinflammatory: IL-6、IL-8、CSF1、COX2、iNOS、Cell proliferation: SOD2、Adhesion molecule: ICAM-1、VCAM-1、Angiogenesis: VEGF、Anti-apoptotic: c-FLIP、A20、BCLX1、cIAPs

CURCUMIN:

Some Other Specific Anti-Cancer Effects

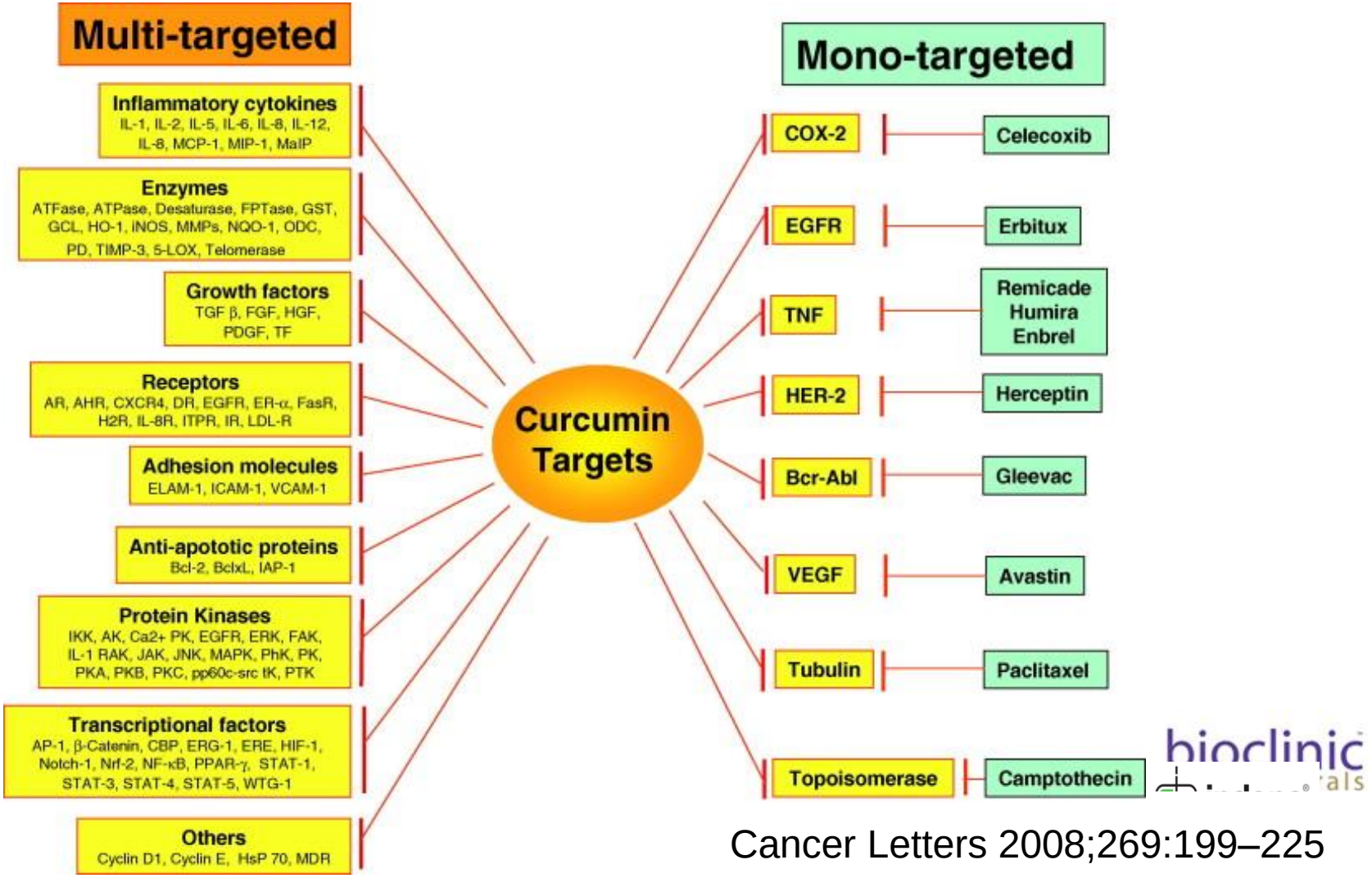
Inhibiting epidermal growth factor (EGF) receptor sites: EGF stimulates cells to proliferate by connecting to a receptor on the cell surface. About two-thirds of all cancers produce an abundance of these receptors, which make them highly sensitive to EGF. By reducing the number of EGF receptors, curcumin decreases the cell's tendency to proliferate.

Inhibiting angiogenesis: Fibroblast growth factor is a protein that promotes the formation of new blood vessels to feed the growing tumour. Curcumin inhibits production of this growth factor.

Increasing the expression of the nuclear p53 protein: This protein is essential for apoptosis, the normal process of cell "suicide."

Inhibiting enzymes that promote cancer cell growth.

THE MASTER SWITCH OF CANCER?



Cancer Letters 2008;269:199–225

CURCUMIN:

Some Encouraging Clinical Data

He ZY, et al. Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin. Cancer Invest. 2011 Mar;29(3):208-13.

This study examined oral curcumin supplementation in newly diagnosed patients with colorectal cancer (CRC). Using the waiting period before surgery as the supplement therapy period, 126 patients were randomized to receive curcumin 360 mg three times daily (n=63) or vehicle capsule (placebo; n=63) prior to primary surgery for a period of 10 to 30 days. Postsurgical treatment included radiotherapy (n=31), chemotherapy (n=84), or both (n=9), but 20 patients received no additional chemotherapy. Treatment with curcumin led to body weight gain, with observed increases in p53 expression, DNA fragmentation, and Bax and Bcl-2 modulation. No significant differences between groups were noted for calorie intake or diarrhea events, and there were no cases of CRC-caused obstruction to affect interpretation of results. Investigators concluded that a supplemental remedy of presurgical curcumin could improve the general health of patients with CRC and provide a novel method to improve cachexia.

CURCUMIN:

Some Encouraging Clinical Data (cont'd)

Dhillon N, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res. 2008 Jul 15;14(14):4491-9.

Twenty-five patients with advanced pancreatic cancer were given 8 g curcumin daily, orally, until disease progression, with restaging every 2 months. Serum cytokine levels for interleukin (IL)-6, IL-8, IL-10, and IL-1 receptor antagonists and peripheral blood mononuclear cell expression of NF-kappaB and cyclooxygenase-2 were monitored. Researchers observed downregulated expression of NF-kappaB, cyclooxygenase-2, and phosphorylated signal transducer and activator of transcription 3 in peripheral blood mononuclear cells from patients, many of whom had high baseline values compared with healthy volunteers. Clinically relevant biological activity was seen in two patients. Curcumin should be evaluated in larger, randomized trials. Increasing its bioavailability may render it more effective.

CURCUMIN HAS POOR PK PROPERTIES in HUMANS

In humans, curcumin shows:

- **Extremely poor oral absorption**. A **12 g** dose of curcumin produced a maximum serum concentration of only **51 ng/ml**!
- **High rate of metabolic conjugation** (sulfation and glucuronidation) and reduction
- **Rapid clearance from the body**

Mol. Pharmaceutics 4 **(6), 807–818 (2007)**

THERACURMIN

"Particle Surface Controlled Curcumin"

- Number one absorbed form of curcumin
- Easily dispersed in water
- Stable against heat and light
- In vivo and clinically proven technology
- Clinical validation of therapeutic effects
- Safe

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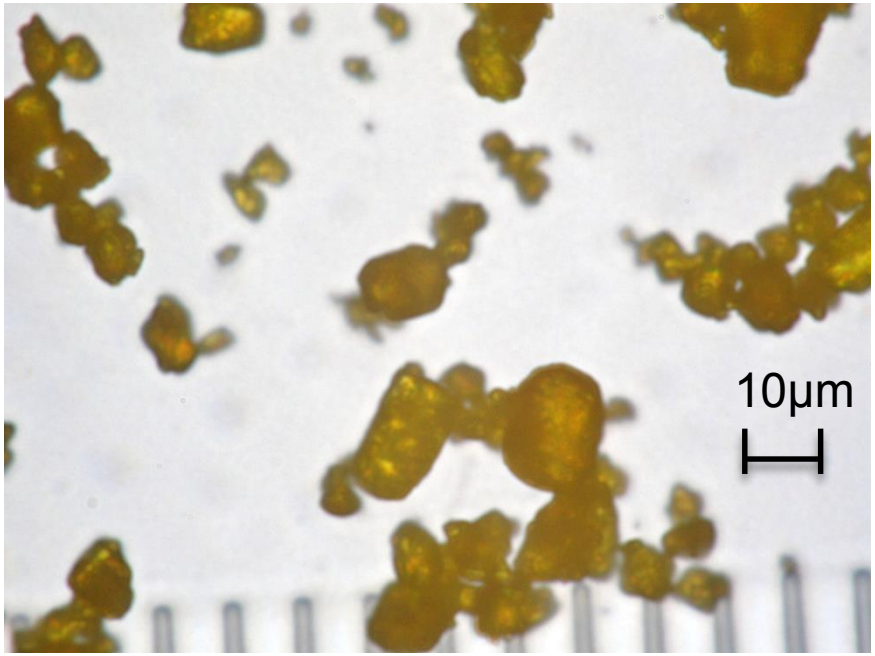
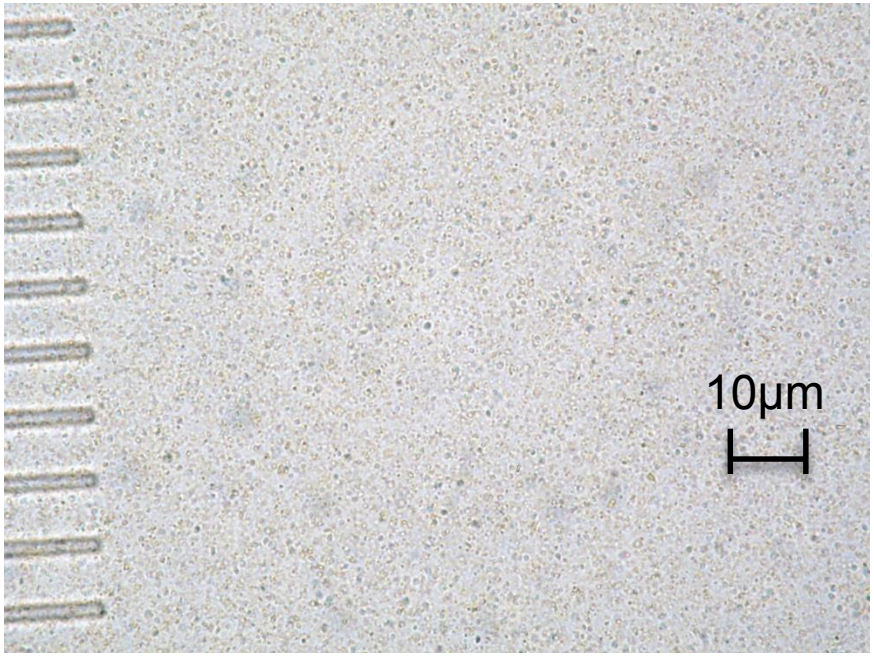
Particle Size
Curcumin vs. Theracurmin



Curcumin powder



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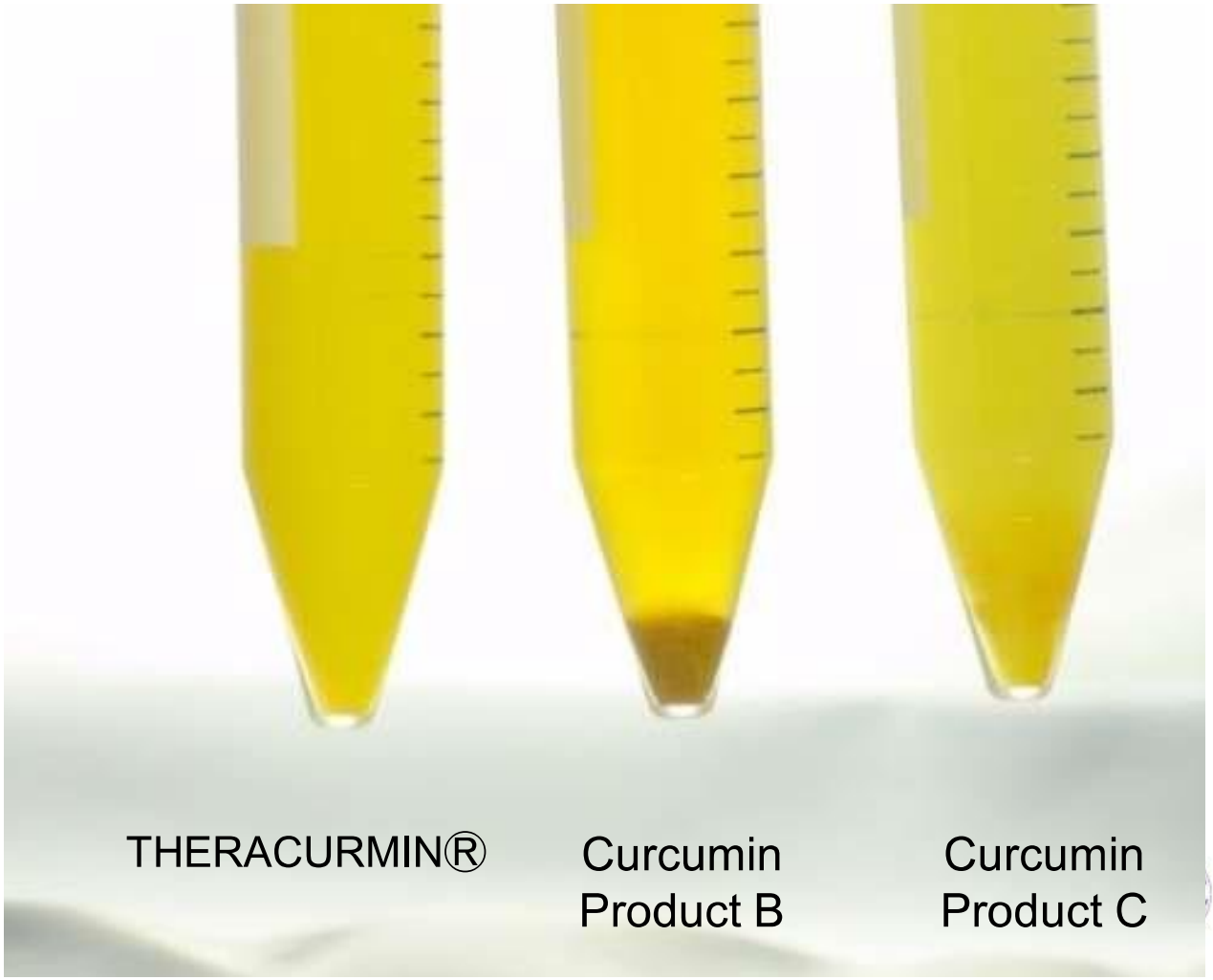
Theracurmin Solubility in Water Compared to Other Absorbable Forms of Curcumin



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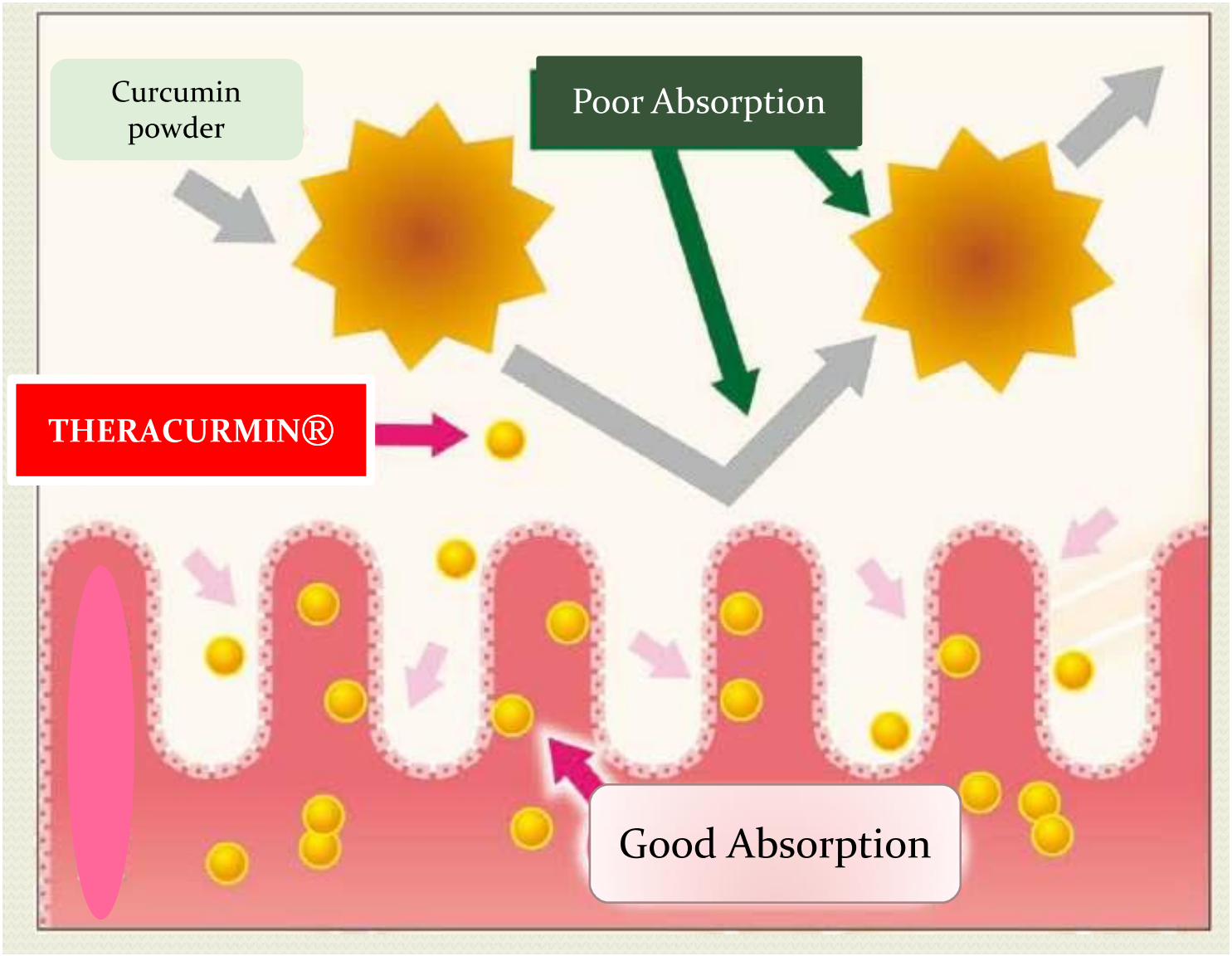

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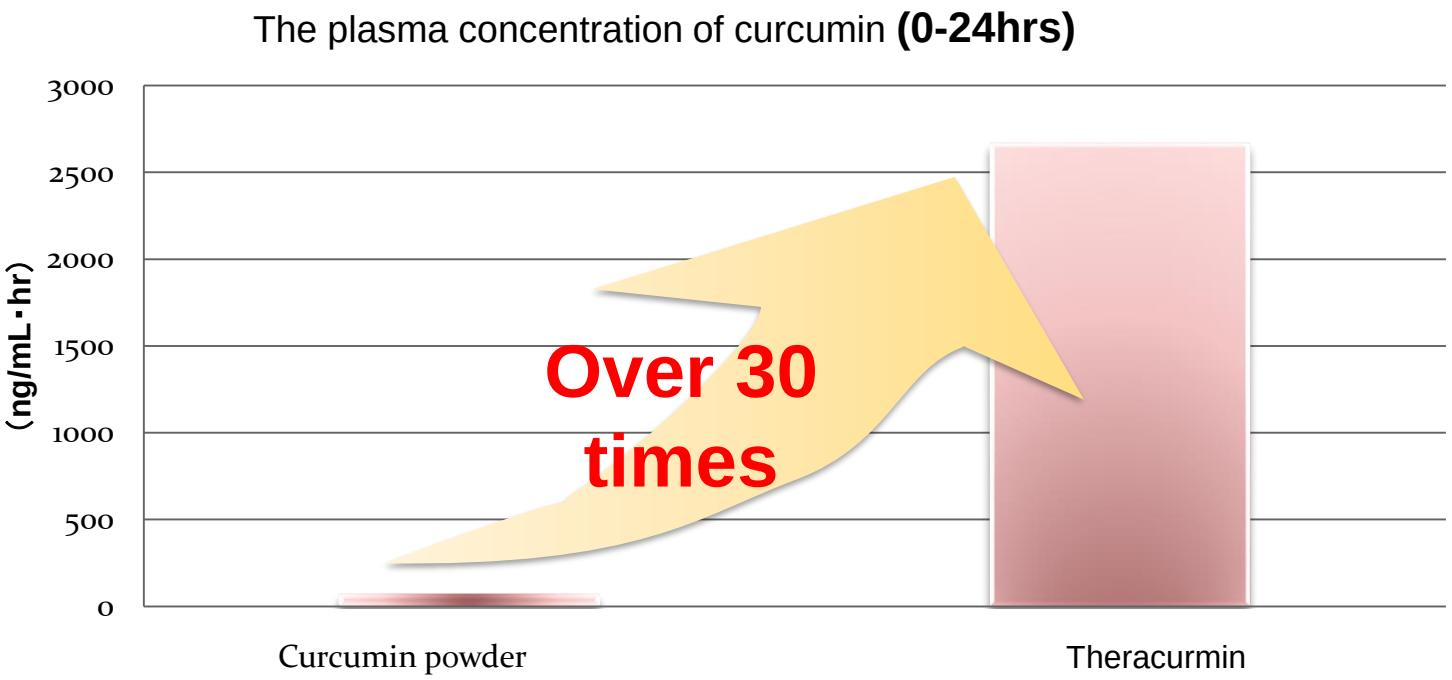
THERACURMIN

"Particle Surface Controlled Curcumin"

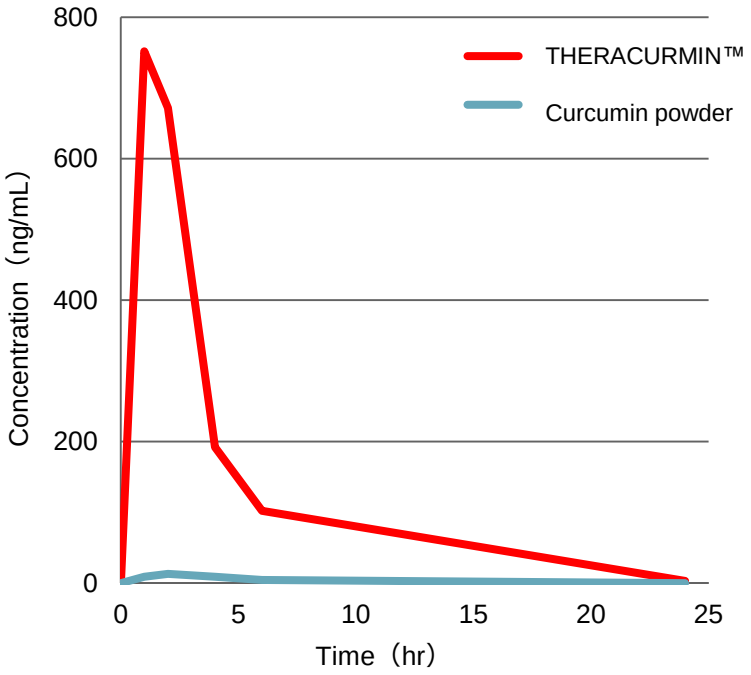
The plasma concentration of curcumin after oral administration in rats



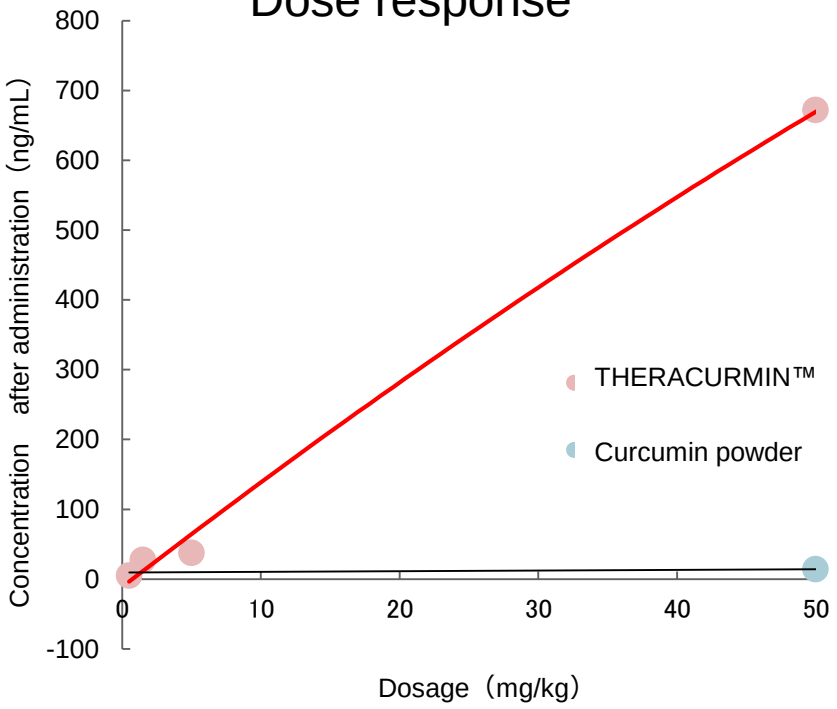
Absorption Study in Rats

THERACURMIN produces a clear dose response.

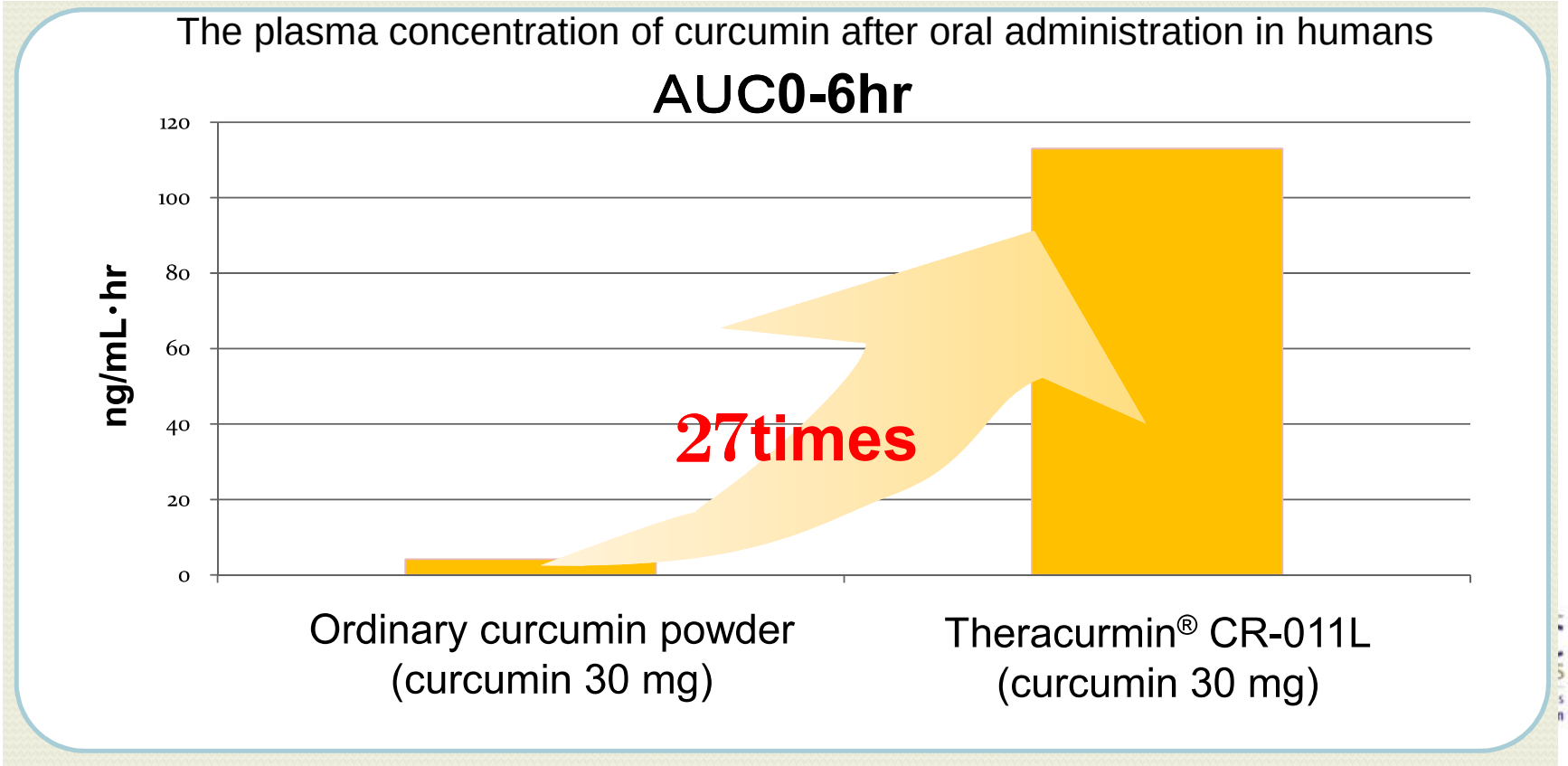
The plasma concentration of curcumin after oral administration in rats



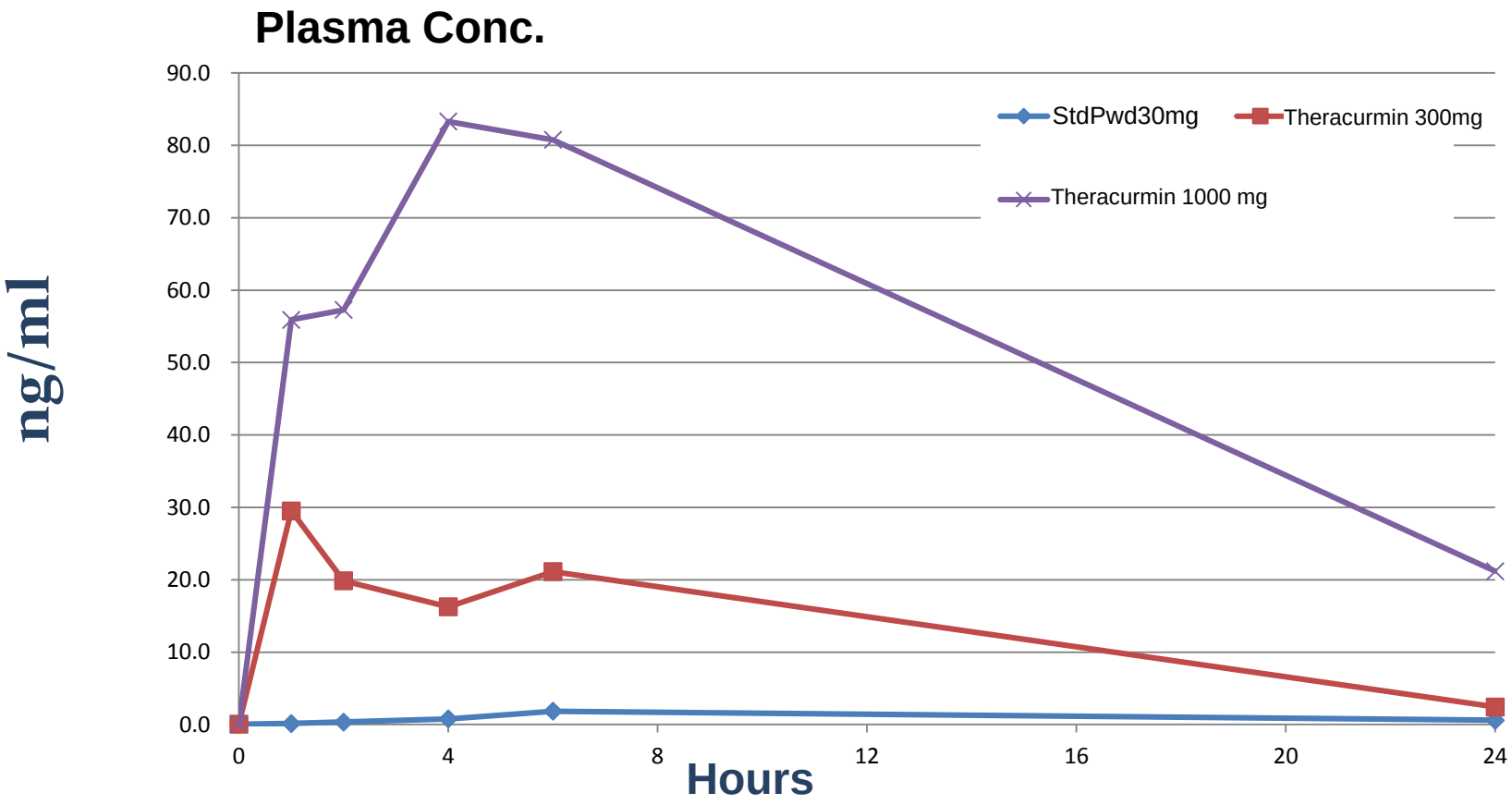
Dose response



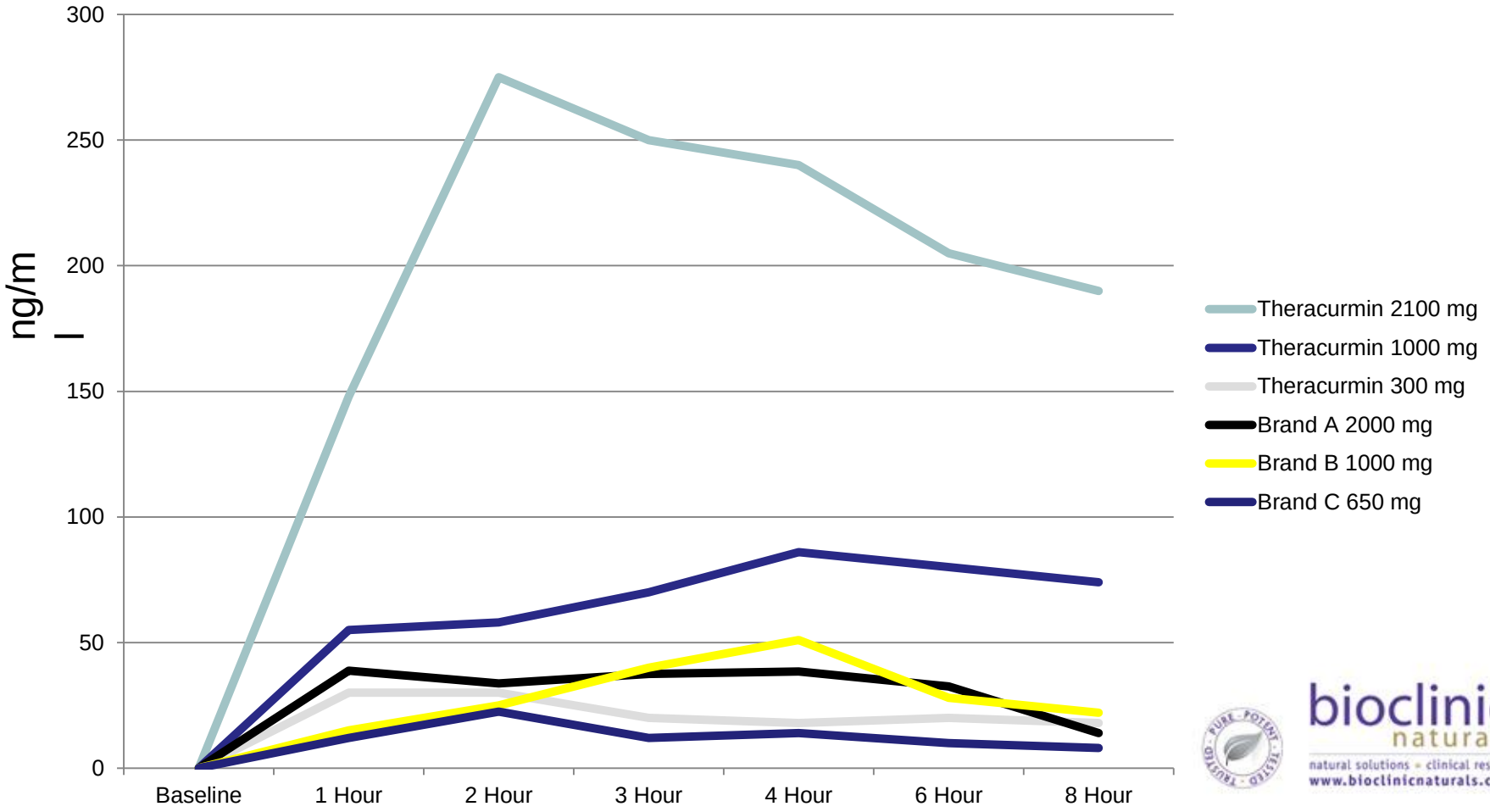
“Particle Surface Controlled Curcumin”



Theracurmin vs. “standard” curcumin powder (Results of Human PK Study)



Human Bioavailability from Published Pharmacokinetic Trials



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References

Theracurmin: Biol. Pharm. Bull. 2011;34(5) 660-665; Cancer Chemother Pharmacol (2012) 69:65–70

Brand A: Indian J Pharm Sci. 2008;70(4):445–449.

Note: converted data from dry weight

Brand B: J Nat Prod. 2011;74(4):664-9

Brand C: J. Agric. Food Chem. 2010, 58, 2095–2099

Safety

- Various animal models or human studies proved that curcumin is extremely safe even at very high dose.
- **There is no toxicity with THERACURMIN.**

Results of safety trial about THERACURMIN

- **Acute toxicity Test (Rat) :**
  - **No toxicity up to 20 g/kg (oral)**
- **Two weeks repeated high dose test (Rat):**
  - **No toxicity for 2 weeks at 10 g/kg/day dose (oral)**
- **Mutagenesis Test : Negative**
- **6 weeks Sub-acute toxicity Test (Rat) :**
  - **No toxicity at 50 mg/kg /day repeated dose (oral)**

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Human Safety Studies with THERACURMIN

Single administration

- Healthy volunteers：2100 mg (n=6, blood curcumin: 275±67 ng/mL)
  Kanai M, et al. Cancer Chemother Pharmacol, 2011

Repetitive administration

- Heart hypertrophy patients: 600 mg/day (n=30, 6 months)
- Pancreatic cancer patients: 2000 mg/day (n=6, 6 months)
  4000 mg/day (n=2, 2 months)
- Osteoarthritis patients: 1800 mg/day (n=11, 2 months)

Consumers taking commercially available THERACURMIN

- capsules (300 mg), chewable type (50 mg), and gummy type (100 mg)

Completed Clinical Studies with Theracurmin

Research Area	Institute/University	Results
Alcohol metabolism	Theravalues Corp.	Significantly reduced blood-acetaldehyde level
Hepatic function	Takanawa Medical Clinic	Significantly improved γ-GTP, GPT and GOT
Skin conditions	Theravalues Corp.	Significantly improved skin moisture content
Muscle fatigue / Exercise	Tsukuba Univ., Waseda Univ.	Significantly accelerated muscle fatigue recovery
Carotid artery stiffness	Tsukuba Univ.	Significantly improved carotid artery stiffness
Heart failure	Kyoto Medical Center, Kyoto Univ., Univ. of Shizuoka	Significantly improved diastolic dysfunction

Clinical Trials in Process with Theracurmin

Research area	Institute / University
Pancreatic cancer, Biliary tract cancer	Kyoto Univ., Akita Univ., Hokkaido Univ.
Progressing malignancy	MD Anderson Cancer Center, Univ. of Texas
Osteoarthritis	Kyoto Medical Center-Orthopedics
Periodontal disease	Tokyo Medical and Dental Univ.
ALS (amyotrophic lateral sclerosis)	Shiga Medical Univ., Kyoto Univ.
Prostate cancer	Teikyo Univ.
Alzheimer's disease	UCLA(double blind placebo control study for 18 months)
Lung cancer	Keio University Hospital
Colorectal polyp	Tokushima University/Hospital

CURCUMIN:

Interactions with Chemotherapy Agents

Enhances sensitivity of micro-organisms to antibiotics.

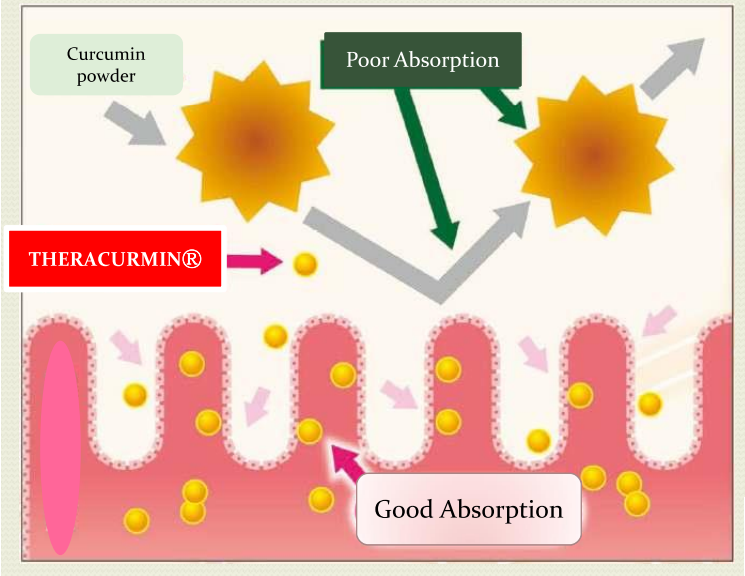
Enhances sensitivity of cancer cells to most chemotherapy.

Protects against chemotherapy-induced damage to heart and other tissues.

Possible negative effects when used with the following agents based upon in vitro studies:

- **Camptothecin** (apoptosis)
- **Mechlorethamine** (apoptosis)
- **Doxorubicin** (apoptosis)
- **Cyclophosphamide** (tumor regression)
- **Norfloxacin** (reduces half-life)

Theracurmin is a “Game Changer”



Major Breakthrough