TO EAT OR NOT TO EAT: CURCUMIN BIOAVAILABILITY AND ACTIVITY

YVAN ROCHON, PHD
Financial Disclosure: Owner of Herbal Vitality
Curcuma longa
Zingiberaceae
Rhizome
Curcuma longa

CONSTITUENTS
“The Whole Team”

CURCUMINOIDs

SESQUITERPENES

TUMERONES

POLYSACCHARIDES

ESSENTIAL OILS
THE CURCUMINOIDs

Curcumin 4.4%

Demethoxycurcumin 2.4%

Tetrahydrocurcumin

Bis-Demethoxycurcumin 3.6%

INCREASE STABILITY OF CURCUMIN
THE CURCUMINOIDS ARE POLYPHENOLS

Resveratrol

Catechin
CURCUMIN

FIRST ISOLATED IN 1815
BY VOGEL & PELLETIER

PRIOR TO THE 1990’S
100 JOURNAL ARTICLES

ALMOST 10,000 ARTICLES
CURCUMIN METABOLISM

- **Tetrahydrocurcumin**
- **Curcumin glucuronide**
- **Bicyclopentadione**
- **Vanillin**
- **Ferulic acid**

**Conjugation**

**Oxidation**

**Cleavage**
The metabolites of curcumin are present in high concentrations in the circulation after curcumin consumption.
DOSING

2 grams per day a safe dose

3.6 grams per day resulted in pharmacologically relevant concentrations in human colon. (Cancer Epidemiol Biomarkers Prev 2005 Jan;14(1):120-5)
THE IMPORTANCE OF GLYCOSYLATION

❖ Glycosylation helps curcumin pass through the blood-brain barrier

❖ Glycosylation may increase the activity of the molecule that is glycosylated
RESEARCH ON GLYCOSYLATION IN TURMERIC/POLYGONUM

Emodin

Emodin glucuronide

Neuraminidase inhibition

$IC_{50}=5.4\mu M$

$IC_{50}=0.85\mu M$


WHAT IS BIOAVAILABILITY??

THE AMOUNT OF TIME YOU CAN SEE CURCUMIN IN THE CIRCULATION
WHAT IS BIOAVAILABILITY??

BASICALLY BASED ON STUDIES IN THE RAT FROM THE LATE 1970s

IN HUMANS: A LOT OF ABSORPTION THROUGH THE GUT (COLON) WITH SOME CONJUGATION IN THE LIVER.

IN RATS: A LOT OF CONJUGATION IN THE LIVER WITH SOME ABSORPTION IN THE GUT.
STRATEGIES FOR INCREASING CURCUMIN BIOAVAILABILITY

ADD BACK THE MOLECULES THAT EXISTED WITH THE CURCUMIN BEFORE IT WAS ISOLATED.
STRATEGIES FOR INCREASING CURCUMIN BIOAVAILABILITY

ADD EMULSIFIERS
- Sunflower oil
- Whey protein isolates
- Trigonella fiber
- Monooleine
- Caseinate
- Pectin
- Lethicin
- Tween80
- Polysorbate20
- Lysophosphatidylcholine

MAKE MICELLES

MAKE LIPOSOMES
Published by The Royal Society of Chemistry

Polyester
carboxymethyl cellulose-montmorillonite clay
Clinical Trials

30 DAYS

PLACEBO

CURCUMIN

500mg bid

CURCUMIN WITH FENUGREEK FIBER

Reduced stress, anxiety, fatigue
Increased endogenous antioxidant markers
Decreased lipid peroxidation

OCCUPATIONAL STRESS
Clinical Trials

6 WEEKS

PLACEBO (SOYBEAN POWDER)

CURCUMIN  1000mg bid

Reduction on depression rating scale

Increased brain derived neurotropic factor

Decreased IL-1β, TNFα, salivary cortisol
Clinical Trials

12 MONTHS

PLACEBO

Cognition levels dropped

CURCUMIN/CURCUMA ESSENTIAL OIL MIX 1500mg/day

Cognition levels remained stable
Clinical Trials

8 WEEKS

PLACEBO

AMORPHOUS DISPERSION
70mg curcumin/day

NON-ALCOHOLIC LIVER DISEASE

LIVER FAT CONTENT

28% Improvement

79% Improvement

LIVER FAT CONTENT
Clinical Trials

OVERWEIGHT PATIENTS
METABOLIC SYNDROME

8 WEEKS

Had tried to lose weight but loss less than 2%

PLACEBO (Phosphatidylserine from sunflower)

CURCUMIN IN PHOSPHATIDYLSEERINE 800mg 95% curcumin 8mg piperine

Weight loss

<table>
<thead>
<tr>
<th></th>
<th>Weight loss</th>
<th>Body fat</th>
<th>Waistline</th>
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<tbody>
<tr>
<td>Carrier Control</td>
<td>4.91%</td>
<td>8.43%</td>
<td>4.14%</td>
</tr>
<tr>
<td>Curcumin/piperine</td>
<td>1.88%</td>
<td>0.70%</td>
<td>2.36%</td>
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</table>
Alzheimer’s Disease

- Deposition of amyloid beta (Aβ) peptide in the intercellular space (senile plaques)
- Formation of intraneuronal tangle due to hyperphosphorylation of axonal Tau protein
- Diffuse loss of neurons
AMYLOID PRECURSOR PROTEIN PROCESSING

ALZHEIMER'S DISEASE

AMYLOIDOGENIC

NON-AMYLOIDOGENIC

INSIDE THE CELL

Amyloid Precursor Protein Processing

Aβ
NON-AMYLOIDIOGENIC PROCESSING

ALZHEIMER’S DISEASE

$\alpha$

$A_\beta$

$sAPP_\alpha$ (Neuroprotective)
AMYLOIDOGENIC PROCESSING

ALZHEIMER’S DISEASE

AMYLOIDOGENIC PROCESSING

BACE1

sAPPβ

Aβ

Aβ

γ
TNF-α 
Interleukins 
Neuroinflammation & Neuronal Loss
METAL CHELATION

ALZHEIMER’S DISEASE

$\text{Al}^{3+} \equiv \text{Cu}^{2+} > \text{Fe}^{2+}$
ALZHEIMER'S DISEASE

Cytokine Transcription

NF-κB

IκB

NF-κB

P

IκB

Cytokine Transcription

PPARγ

Cytokine Transcription
ALZHEIMER’S DISEASE

- IL-1β
- Aβ → ROS
- Inducible nitric oxide synthase
- Glutathione-s-transferase
- Cytokine Transcription
- Microglia activation
- Apoptosis
- Plaque formation
- Neuronal Stem Cell Proliferation

- NF-κB
- PPARγ
- Cu²⁺
- Fe²⁺
MECHANISMS OF ACTION

CANCER

MOST ANTI-CANCER ACTIVITIES APPEAR TO RESIDE IN THE NON-CURCUMINOID FRACTION OF CURCUMA EXTRACT
Eureka!

Hey, what about the rest of us?
<table>
<thead>
<tr>
<th>CONTRIBUTOR/SIDE EFFECT</th>
<th>CATHARANTHUS</th>
<th>TAXUS</th>
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<tbody>
<tr>
<td>Cancer Resistance</td>
<td>Vincristine</td>
<td>Taxol</td>
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<td>Hypertension</td>
<td>Blood Pressure Reducers</td>
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<td>Viral Origin</td>
<td>Antivirals</td>
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<td>Poor Wound Healing</td>
<td>Wound Healing Properties</td>
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<td>Kidney Trophorestoratives</td>
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<td>Fungal Origin</td>
<td>Anti-Fungals</td>
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<td>Anticonvulsants</td>
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<td>Fever</td>
<td>Antipyretics</td>
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<tr>
<td>Sugar Balance</td>
<td>Hypoglycemics</td>
<td>Hypoglycemics</td>
</tr>
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</table>
MULTI-DRUG RESISTANCE
ATP-BINDING CASSETTE (ABC) TRANSPORTERS

Tip W. Loo & David M Clarke

P-Glycoprotein or MDRI
OUTSIDE THE CELL

Demethoxycurcumin

INSIDE THE CELL

Demethoxycurcumin
BOTANICALS WITH INHIBITORS OF MULTI-DRUG RESISTANCE TRANSPORTERS

- Zingiber officinalis
- Gynostemma pentaphyllum
- Silybum marianum
- Echinacea
- Humulus lupulus
- Berberis vulgaris
- Hypericum perforatum
- Rosemarinus officinalis
- Hypericum perforatum
- Zingiber officinalis
- Gynostemma pentaphyllum
Polygonum cuspidatum

Rhemania glutinosa

Schisandra chinensis

Momordica charantia

Salvia miltiorrhiza

Poria cocos

Andrographis paniculata

Scutellaria baicalensis

Glycyrrhiza uralensis

Rhemia glutinosa

Stephania tetrandra

Coptis chinensis
CANCER

COMMON FINDING

LESS ANTI-NEOPLASTIC DRUG NEEDED

IF ONE INCLUDES SOME POLYPHENOLS
LIKE CURCUMIN/RESVERATROL/BERBERINE
CANCER

INDUCES APOPTOSIS IN LEUKEMIA CELLS
VIA PARP-1 MEDIATED CASPASE-3 DEPENDENT PATHWAY

PROTECTS AGAINST DOXORUBICIN INDUCED CARDIOMYOCYTE APOPTOSIS
CANCER

VEGF INHIBITORY ACTIVITY

Vascular Endothelial Growth Factor
MECHANISMS OF ACTION

CARDIOPROTECTION

DOXORUBICIN – CURCUMIN

DOSE LIMITING USE OF DOXORUBICIN DUE TO ITS ADVERSE EFFECTS ON THE HEART AND ASSOCIATED MYOCYTES
CARDDIOPROTECTION

MAIN ISSUES WITH DOXORIFICIN

Enzymatic degradation of doxorubicin

- Aldo-Keto Reductases (AKR)
- Carbonyl Reductases (CBR)

DOXORUBICINOL / DAUNORUBICINOL

MORE CARDIOTOXIC
MORE EASILY EJECTED BY MDR
DOXORUBICIN CARDIOMYOPATHY

Kills many people
Similar to dilated cardiomyopathy
Harms mitochondria of cardiomyocytes

Increased oxidative stress, reactive O$_2$, lipid peroxidation

Activates SIRT1 (lowers mitochondrial damage)
Activates Nrf2 (turns on production of endogenous antioxidants)

Keeps NF-kB from being activated
OTHER BOTANICALS WITH Nrf2 ACTIVATION ACTIVITY

- Withania somnifera
- Silybum marianum
- Camellia sinensis
- Bacopa monieri
SUPPRESSION OF AGE-RELATED CHANGES IN INFLAMMATORY INDICES COMPARED TO NO CURCUMIN IN THEIR FOOD

<table>
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<tr>
<th></th>
<th>0.5mg/g</th>
<th>1mg/g</th>
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<tbody>
<tr>
<td>MALE</td>
<td>+6%</td>
<td>+12%</td>
</tr>
<tr>
<td>FEMALE</td>
<td>+26%</td>
<td>+15%</td>
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MEAN LIFESPAN | MEAN LIFESPAN
CONNECTIVE TISSUE

ENHANCES PRODUCTION OF MAJOR STRUCTURAL COMPONENTS OF ELASTIC FIBERS

ELASTIN

FRIBRILLIN-1

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