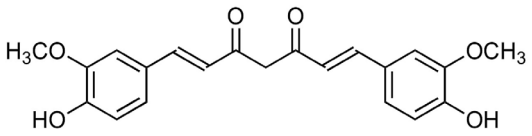
CPRO® Bioactive Curcumin

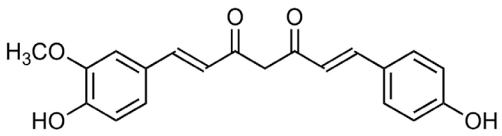
Clinical and Commercial Potential

Curcumin Overview

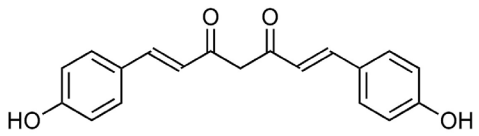
- Curcumin extracted from turmeric (spice derived from *Curcuma longa*)
- Standard curcumin extracts are predominately 3 curcuminoids



Curcumin



Demethoxycurcumin



Bisdemethoxycurcumin

- Benefits
  - >13,000 peer-reviewed articles on clinical potential and MOAs
  - Promotes health and ameliorates disease in a starting number of areas
    - cardiovascular, musculoskeletal, dermatologic, metabolic, endocrine, neurologic, autoimmune, inflammatory, GI, hepatic, cardiovascular, oncologic, psychological, and age-related disorders, improved health, longevity, etc.
- Safety
  - Tumeric is GRAS
  - No dose-limiting toxicity at doses up to 12 g/d in dose escalation study

Examples of Indications

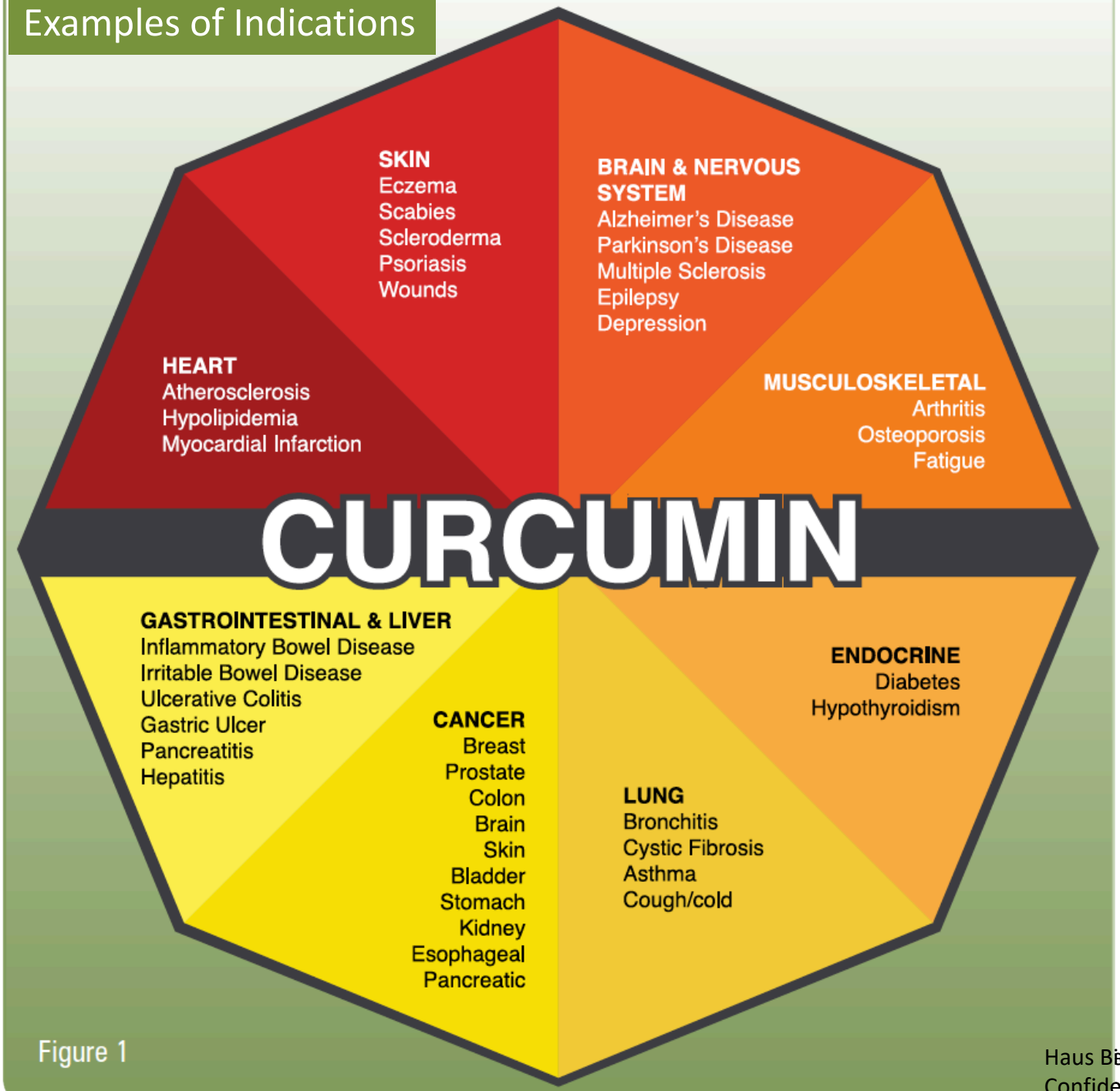


Figure 1

Standard Curcumin has Limited Clinical Potential Due to Low Bioavailability

- Very poorly absorbed
  - Hydrophobic, low water solubility
- Rapidly metabolized (liver glucuronidation), and excreted
- Low to no clinical efficacy
- Bulk wholesale costs low
  - $149/kg Naturex US
  - ~$50/kg bulk Chinese and Indian suppliers
  - Used in many retail SKUs and brands

Higher Bioavailability Formulations I
Decrease Metabolism and Excretion with Liver Metabolism Inhibitor

- Liver glucuronidase inhibitor is a black pepper-derived excipient containing piperine
- Demonstrated increased bioavailability relative to standard curcumin
- Moderate clinical efficacy, limited number of studies
- Slows elimination of many common prescription meds
  - More significant potential issue in aging populations on multiple meds
- Many brands of curcumin piperine on market
- Retail costs somewhat higher than standard curcumin

Higher Bioavailability Formulations II

Increased Absorption with Polar Particle Carrier

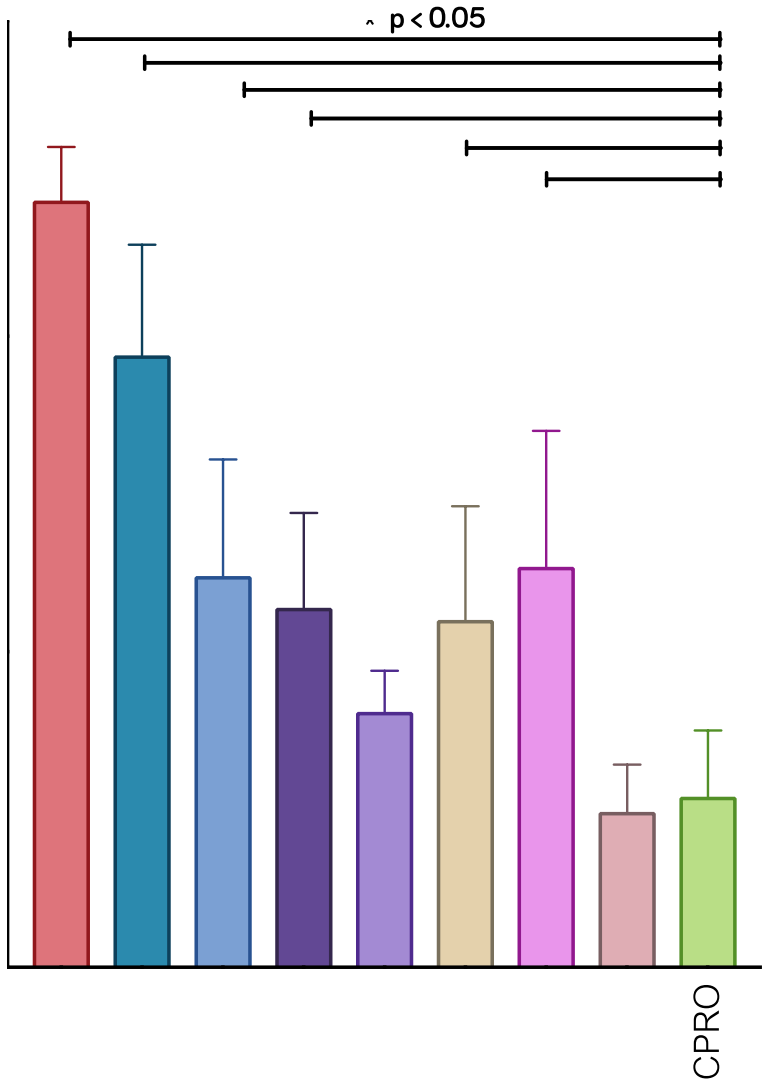
- Polar particles derived from lipid, phospholipid, and polysaccharide excipients
- Proprietary formulations
- Limited number of wholesale (bulk) and retail brands
  - BCM-95, Meriva, Theracumin, Longvida, etc.
- High clinical efficacy, large number of studies
  - Collectively, studies demonstrate striking efficacy in many indications and health and wellness issues
- High bulk wholesale and retail costs
  - ~2-4x standard curcumin (~$180-$230/kg)

Higher Bioavailability Formulations III
CPRO® Bioactive Curcumin

- Proprietary technology utilizing protein, peptide, and amino acid excipients to create polar carrier
  - Initial composition of matter patent filled 5/2014
  - Additional IP to be filed on process and use
- High clinical activity
  - Relative activity assessed by bioassay (type 2 diabetes model)
    - Higher than standard and other bioavailable curcumins
  - Demonstrated activity in variety of indications
    - Preclinical models: diabetes, Alzheimer's, Parkinson's, and rheumatoid arthritis (CIA)
    - Active in ongoing open label type 2 diabetes clinical trial
- Low bulk wholesale cost (estimates)
  - ~$95/kg at scale, at low range of wholesale bulk standard curcumin costs

Relative Clinical Activity by Bioassay

Type 2 Diabetes Model



Curcumin Healthy Aging Studies

Subset of interesting topics from the massive literature in this space

Curcumin Healthy Aging Studies Overview I
Non-Diseased and Healthy Subjects

- Increased endurance, strength, balance, flexibility, muscle mass in healthy aging subjects
- Slowed age-related cognitive decline; increased long-, short-term memory, attention span in aging, nondemented subjects
- Increased bone mineral density in healthy aging subjects with low BMD
  - Prevents drug-induced osteoporosis in preclinical models
- Effects in prediabetes
  - Prevented transition from prediabetes to type 2 diabetes
  - Reduced glycemia and hyperlipidemia, increased insulin sensitivity
- Elevated mood, increased energy

Curcumin Healthy Aging Studies Overview II
Clinical Indications

- Pain relief
  - Human subjects
    - OA, RA, headache, muscular, exercise, neuropathic, post-surgical, and odontectomy-associated pain in human subjects
  - Preclinical models
    - As above and also mechanical-, and thermal-induced hyperalgesia
  - Well defined MOA
- Metabolic syndrome and obesity
  - Reduced weight, waistline, BMI, and body fat, improved lipid profiles
- Diabetes
  - Reduced glycemia and hyperlipidemia, increased insulin sensitivity
- Ameliorates atherosclerosis, hypertension, and CVD
- Decreased depression
- Potent anti-cancer activity
- Reduced benign prostatic hyperplasia

Curcumin Healthy Aging Studies
BioSoluble Curcumins
Details on Study Designs and Results

Study Overviews and a Few Key Figures and Tables

Muscle Mass Preservation; Enhanced Endurance, Strength, Balance, Flexibility

Healthy Aging Population (>65 years old, n=86)

3 Month Open-label Trial

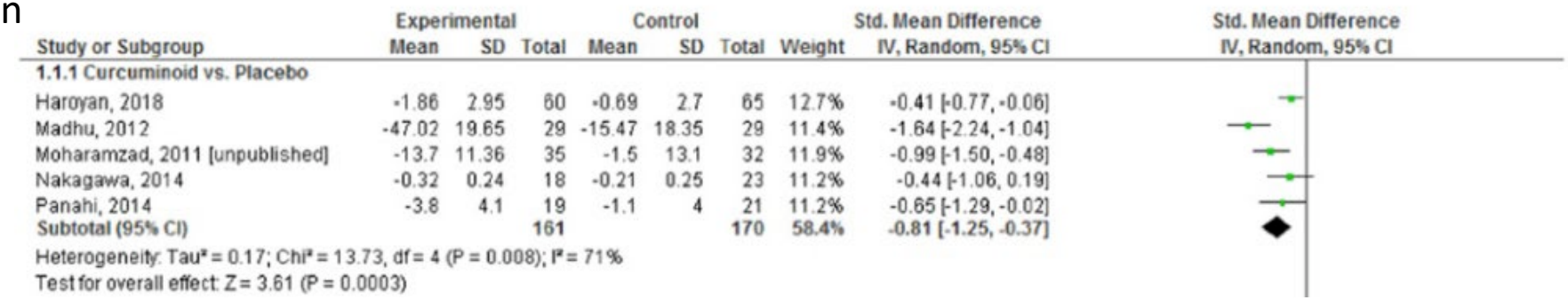
	Standard Management (Exercise) n=33		Standard Management with Curcumin n=31	
	Baseline	3 months	Baseline	3 months
Hand grip, kg	32.2 (2.1)	31.8 (2.0)	31.2 (1.5)	33.9 (1.8)*
Weight lifting	12 (2)	11 (1)	13 (1)	16 (2)*
Time/distance before eeling tired, minutes (meters for the walking test)				
Cycling	2' 20" (18")	2' 16" (12")	2' 29" (18")	3' 11" (11")*
Walking	234 (21)	239 (12)	251 (11)	311 (14)*
Climbing stairs	58" (6")	69" (5")	54" (6")	75" (3")*
General fitness, score	1.1	1.1	1.2	2.2*
Proteinuria, mg/die	244 (37)	239 (46)	239 (28)	154 (39)*
Oxidative stress, carr units	368 (24)	359 (26)	379 (31)	334 (26)*
Karnofsky scale, units	75.4 (3.2)	72.2 (1.3)	76.2 (3.4)	81.1 (2.0)*
Left ventricular ejection fraction, %	54.8 (0.2)	55 (0.4)	56.2 (0.5)	59.8 (0.3)*

*$p < 0.05$ *vs.* baseline and *vs.* standard management-only.

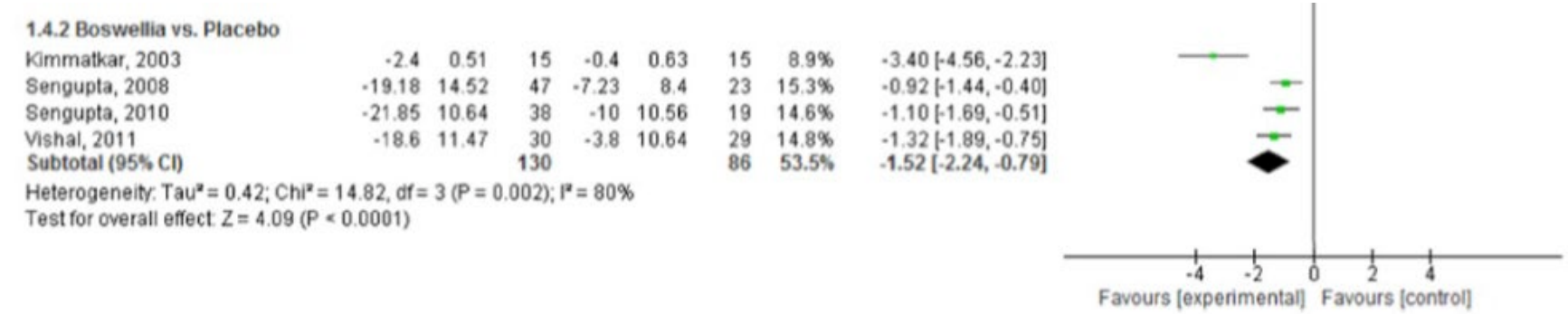
Eur Rev Med Pharmacol Sci 2016

Efficacy in Knee Osteoarthritis:
Meta-analysis of 9 Randomized Clinical Trials (n=1009)

Pain



Function



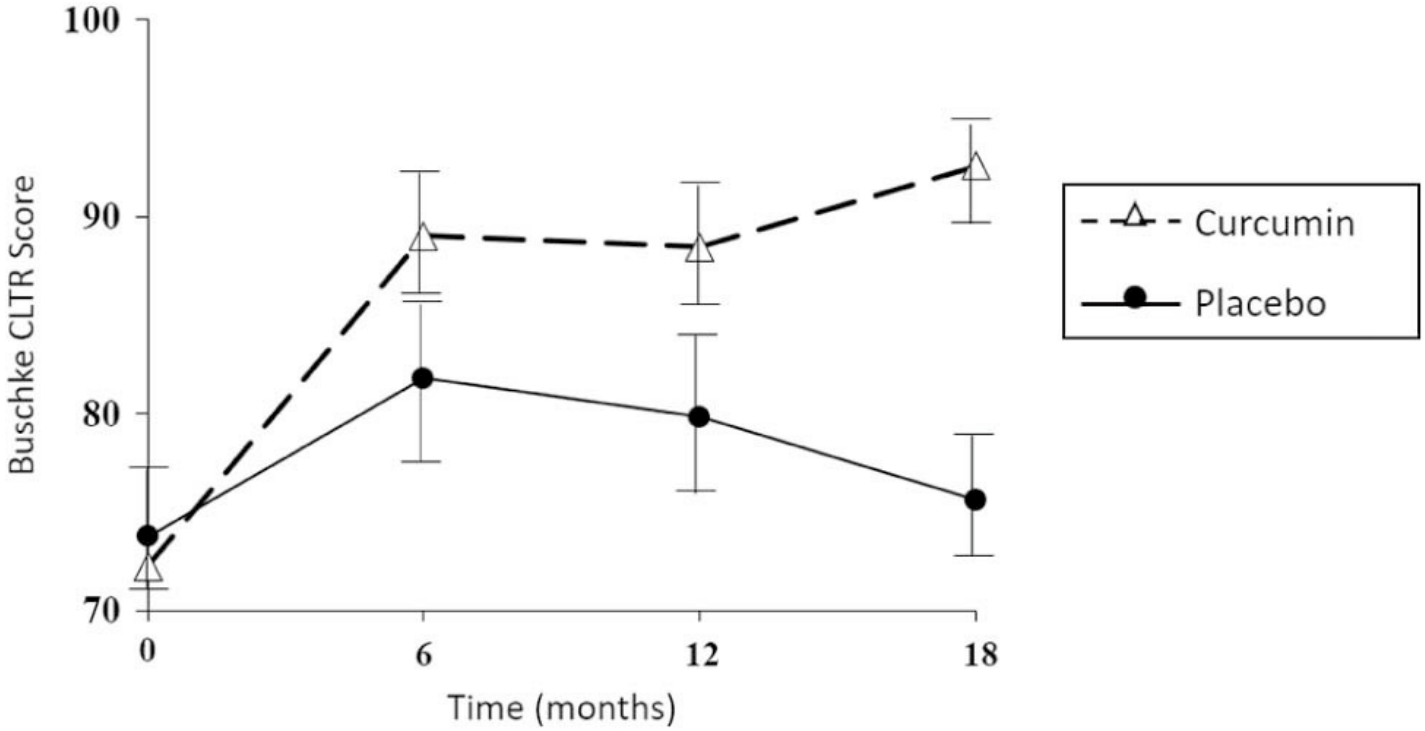
Semin Arthritis Rheum. 2018

Increased Long- & Short-term Memory, & Attention Span

Aging, Nondemented Subjects (n=40, 51-84 years old)

Randomized, Double-blind, Placebo-controlled

Buschke Selective Reminding Test of Consistent Long-Term Recall



Biosoluble curcumin - significant change from baseline @ 18m (p = 0.002)

Placebo - no significant change (p = 0.8)

Between group differences (p = 0.05)

Am J Geriatr Psychiatry 26:3, 2018,

Buschke Selective Reminding Test

- Standardized validated measure of verbal learning and memory
  - Effective predictor of dementia incidence (Masur et. al. 1990, 1994)
  - Associated with striatal L-DOPA uptake (Holthoff 1994)
- Testing Procedure
  - Subject read a list of 12 unrelated words, asked to recall words
  - After 1st trial, only words not recalled on preceding trial presented
  - Repeat until 12 words recalled 3 consecutive trials, or until 12 trials completed
- Biosoluble curcumin arm
  - Baseline recalled ~8/12 words, at 24 weeks ~11/12 words
- Placebo arm
  - Similar at baseline and 24 weeks (~8/12 words recalled)

Significant Effect Size Observed in BS Curcumin-treated Subjects with Standard Indices of Memory and Depression in Aging, Nondemented Subjects

TABLE 2. Baseline and 18-Month Cognitive and Mood Scores, Percent Changes, and Effect Sizes

	Curcumin			Placebo			Effect Size		
Measures	Baseline	18-Month	% Change	Baseline	18-Month	% Change	Within Curcumin	Within Placebo	Between Group
Buschke Selective Reminding Test									
Consistent Long Term Recall	72.3 (31.6)	92.6 (30.9)	28.1	73.7 (31.8)	75.6 (36.4)	2.6	0.63	0.06	0.68
Total	113.7 (13.9)	121.7 (13.2)	7.9	111.3 (15.6)	112.9 (18.4)	1.4	0.53	0.02	0.51
Long-Term Storage	112.1 (18.7)	119.9 (15.5)	7.0	108.0 (20.0)	111.2 (23.8)	3.0	0.40	0.08	0.33
Brief Visual Memory Test									
Recall	19.2 (6.9)	22.4 (6.4)	16.7	20.3 (6.0)	22.5 (7.8)	10.8	0.50	0.26	0.24
Delay	7.3 (2.7)	8.5 (2.1)	16.4	8.3 (2.5)	8.5 (2.8)	2.4	0.51	0.02	0.48
Trail Making Test Part A	32.6 (9.3)	24.9 (5.3)	23.6	30.5 (8.3)	28.4 (10.8)	7.4	0.96	0.28	0.67
Beck Depression Inventory	4.6 (4.5)	2.7 (2.5)	41.3	4.4 (3.4)	4.0 (5.0)	10.0	0.55	0.07	0.48

Notes: Values are provided as mean (standard deviation).

Conclusions

Daily oral Theracurmin may lead to improved memory and attention in nondemented adults

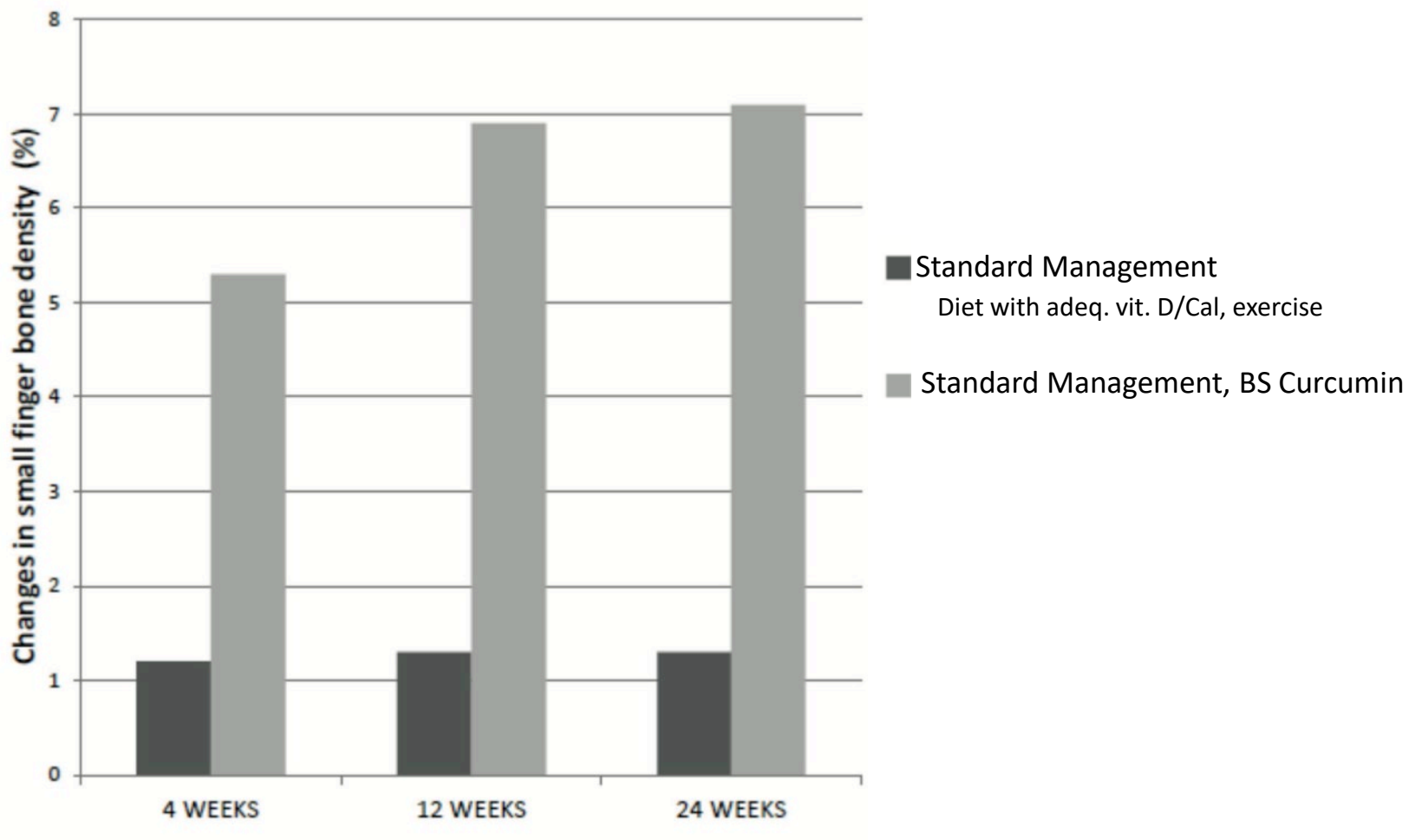
FDDNP-PET suggest symptom benefits associated with decreased amyloid and tau accumulation in mood and memory modulating brain regions

Am J Geriatr Psychiatry 26:3, 2018

Improvement in Bone Health

Asymptomatic Healthy Elderly Subjects, Low BMD (n=57, avg. age=71)

24 Week Open-label Trial



Eur Rev Med Pharmacol Sci 2017

Significant Improvement in BMD Across Multiple Assessments in BS Curcumin-treated Subjects

Table II. Assessment of the bone density in the heel bone, small finger and upper jaw.

	Standard Management				Standard Management + Meriva®			
	Inclusion	4 weeks	12 weeks	24 weeks	Inclusion	4 weeks	12 weeks	24 weeks
Heel bone density, %	100	-4	-5.4	-6	100	-12.3	-18.4*	-21.0*
Small finger bone density, GSM (range)	30.3 (13.0-36.0)	+1.2% (0.0-3.4)%	+1.3% (0.0-3.0)%	+1.3% (0.0-2.2)%	31.2 (11.0-39.0)	+5.3% (0.0-8.4)%	+6.9%* (3.0-9.0)%	+7.1%* (4.1-9.0)%
Upper jaw bone density, GSM (range)	32.7 (10.0-43.0)	+0.2% (0-2)%	+0.3% (0.0-2.4)%	+0.3% (0.0-1.9)%	33 (12.0-38.0)	+2.3% (1.0-7.7) %	+3.8 %* (2.0-7.6)%	+4.8%* (2.2-6.9)%

Data are expressed as mean (range). *$p<0.05$ vs. inclusion.

- Scans performed on 2 different devices, with different readouts
  - Bone sonometer (%) - attenuation in ultrasound transmission. Decreased transmission, increased BMD
  - Ultrasound (GSM) - grey scale measurement. Increased GSM, increased BMD

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Type 2 Diabetes Prevention

Prediabetic Subjects (n=235 >35 years old)

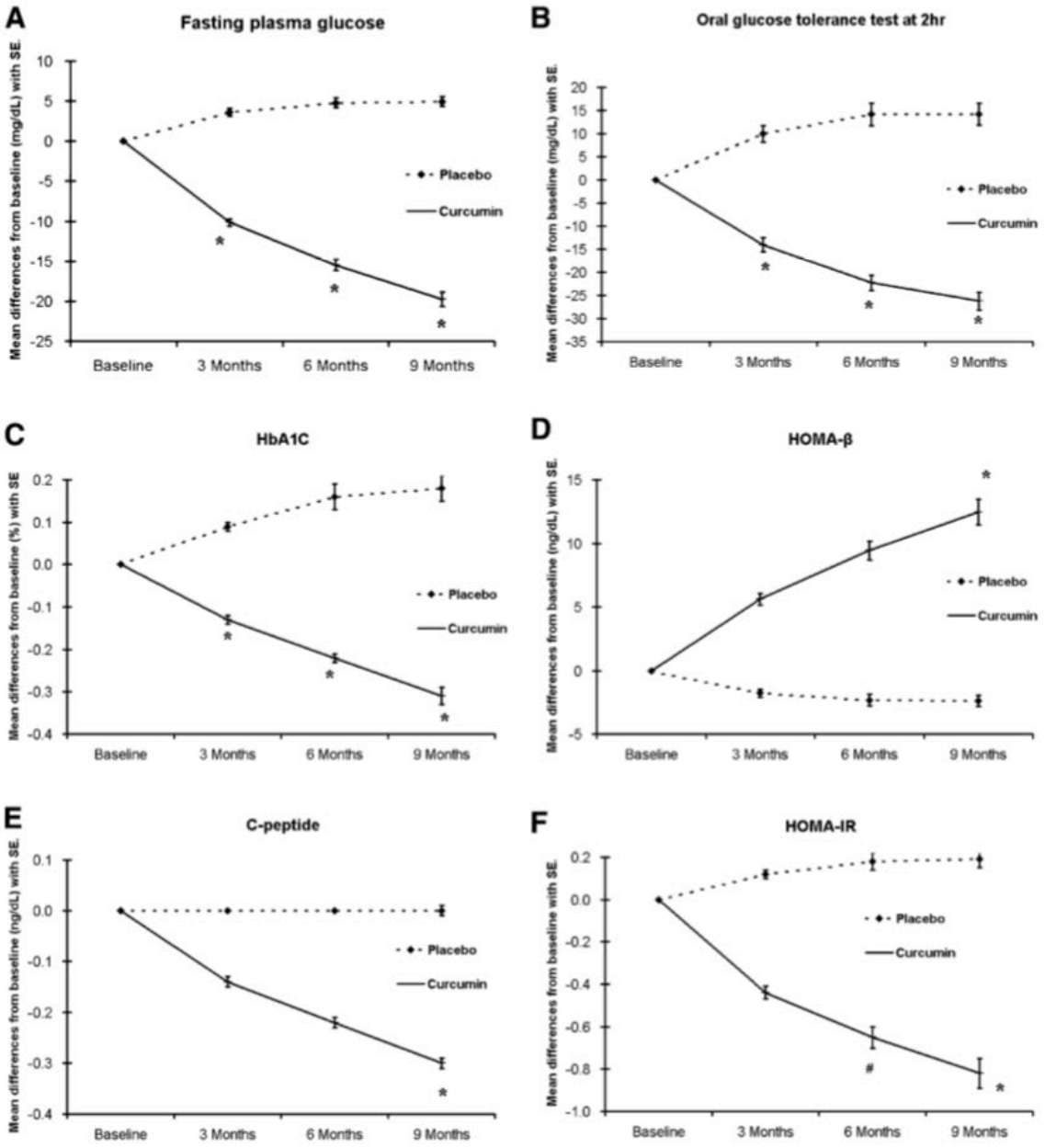
9 month Randomized, Double-blind, Placebo-controlled

Number and percent of diabetic newly diagnosed subjects during following period

Months after enrollment	Number (%) in placebo group (N = 116)	Number (%) in curcumin group (N = 119)	P value
6 months (3-month visit)	11 (9.5)	0 (0)	0.001
9 months (6-month visit)	18 (15.5)	0 (0)	<0.001
12 months (9-month visit)	19 (16.4)	0 (0)	<0.001

Diabetes Care 2012

Curcumin Improved Glycemia, Insulin Resistance, β-Cell Function



Diabetes Care 2012

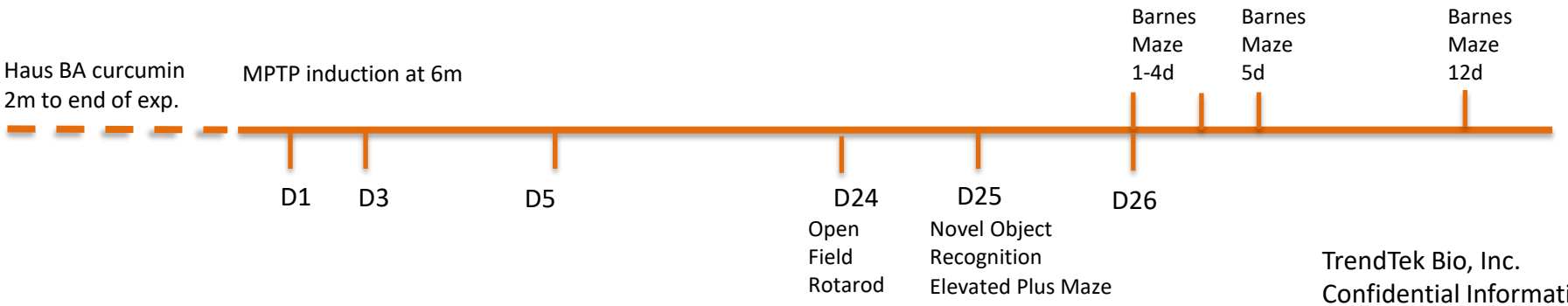
Figure 1—*Mean of parameters with SEM at baseline, 3, 6, and 9 months were compared between placebo- and curcumin-treated group.* A: *FPG.* *P < 0.01. B: *OGTT at 2 h.* *P < 0.01. C: *HbA_{1c}.* *P < 0.01. D: *HOMA-β.* *P < 0.01. E: *C-peptide.* *P < 0.05. F: *HOMA-IR.* *P < 0.001, #P < 0.05.

CPRO® Bioactive Curcumin Studies

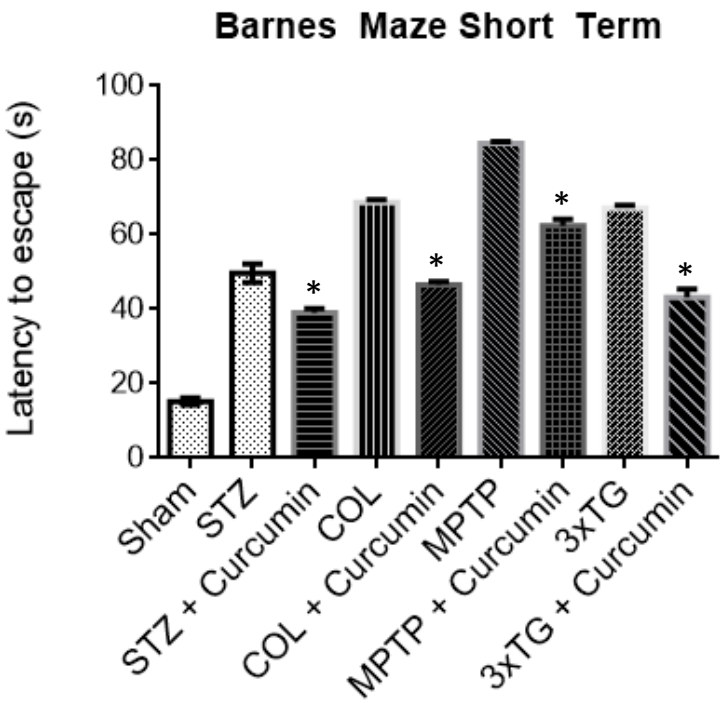
- Demonstrated preclinical efficacy
  - Diabetes, Alzheimer's, Parkinson's, and arthritis models
- Clinical studies in diabetes ongoing
  - Promising initial POC results, similar to preclinical model

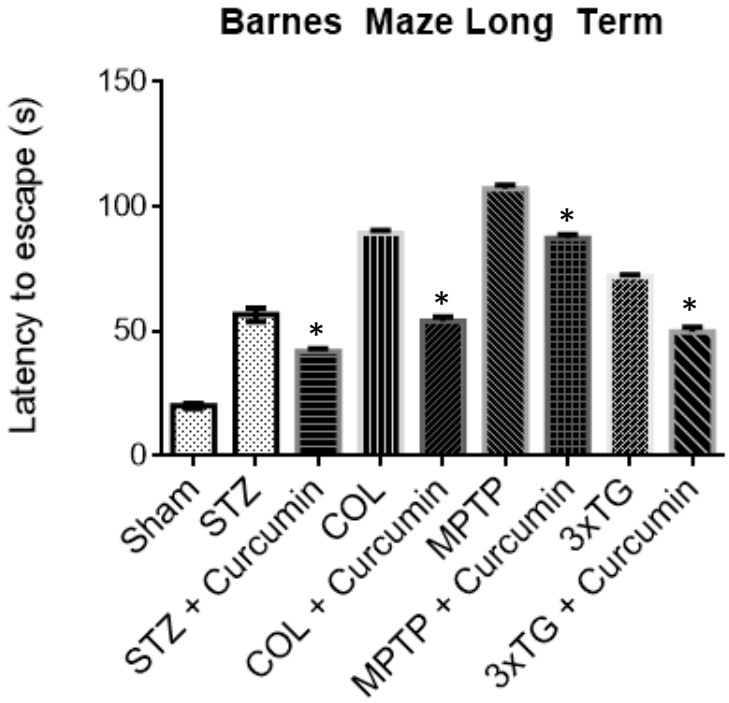
CPRO® Bioactive Curcumin Improved Short and Long-term Memory in Alzheimer's and Parkinson's Models

- Models
  - 2 spontaneous transgenic AD models
    - 3xTgAD - 3 human familial Alzheimer's disease-associated mutations
    - 5xFAD - 5 human familial Alzheimer's disease-associated mutations
  - 2 drug-induced AD models
    - Streptozotocin, Colchicine
  - 1 drug-induced Parkinson's model
    - MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
- Results of Bioactive Curcumin gavage
  - Ameliorated age-related short, long-term memory impairment (2/2 Tg models)
  - Ameliorated drug-induced short, long-term memory impairment (3/3 models)



CPRO® Bioactive Curcumin Improved Short and Long-term Memory in Alzheimer's and Parkinson's Models





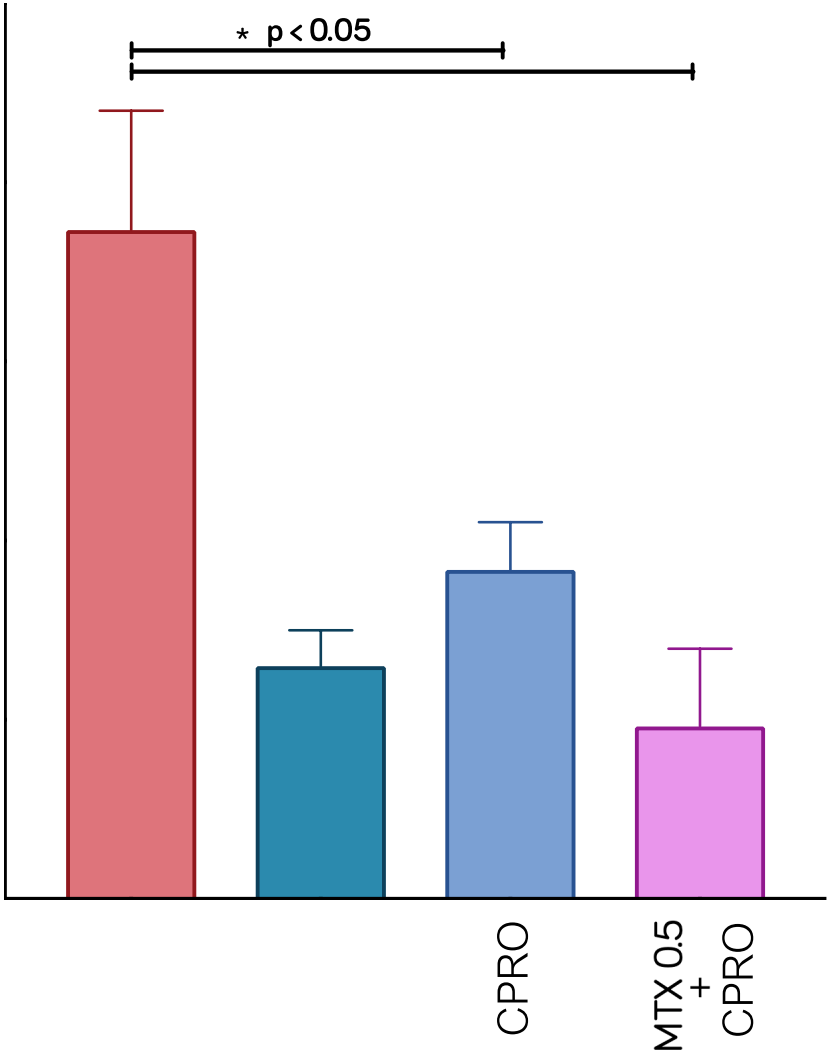
Data presented as mean +/- SEM

*p<0.05 - difference curcumin vs. sham-treated arms for given model

n=28/arm

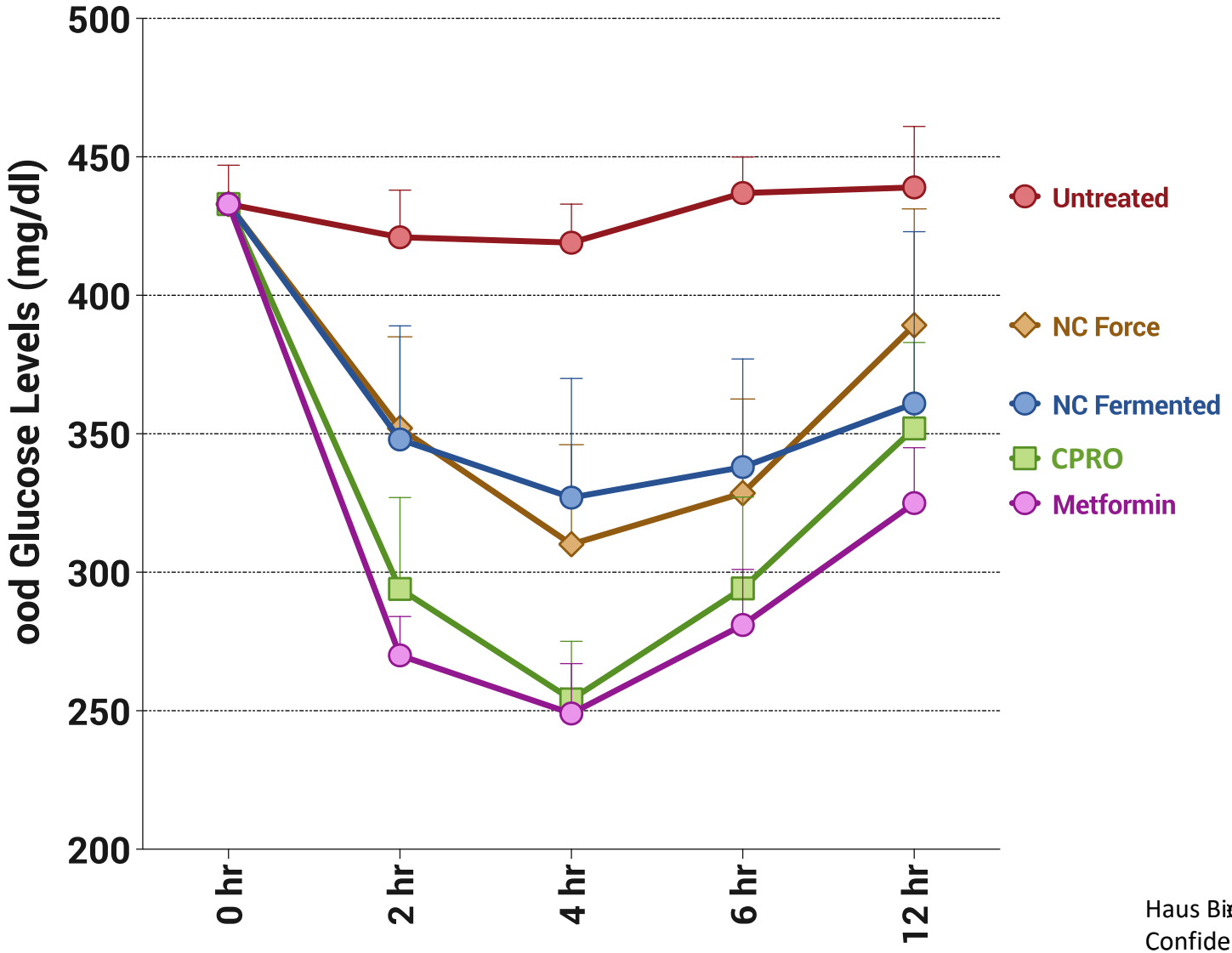
CPRO® Bioactive Curcumin

Ameliorated Disease Activity in Collagen-Induced Arthritis



Mean +/- SEM
n=6/arm

CPRO® Bioactive Curcumin Reduced Fasting Blood Glucose in a Type 2 Diabetes Model

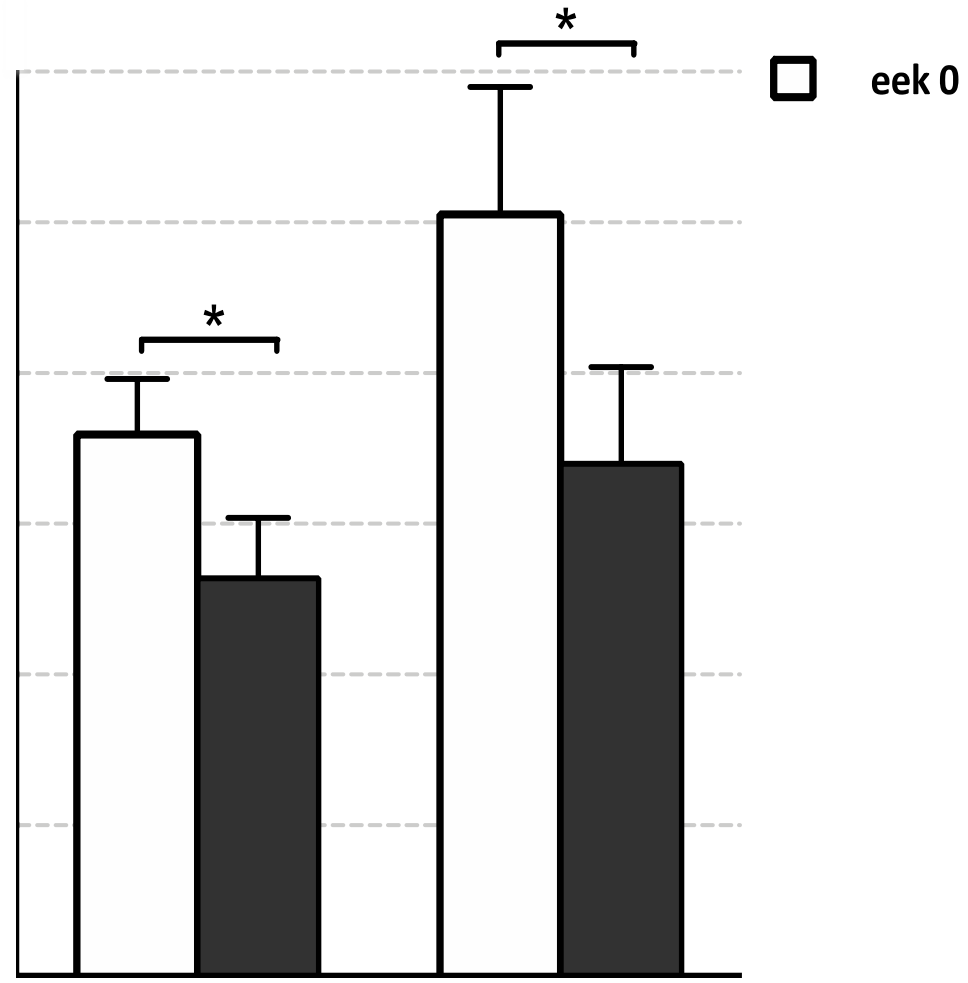


Mean +/- SE
n=6/arm

CPRO® Bioactive Curcumin Reduced Blood Glucose

Type 2 Diabetes Patients (n=17)

7 Week Open-label Trial, Fasting and Post-prandial Blood Glucose



FBG – Diabetes cutoff <126

Manufacturing, Supply Chain

- Developed proprietary production methodology
  - Optimized potency, COGs, and logistics
- Engaged high capacity pharma/supplement CMO
  - Current conjugate capacity 30 metric tons/yr, scalable
  - Q3 finish vetting suppliers, lock process, run first QC batch
- Price modeling (estimates)
  - CPRO® bulk wholesale price similar to low range of standard curcumin bulk wholesale costs
    - CPRO® curcumin bulk wholesale price ~$95/kg, at scale
      - Private label bottle available per client request bottle
  - Other bioavailable curcumins
    - Wholesale bulk price ~$200/kg

Opportunities

- Assess feasibility and potential of integrating CPRO® into ongoing programs
  - CPRO® branding or private label
    - New formulations
    - Component in existing formulations
  - Program-specific POC studies
    - Additional R&D if warranted
    - Study partnerships available upon request