ON-GOING CLINICAL STUDIES (International)

STUDY TITLE / LOCATION	PURPOSE
An evaluation of the efficacy of curcumin (BCM-95®) and saffron for the treatment of depression: a randomized, double-blind, placebo controlled trial *Murdoch University*	Randomized, double-blind, placebo-controlled 3-month study to examine the anti-depressant effects of curcumin and saffron in people with Major Depressive Disorder. **Update**: Currently enrolling
Investigating the role of curcumin (BCM-95®) in preventing Alzheimer's Disease *McCusker KARVIAH in Sydney Australia*	The study is designed to examine the lifestyle and health risk factors of participants in an older age group, living in retirement setting. Those most at risk of Alzheimer's disease (AD) will then be given BCM-95 /placebo to examine its ability to reduce or slow the risk of developing the AD. In this randomized controlled trial, 200 participants will undertake a comprehensive health assessment, including cognition, blood and buccal cell swab and lifestyle questionnaires. 100 participants, assessed as most at risk of AD aged 65-90 years, with good health and no significant cerebral vascular disease, adequate vision and hearing, with memory complaint but no objective memory impairment, Montreal Cognitive Assessment (MoCA) score greater than or equal to 26, no or minimal impairment in activities of daily living during screening will proceed to the intervention (curcumin / placebo). **Update:** Ongoing
Curcumin (BCM-95®) for the treatment of attention in children with attention deficit disorder, a randomized, double-blind, placebo controlled study *Murdoch University*	Randomized, double-blind, placebo-controlled, cross-over trial, to examine the benefits of curcumin in children with attention deficit disorder (ADD) or in children with significant attention problems. **Update**: Currently enrolling
Curcumin (BCM-95®) for the treatment of major depression: a replication and extension study *Murdoch University*	Randomized, double-blind, placebo-controlled study to examine the antidepressant effects of curcumin in people with major depressive disorder. **Update**: Currently enrolling
Modulation of endotoxaemia via curcumin (BCM-95®) intake in health overweight adults *University of Glasgow*	Participants will either consume curcumin (350mg) or placebo for 21 consecutive days and will be challenged by a high-fat high-calorie meal before and after intervention. **FDA Approved**
A Preclinical Evaluation of Curcumin Formulation (BCM-95®) alone and in combination with prednisone in FCA induced arthritic rats	Rats will be subjected to histopathological evaluation (RBC, WBC, PLT, HGB, HCT, MCV, MCH, MCHC).

ON-GOING CLINICAL STUDIES IN USA USING BCM-95

STUDY TITLE / LOCATION	PURPOSE
Randomized Trial of Adjuvant Curcumin (BCM-95®) after Radical Prostatectomy *UT Southwestern University*	To determine whether adjuvant BCM-95 improves recurrence-free survival in patients after radical prostatectomy compared to placebo. **Update:** Ongoing

	FDA APPROVED STUDY with IND Status
Placebo-Controlled Blinded Trial of Curcumin (BCM-95®) in the treatment of Cervical Intraepithelial Neoplasias (CIN) *Baylor University Medical Center*	The study is designed to determine whether curcumin can facilitate the regression of CIN3 and to evaluate the CIN3 patients for the presence of high-risk HPV. Also inflammatory panel on dysplasia biopsies will be measured to determine which factors play a role in the persistence of CIN. **Update:** Patient enrollment **FDA APPROVED STUDY with IND Status**
A Pilot, Proof of Concept Study of Curcumin (BCM-95®) in Combination with 5-FU for Patients with 5-FU Resistant Metastatic Colon Cancer *Baylor University Medical Center*	**Purpose:** The purpose of this study is to evaluate the efficacy of BCM-95 curcumin as an adjunct to conventional chemotherapy in patients with metastatic colorectal cancer. The primary objective of the study is to confirm clinical safety and determine maximum tolerated dose (if reached) of oral curcumin. The secondary objectives of the study are to identify preliminary clinical efficacy of curcumin in combination with 5-FU in chemo resistant CRC. Another purpose of the study is to retrospectively determine DNA methylation status of peripheral blood circulating tumor cells (CTC) pre-and post-curcumin treatment using archived blood from clinical responders and non-responders. **Update:** Patient enrollment **FDA APPROVED STUDY with IND Status**
Essential turmeric oil coated curcumin (BCM-95®) attenuates dextran sulfate sodium induced colitis through alteration of cytokines *Baylor University Medical Center*	**Colitis induced model to understand the pharmacology of curcumin.**
To Study the Therapeutic Effect of Curcumin (BCM-95®) in Pancreatic Cancer using PDX (Patient Derived Xenograft) *Baylor University Medical Center*	**To study, for the first time, the effect of curcumin on pancreatic cancer in the humanized animal model. Also, to measure the effect of curcumin on animal's resistance to pancreatic chemotherapy drugs.**

COMPLETED AND PUBLISHED CLINICAL TRIALS USING BCM-95

STUDY TITLE / JOURNAL	SUMMARY
BCM95 and (2-hydroxpropyl)-βcyclodextrin reverse autophagy dysfunction and deplete stored lipids in Sap C-deficient fibroblasts *Human Molecular Genetics 2015*	No effective therapies are currently available for the treatment of Sap C deficiency. It is a rare variant form of Gaucher disease caused by accelerated Sap C degradation and associated with accumulation of glucosylceramide and other lipids in the end/lysosomal dcompartment. The study provides evidence that BCM95 and HP-β-CD ehance lysosomal function promoting autophagic clearance capacity and lysosome reformation.
Curcumin potentiates antitumor activity of 5-fluorouracil in a 3D alginate tumor microenvironment of colorectal cancer *BMC Cancer 2015*	Colorectal cells encapsulated in alginate were able to proliferate in 3D-colonospheres in a viv-like phenotype and invaded from alginate. Three stages of cells were isolated, alginate proliferating, invasive, and adherent cells. Curcumin potentiated 5-FU-induced decreased capacity for proliferation, invasion, and increased more sensitivity to 5-FU of HCT116R compared to the HCT116 cells. These effects were also accompanied by a down-regulation of NF-kB activation.

Novel evidence for curcumin and boswellic acid induced chemoprevention through regulation of miR-34a and miR-27a in colorectal cancer *Cancer Prevention Research 2015*	Both curcumin and boswellic acids are well-established dietary botanicals with potent anti-tumorigenic properties which have been shown to modulate multiple oncogenic pathways. This study investigated the anti-tumorigenic effects of curcumin and 3 acetyl-11-keto-β-boswellic acid (AKBA) on modulation of specific cancer-related miRNA's in CRC cells and validated their protective effects in vivo using a xenograft mouse model. Both curcumin and AKBA inhibited cellular proliferation, induced apoptosis and cell cycle arrest in CRC cell lines, and these effects were significantly enhanced with combined treatment. Curcumin and AKBA induced upregulation of tumor-suppressive miR-34a and downregulation of miR27a in CRC cells. This provides novel mechanistic evidence for the chemopreventive effects of curcumin and AKBA through regulation of specific miRNAs in colorectal cancer.
Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colon cancer *Carcinogenesis 2015*	Resistance to chemotherapy is a major cause of mortality in colorectal cancer (CRC) patients. Chemoresistance has been linked primarily to a subset of cancer cells undergoing going epithelial-mesenchymal transition (EMT). Combined treatment with curcumin and 5FU enhanced cellular apoptosis and inhibited proliferation in both parental and 5FUR cells, whereas 5FU alone was ineffective. Curcumin suppressed EMT in 5FUR cells by downregulating BMI1, SUZ12, and EZH2 transcripts, key mediators of cancer stemness-related polycomb repressive complex subunits. This study provides novel mechanistic evidence for curcumin-mediated sensitization to 5FU-related chemoresistance through suppression of EMT in 5FUR cells via upregulation of EMT-suppressive miRNA's. This study highlights the potential therapeutic usefulness of curcumin as an adjunct in patients with chemoresistant CRC.
Curcumin and major depression: A randomized, double-blind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change *European Neuropsychopharmacology 2014*	A recent randomized, double-blind, placebo controlled study provided partial support for the efficacy of supplementation with a patented curcumin extract (500mg, twice daily) for 8 weeks in reducing depressive symptoms in people with major depressive disorder. A second exploratory analysis of salivary, urinary, and blood biomarkers collected during this study was conducted to identify potential antidepressant mechanisms of action of curcumin. Pre and post-intervention samples were provided by 50 participants diagnosed with major depressive disorder, and the IDS-SR30 was used as the primary depression outcome measure. Compared to placebo, 8 weeks of curcumin supplementation was associated with elevations in urinary thromboxane, and substance P; while placebo supplementation was associated with reductions in aldolsterone and cortisol. Higher baseline plasma endothelin-1 and leptin in curcumin-treated individuals was associated with greater reductions in IDS-SR30 score after 8 weeks of treatment. Our findings demonstrate that curcumin supplementation influences several biomarkers that may be associated with antidepressant mechanisms of action.
Curcumin (BCM-95) Suppresses Crosstalk between Colon Cancer Stem Cells and Stromal Fibroblasts in the Tumor Microenvironment: Potential Role of EMT *PLOS ONE 2014*	Interaction of stromal and tumor cells plays a dynamic role in initiating and enhancing carcinogenesis. In this study, we investigated the cross talk between colorectal cancer (CRC) cells with stromal fibroblasts and the anti-cancer effects of curcumin and 5-Fluoruracil (5-FU), especially on cancer stem cell (CSC) survival in a 3D-co-culture model that mimics *in vivo* tumor microenvironment. Study will analyze the effects on tumor microenvironment in co-cultures supported by intensive cross-talk between cancer cells and fibroblasts (abundant cell-cell-contacts; vesicle exchange), and enhanced up-regulation of metastatic active adhesion molecules (β1-integrin, ICAM-1), transforming growth factor-β (TGF-β) and down-regulation of proliferation associated proteins (cyclin D1; Ki-67). Study will study the effect of this model on various stem cell markers such as MMP-1/-9/-13, Cox-2, NF-kB, TGF-β3 and cancer stem cell survival factors such as CD133, CD44 and ALDH1 in HCT116 monolayers vs. high-density 3D-co-cultures. A better understanding of such a unique, state-of-the-art 3D model system in studying tumor microenvironment for cancer preventative and therapeutic interventions will revolutionize approach for developing treatment approaches for various human cancers.
Curcumin for the treatment of major depression: A randomized, double-blind, placebo controlled study *Journal of Affective Disorders 2014*	This is a double blind, placebo controlled study assessing the antidepressant, antioxidant and anti-inflammatory effects of curcumin in 40-60 adults suffering from major depression (mild to moderate severity). Participants will be randomly allocated into either a curcumin (BCM-95® - 500mg twice daily) or placebo group and changes in depression, anxiety and general health will be measured over an 8-week period. The aim of this study is also to investigate potential mechanisms of action of curcumin. Urine, saliva and blood samples will be collected at the beginning and completion of the study. Levels of cortisol, kynurenine pathway metabolites (measure of inflammation) and oxidative stress markers will be assessed over time.

Curcumin Chemosensitizes 5-Fluorouracil Resistant MMR-Deficient Human Colon Cancer Cells in High Density Cultures *PLOS ONE 2014*	This *in vitro* study investigated the effectiveness of 5-FU and plant polyphenol (curcumin) in context of DNA mismatch repair (MMR) status and CSC activity in 3D cultures of CRC cells. High-density 3D cultures of CRC cell lines HCT116, HCT116+ch3 (complemented with chromosome 3) and their corresponding isogenic 5-FU-chemo-resistant derivative clones (HCT116R, HCT116+ch3R) were treated with 5-FU either without or with curcumin in time- and dose-dependent assays. Pre-treatment with BCM-95® significantly enhanced the effect of 5-FU on HCT116R and HCR116+ch3R cells, in contrast to FU alone as evidenced by increased disintegration of colonospheres, enhanced apoptosis and by inhibiting their growth.
A Pilot Clinical Trial of Radioprotective Effects of Curcumin Supplementation in Patients with Prostate Cancer *Journal of Cancer Therapy 2013*	Some previous *in vitro* and *in vivo* studies have proposed a radioprotective role for curcumin, the yellow pigment of turmeric. The purpose of this investigation was to assess the radioprotective effects of curcumin supplementation in subjects undergoing external beam radiotherapy (EBRT) were randomly assigned to curcumin group, taking 3 g/d curcumin (6 × 500 mg capsules of BCM95 n=20), or placebo group (n=20). Quality of life was assessed by the quality of life questionnaire (QLQ-PR25). Analysis of covariance was used to compare radiotherapy related symptoms between groups following the intervention, adjusted for baseline symptoms. No differences in urinary symptoms, bowel symptoms, treatment related symptoms and sexual activity were observed between the curcumin and placebo groups before the intervention. **The change in urinary symptoms across the 20-week period differed significantly between groups (p=0.011) and subjects in the curcumin group experienced much milder urinary symptoms compared with the placebo group**. No group differences were observed in any other domain of the QLQ-PR25. Curcumin can confer radioprotective effect through reducing the severity of radiotherapy related urinary symptoms.
Efficacy and Safety of Curcumin in Major Depressive Disorder: A Randomized Controlled Trial *Phytotherapy Research 2013*	A randomized comparative human clinical study was done to evaluate the effect of curcumin on mood. Sixty subjects were randomized to receive 20 mg/d of a SSRI (n=20), 500 mg BCM-95® (n=20), and SSRI plus BCM-95® (n=20) for 6 weeks. The 17-item Hamilton Rating Scale (HAMD-17) was the primary efficacy measurement. CGI-S was the secondary efficacy measure. Overall compliance by the study participants was excellent. The proportion of responders as measured by the HAM-D17 scale was higher in the combination group (77.8%) than in the SSRI (64.7%) and the curcumin (62.5%) groups; however, these data were not statistically significant (P = 0.58). **Interestingly, the mean change in HAM-D17 score at the end of six weeks was comparable in all three groups (P = 0.77).**
Clinical Evaluation of a formulation containing curcuma longa and boswellia serrate extracts in the management of knee osteoarthritis *Molecular Medicine Reports 2013*	A formulation containing Curcuma longa (BCM95) and Boswellia serrata (Bospure) extracts was evaluated for safety and efficacy in subjects and directly compared with a selective COX-2 inhibitor. In total, 54 subjects were screened, 30 subjects were enrolled and 28 completed the study. The treatment was well tolerated and did not produce any adverse effect in subjects, as judged by the vital signs, hemogram, liver and renal function tests. **The formulation at 500 mg administered twice a day, was more successful than administration of the COX-2 inhibitor (100 mg twice a day) for symptom scoring and clinical examination.** The formulation was found to be safe and no dose-related toxicity was found.
A Randomized, Pilot Study to Assess the Efficacy and Safety of Curcumin in Patients with Active Rheumatoid Arthritis *Phytotherapy Research 2012*	This pilot clinical study evaluated the safety and effectiveness of curcumin alone, and in combination with an NSAID. Forty-five subjects were randomized into three groups with subjects receiving Curcumin BCM-95 (500 mg) and NSAID (50 mg) alone or their combination. The primary and secondary endpoints were reduction in (DAS) 28 Score and ACR score, assessments used by clinicians that measures various joint-related parameters. Subjects in all three-treatment groups showed statistically significant changes in their DAS scores. Interestingly, **the Curcumin group showed the highest percentage of improvement in overall DAS and ACR scores (ACR 20, 50 and 70) and these scores were significantly better than the subjects in the NSAID group.** More importantly, curcumin treatment was found to be safe and did not relate with any adverse events.
The Effects of Exercise and Nutritional	

Supplementation on Proinflammatory Cytokine Expression in Young Racehorses During Training *Journal of Equine Veterinarian Science 2012*	The inflammatory response to vigorous exercise ranges from the mild symptoms of delayed-onset muscle soreness to debilitating injuries affecting soft tissue, joint, and bone. Although there is a great deal of information available on the inflammatory response to exercise in human athletes, less information is available regarding the inflammatory response to exercise in young horses undergoing training for racing careers. Here, we assessed the cytokine response to exercise in a group of young Thoroughbred racehorses during their initial training. Because there is interest in nonpharmacologic approaches to control or ameliorate exercise-induced inflammation, we also examined the anti-inflammatory effect of a nutritional supplement fed to half of the horses undergoing training. Twenty-five Thoroughbred horses aged 2 years were followed through their initial race training. Peripheral blood samples were collected at various times during the exercise for the quantitation of lactic acid, oxidative stress, and inflammatory cytokine gene expression. There was an intensity-dependent effect of exercise on lactate, malondialdehyde, and proinflammatory cytokine gene expression. Although training itself was associated with an overall reduction in inflammatory markers, horses receiving the supplement exhibited further reductions in their indicators of inflammation. As such, this study provides novel evidence of nutritional supplementation reducing post-exercise inflammation. The nutritional supplement consist of formulation made from BCM-95®, BosPure, HydroQSorb, Glycocarn and d-Ribose was fed to the horses twice daily with meals provided everyday throughout the study period. Although exercise-induced changes in cytokine gene expression have been widely studied using treadmill-based exercise tests, the cytokine response to race training had not been investigated in Thoroughbred racehorses. Here, the exercise under race training conditions is associated with the temporal induction of cytokines characteristic of the initial elevation in LAK cell activity immediately after exercise and the subsequent expression of proinflammatory cytokines 2 hours later. These time- and intensity-dependent changes in cytokine gene expression parallel data from previous studies using treadmill-based exercise testing. There were signs of adaptation to exercise over the training period as indicated by an overall reduction in the expression of proinflammatory cytokines and increased expression of IL-6. Although dietary supplements have been used in horses in the past for various reasons, including performance enhancement, their effect on race training has not been investigated. **The nutritional supplement used in this study was associated with an enhanced adaptation to exercise in terms of a significant reduction in proinflammatory cytokine expression before and after exercise**. This underscores the potential for nutritional supplementation to reduce exercise-induced inflammatory pathologies in racehorses.
Effect of Citrus Polyphenol – and Curcumin- supplemented Diet on Inflammatory State in Obese Cats *British Journal of Nutrition 2011*	Among obesity-associated disorders, low-grade inflammation has been described. The putative therapeutic properties of citrus and Curcumin polyphenols could be associated with their anti-inflammatory properties. Two diets supplemented either with hesperidin (0•05 %) and naringin (0•1 %) from citrus extract or with highly bioavailable Curcumin (BCM-95®) from Curcuma longa extract (0•09 %) were fed to eight obese cats for two 8-week periods (cross-over study design) while maintaining animals in an obese state. Plasma acute-phase protein (APP; a1-acid glycoprotein (AGP), serum amyloid A and ptoglobin) levels were assessed before and at the end of each test period. TNFa, IL-1b, IL-2, IL-4, IL-5, IL-10, IL-12, IL-18, transforming growth factor-b, interferon (IFN)-g mRNA levels were determined in peripheral blood mononuclear cells (PBMC) by real-time PCR. Compared with pre-study values, supplementation with citrus polyphenols resulted in lower plasma AGP and haptoglobin concentrations, while that with curcumin resulted in lower plasma AGP concentration. There were no differences between the supplementations. TNF-a, IL-1b, IL-4, IL-5, IL-10, IL-12, IL-18, transforming growth factor-b, mRNA levels remained unaffected by either dietary supplementation. In contrast, IFN-g and IL-2 mRNA levels were lower at the end of the citrus and the curcumin supplementation, respectively. There were no differences between the supplementations. **The present study results show a slight effect of citrus and curcumin supplementation on inflammatory markers expressed by PBMC**, and a decreased concentration of APP, which are mainly expressed by the liver. This would confirm that hesperidin and naringin or highly bioavailable curcumin extract have beneficial effects, targeted in the liver and could improve the obesity-related inflammatory state.
Evaluation of antidepressant like activity of curcumin and its combination with Fluoxetine and Imipramine: an Acute and Chronic Study	Curcumin is the active ingredient of commonly used spice Curcuma longa Linn. In the present study, the mood-modulating activity of curcumin (BCM-95®) and its combination with SSRIs was studied in acute model (three doses 24, 5 and 1 h before test) of forced swimming test (FST) in glass jar and tail

Acta Pol Pharmaceuticals 2011	suspension test (TST) in mice and in chronic model (14 day study) of FST with water wheel in rats. All the tests were carried out in the following seven groups (n = 6 in each group), administered orally (doses for mice): Both the acute model of FST and TST, and the chronic model of FST with water wheel showed significant activity of curcumin in 100 mg/kg dose as compared to vehicle control ($p < 0.05$). The effect of curcumin (100 mg/kg) was similar to that of SSRIs ($p > 0.05$) but its addition to SSRIs did not improve their activity ($p > 0.05$). Curcumin increased both the swimming and climbing behavior in FST, thus its mood-modulating activity could be due to an increase in serotonin, norepinephrine and dopamine levels in the brain. **Curcumin can be a useful mood-modulator especially in cases which respond to drugs having mixed effects on serotonin and catecholamines levels in the brain.**
Suppression of Proliferation and Invasive Behavior of Human Metastatic Breast Cancer Cells by Dietary Supplement *Integrative Cancer Therapies 2011*	The study was to evaluate the effect of the dietary supplement BreastDefend (BD) containing BCM-95 on proliferation and invasive behavior of highly metastatic human breast cancer cells in vitro. Methods: Cell proliferation and cytotoxicity of supplement was evaluated in MDA-MB-231 cells treated with BD (0-40 µg /ml) by MTT assay and trypan blue staining respectively. Expression of cell cycle regulatory genes was determined by DNA-microarray analysis. Effect of BD on invasiveness was assessed by cellular adhesion, migration and invasion assays. BD treatment of cells MDA-MB-231 resulted in the cytostatic inhibition of cell proliferation with IC50 22.2, 19.1, 17.5 µg /ml for 24, 48 and 72 hours. The inhibition of proliferation was mediated by the upregulation expression of CCNG1, CHEK1, CDKNiC, GADD45A and E2F2 whereas BD down regulated expression of CCNA1 and CDK6 genes. The induction of expression of GADD45A and inhibition of expression of cyclin A1 (gene CCNA1) by BD was also confirmed on the protein level. BD treatment suppressed the invasive behavior of MDA-MB-231 cells by the inhibition of cellular adhesion, migration and invasion. This inhibition of invasiveness was mediated by the suppression of secretion of urokinase plasminogen activator (uPA) and by the down regulation of expression of CXCR4 in breast cancer cells treated with BC. **BD inhibits proliferation and invasive behavior of the highly metastatic human breast cancer cells in vitro.**
Suppression of growth and invasive behavior of human prostate cancer cells: mechanism of activity *International Journal of Oncology 2011*	In the present study we have evaluated the r effects of dietary supplement ProstaCaid™ (PC) which contains mycelium from medicinal mushrooms (Ganoderma lucidum, Coriolus versicolor, Phellinus linteus), saw palmetto berry, pomegranate, pumpkin seed, green tea [40% epigallocatechin-3-gallate (EGCG)], Japanese knotweed (50% resveratrol), extracts of turmeric root (BCM-95®), grape skin, pygeum bark, sarsaparilla root, Scutellaria barbata, eleuthero root, Job's tears, astragalus root, skullcap, dandelion, coptis root, broccoli, and stinging nettle, with purified vitamin C, vitamin D3, selenium, quercetin, citrus bioflavonoid complex, ß sitosterol, zinc, lycopene, alpha lipoic acid, boron, berberine and 3.3'-diindolymethane (DIM). We show that PC treatment resulted in the inhibition of cell proliferation of the human hormone refractory (independent) PC-3 prostate cells in a dose- and time-dependent manner with IC50 56.0, 45.6 and 39.0 µg/ml for 24, 48 and 72 h, respectively. DNA microarray analysis demonstrated that PC inhibits proliferation through the modulation of expression of CCND1, CDK4, CDKN1A, E2F1, MAPK6 and PCNA genes. In addition, PC also suppresses behavior of PC-3 by the inhibition of cell adhesion, cell migration and cell invasion, which was associated with the down-regulation of expression of CAV1, IGF2, NR2F1, and PLAU genes and suppressed secretion of the urokinase plasminogen activator (uPA) from PC3 cells. **In conclusion, the dietary supplement PC is a promising natural complex for support of prostate health.**
Comparative bioavailability of curcumin, turmeric and BCM-95 in traditional vehicles using non-everted rat intestinal sac model *Journal of Functional Foods 2010*	The bioavailability of curcumin from turmeric, BCM-95® and as plain curcumin was investigated using conventional vehicles by a non-everted rat intestinal model. Results of *ex vivo* intestinal permeability studies showed an enhancement in the permeability of curcumin with increase in lipophilicity of the vehicle used. Maximum permeability of curcumin was obtained from corn oil (13.4%) followed by clarified butter (9.82%), milk (4.24%) and aqueous suspension (1.66%) in 8 h. Another very interesting and important observation was that **the permeation of curcumin was more from BCM-95® than from plain curcumin.** These studies strongly suggest that curcumin may be consumed as turmeric/BCM-95® in lipophilic vehicles instead of plain curcumin for maximum beneficial effects
ProstaCaid Induces G2/M Cell Cycle	

Arrest and Apoptosis in Human and Mouse Androgen-Dependent and Independent Prostate Cancer Cells *Integrative Cancer Therapies 2010*	ProstaCaid containing BCM-95®, a novel integrative blend of vitamins, minerals, multi-herb extracts, and derivatives, were tested in human and mouse androgen–dependent (AD) and –independent (AI) prostate cell lines. ProstaCaid shows growth inhibitory effects on both human and mouse AD prostrate cells (LNCaP and CASP 2.1) and AI prostate cells (PC3 and CASP 1.1) in a dose-/time-dependent manner. Consistently, long-term treatment with ProstaCaid also reduced colony formation capacities these cells. Flow cytometry assays revealed that ProstaCaid induces G2/M arrest and apoptosis in LNCaP and PC3 cells after 72 hours of treatment. Immunoblotting assay demonstrated that 25 mg/mL of ProstaCaid treatment resulted in (1) the reduction of cyclin D1, cyclin B1, and Cdc2 expression in a time-dependent way; (2) increase in p21WAF1/Cip1 as early as 12 hours after the treatments in PC3 cells and reduction to base line at the 72-hour time point; and (3) repression of Bcl-2, BclxL, and induction of Bim as well as the cleavages of caspase-3 and poly(ADP-ribose) polymerase (PARP) at 72 hours of treatment, suggesting caspase-3-dependent apoptosis. Moreover, ProstaCaid suppressed activation of AKT and MAPK signaling pathways in PC3 and LNCaP cells by reducing phosphorylation levels of AKT, its downstream target S6 ribosomal protein and GSK3b, and ERK1/2, respectively. In summary, **these findings strongly suggest that ProstaCaid may be a potential therapeutic agent for prostate health.**
Six Month Randomized Placebo-Controlled, Double-Blind, Pilot Clinical Trial in Patients with Alzheimer's Disease *Journal of Clinical Psychopharmacology 2008*	Thirty-four subjects were eligible for this double blind, placebo-controlled, randomized, 6-month trial if they were 50 years old or older, ethnic Chinese in Hong Kong, had progressive decline in memory and cognitive function for 6 months, and had met NINCDS-ADRDA criteria. Subjects were randomized in 3 Groups each taking 4 grams of placebo, 1 gram of Bioavailable Curcumin (BCM-95®) and 4 grams of conventional curcumin extract. At 0, 1 and 6 months plasma was taken to measure antioxidants and serum to monitor AB and liver and kidney functions. **Over 1 month, Vitamin E levels in plasma were significantly increased in bioavailable Curcumin group compared to others. Moreover, subjects taking bioavailable curcumin had greater levels of curcuminoids than the other. Serum beta-Amyloids tended to rise possibly reflecting an ability of curcumin to disaggregate beta-Amyloids deposits in the brain, releasing them for circulation and disposal.** There were no side effects reported in highly bioavailable curcumin group, rather there were few adverse events on conventional curcumin group.
A Pilot Cross-Over Study to Evaluate Human Oral Bioavailability of BCM-95, A Novel Bioenhanced Preparation of Curcumin *I Journal of Pharmaceutical Science 2008*	Curcumin, the bioactive component of turmeric, Curcuma longa has an exceptionally wide spectrum of health-promoting activities. However, although in vitro and animal studies have shown reported beneficial activities of curcumin, its poor bioavailability in the human body has severely limited its application. Methods to increase its oral bioavailability are a subject of intense current research. Reconstituting curcumin with the noncurcuminoid components of turmeric has been found to increase the bioavailability substantially. In the present clinical study to determine the bioavailability of curcuminoids, BCM-95® was tested on human volunteer group. Normal curcumin was used in the control group. Curcumin content in blood was estimated at periodical intervals. After a washout period of two weeks the control group and drug group were crossed over BCM-95®CG and curcumin, respectively. It was also compared with a combination of curcumin-lecithin-piperine which was earlier shown to provide enhanced bioavailability. **The results of the study indicate that the relative bioavailability of BCM-95®CG (BCM-95) was about 6.93-fold compared to normal curcumin and about 6.3-fold compared to curcumin-lecithin-piperine.**
Curcumin Effects on blood lipid profile in 6-month human study *Pharmacological Research 2007*	Study in animals and a short-term human study have suggested that curcumin decreases serum cholesterol concentration. However, no controlled human trials have examined the effect of curcumin on cholesterol. This study investigated the effects of consuming curcumin on the serum lipid profile in men and women. Elderly subjects (n=36) consumed 4 g/d conventional curcumin, 1g/d BCM-95 or placebo in 6 month randomized double-blind trial. Plasma curcumin and its metabolites were measured at 1 month, and the serum lipid profile was measured at baseline, 1 month and 6 months. The plasma concentration was greater for BCM-95 than conventional curcumin. Consumption of either dose of curcumin did not significantly affect triglycerols or total LDL over 1 month or 6 month. However **there was increase in HDL for BCM-95 group without any side effects but there was a tendency toward fewer adverse events with conventional curcumin group.**

