PUBLISHED STUDIES ON

Bio-Curcumin®

BCM-95®

With Study Results Summary

1. **Effect of citrus polyphenol-and curcumin-supplemented diet on inflammatory state in obese cats**. 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 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 haptoglobin) levels were assessed before and at the end of each test period. TNF-a, 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. [Leray V, Freuchet B, Le Bloc'h J, Jeusette I, Torre C, Nguyen P. Effect of citrus polyphenol-and curcumin-supplemented diet on inflammatory state in obese cats. British Journal of Nutrition. 2011 Oct;106(S1):S198-201.]

2. **A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis.** Curcumin is known to possess potent anti-inflammatory and antiarthritic properties. This pilot clinical study evaluated the safety and effectiveness of curcumin alone, and in combination with diclofenac sodium in patients with active rheumatoid arthritis (RA). Forty-five patients diagnosed with RA were randomized into three groups with patients receiving curcumin (500 mg) and diclofenac sodium (50 mg) alone or their combination. The primary endpoints were reduction in Disease Activity Score (DAS) 28. The secondary endpoints included American College of Rheumatology (ACR) criteria for reduction in tenderness and swelling of joint scores. Patients 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 patients in the diclofenac sodium group. More importantly, curcumin treatment was found to be safe and did not relate with any adverse events. Our study provides the first evidence for the safety and superiority of curcumin treatment in patients with active RA, and highlights the need for future large-scale trials to validate these findings in patients with RA and other arthritic conditions. [Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytotherapy research. 2012 Nov;26(11):1719-25.]

3. **Synergistic and additive effects of modified citrus pectin with two polybotanical compounds, in the suppression of invasive behavior of human breast and prostate cancer cells.** The objective of this study was to evaluate the combined effect of a known galectin-3 inhibitor, PectaSol-C modified citrus pectin (MCP), and 2 novel integrative polybotanical compounds for breast and prostate health, BreastDefend (BD) and ProstaCaid (PC), on invasive behavior in human breast and prostate cancer cells in vitro, respectively. The effect of MCP and BD and of MCP and PC on invasiveness was assessed by cell adhesion, cell migration, and cell invasion assays. Secretion of urokinase plasminogen activator (uPA) was determined by Western blot analysis. Although low concentrations of MCP (0.25-1.0 mg/mL) do not suppress cell adhesion of breast or prostate cancer cells, the combination of MCP with BD or PC synergistically inhibits adhesion of these cells. Dose-dependent inhibition of breast and prostate cancer cell migration by MCP (0.25-1.0 mg/mL) is synergistically enhanced by BD (20 µg/mL) and

PC (10 µg/mL), respectively. BD or PC did not further inhibit the invasion of breast and prostate cancer cells by MCP; however, the combination of MCP with BD or PC suppressed secretion of uPA from breast and prostate cancer cells, respectively. The combination of MCP with BD and of MCP with PC synergistically inhibits the metastatic phenotypes of human breast and prostate cancer cells, respectively. Further studies confirming these observations in animal models of breast and prostate cancer metastasis are warranted. [Jiang J, Eliaz I, Sliva D. Synergistic and additive effects of modified citrus pectin with two polybotanical compounds, in the suppression of invasive behavior of human breast and prostate cancer cells. Integrative cancer therapies. 2013 Mar;12(2):145-52.]

4. **A pilot clinical trial of radio protective effects of curcumin supplementation in patients with prostate cancer.** Patients with prostate cancer who accede to radiation therapy usually experience several side effects and these toxicities are sometimes dose limiting. 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 patients with prostate cancer. Forty prostate cancer patients 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 Persian version of the European Organization for Research and Treatment of Cancer prostate cancer-specifc 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 signifcantly between groups (p=0.011) and patients 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 in patients with prostate cancer who undergo radiation therapy through reducing the severity of radiotherapy related urinary symptoms. However supplementation with 3 g/day curcumin could not reduce the severity of bowel symptoms or other treatment related symptoms. [Hejazi J, Rastmanesh R, Taleban FA, Molana SH, Ehtejab G. A pilot clinical trial of radioprotective

effects of curcumin supplementation in patients with prostate cancer. J Cancer Sci Ther. 2013;5(10):320-4.]

5. **Clinical evaluation of a formulation containing Curcuma longa and Boswellia serrata extracts in the management of knee osteoarthritis.** A formulation containing *Curcuma longa* and *Boswellia serrata* extracts (CB formulation) was evaluated for safety and effcacy in osteoarthritic patients and directly compared with the selective COX-2 inhibitor, celecoxib. 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 patients, as judged by the vital signs, hemogram, liver and renal function tests. The CB formulation at 500 mg administered twice a day, was more successful than administering celecoxib 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. [Kizhakkedath R. Clinical evaluation of a formulation containing Curcuma longa and Boswellia serrata extracts in the management of knee osteoarthritis. Molecular medicine reports. 2013 Nov 1;8(5):1542-8.]

6. **Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial**. Curcumin, an active ingredient of Curcuma longa Linn (Zingiberaceae), has shown potential antidepressant-like activity in animal studies. The objectives of this trial were to compare the efficacy and safety of curcumin with fluoxetine in patients with major depressive disorder (MDD). Herein, 60 patients diagnosed with MDD were randomized in a 1:1:1 ratio for six weeks observer-masked treatment with fluoxetine (20 mg) and curcumin (1000 mg) individually or their combination. The primary efficacy variable was response rates according to Hamilton Depression Rating Scale, 17-item version (HAM-D17). The secondary efficacy variable was the mean change in HAM-D17 score after six weeks. We observed that curcumin was well tolerated by all the patients. The proportion of responders as measured by the HAM-D17 scale was higher in the combination group (77.8%) than in the fluoxetine (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). This study provides first clinical evidence that curcumin may be used as an effective and safe modality for treatment in patients with MDD without concurrent suicidal ideation or other psychotic disorders. [Sanmukhani J, Satodia V, Trivedi J, Patel T, Tiwari D, Panchal B, Goel A, Tripathi CB. Efficacy

and safety of curcumin in major depressive disorder: a randomized controlled trial. Phytotherapy research. 2014 Apr;28(4):579-85.]

7. **Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study.** Curcumin, the principal curcuminoid derived from the spice turmeric, influences several biological mechanisms associated with major depression, namely those associated with monoaminergic activity, immune-inflammatory and oxidative and nitrosative stress pathways, hypothalamus-pituitaryadrenal (HPA) axis activity and neuroprogression. It was hypothesised that curcumin would be effective for the treatment of depressive symptoms in individuals with major depressive disorder. In a randomised, double-blind, placebo-controlled study, 56 individuals with major depressive disorder were treated with curcumin (500 mg twice daily) or placebo for 8 weeks. The primary measure was the Inventory of Depressive Symptomatology self-rated version (IDS-SR30). Secondary outcomes included IDS-SR30 factor scores and the Spielberger State-Trait Anxiety Inventory (STAI). From baseline to week 4, both curcumin and placebo were associated with improvements in IDS-SR30 total score and most secondary outcome measures. From weeks 4 to 8, curcumin was significantly more effective than placebo in improving several mood-related symptoms, demonstrated by a significant group x time interaction for IDS-SR30 total score ($F_{1, 53}$=4.22, p=.045) and IDS-SR30 mood score ($F_{1, 53}$=6.51, p=.014), and a non-significant trend for STAI trait score ($F_{1, 48}$=2.86, p=.097). Greater efficacy from curcumin treatment was identified in a subgroup of individuals with atypical depression. Partial support is provided for the antidepressant effects of curcumin in people with major depressive disorder, evidenced by benefits occurring 4 to 8 weeks after treatment. Investigations with larger sample sizes, over extended treatment periods, and with varying curcumin dosages are required. [Lopresti AL, Maes M, Maker GL, Hood SD, Drummond PD. Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. Journal of affective disorders. 2014 Oct 1;167:368-75.]

8. **Curcumin suppresses crosstalk between colon cancer stem cells and stromal fibroblasts in the tumor microenvironment: potential role of EMT.** Interaction of stromal and tumor cells plays a dynamic role in initiating and enhancing carcinogenesis. In this study, we investigated the crosstalk between colorectal cancer (CRC) cells with stromal fibroblasts and the anti-cancer effects of curcumin and 5-Fluorouracil (5-FU), especially on cancer stem cell (CSC)

survival in a 3D-co-culture model that mimics in vivo tumor microenvironment. Colon carcinoma cells HCT116 and MRC-5 fibroblasts were co-cultured in a monolayer or high density tumor microenvironment model in vitro with/without curcumin and/or 5-FU. Monolayer tumor microenvironment co-cultures supported intensive crosstalk between cancer cells and fibroblasts and enhanced up-regulation of metastatic active adhesion molecules (b1-integrin, ICAM-1), transforming growth factor-b signaling molecules (TGF-b3, p-Smad2), proliferation associated proteins (cyclin D1, Ki-67) and epithelial-to-mesenchymal transition (EMT) factor (vimentin) in HCT116 compared with tumor mono-cultures. High density tumor microenvironment co-cultures synergistically increased tumor-promoting factors (NF-kB, MMP-13), TGF-b3, favored CSC survival (characterized by up-regulation of CD133, CD44, ALDH1) and EMT-factors (increased vimentin and Slug, decreased E-cadherin) in HCT116 compared with high density HCT116 mono-cultures. Interestingly, this synergistic crosstalk was even more pronounced in the presence of 5-FU, but dramatically decreased in the presence of curcumin, inducing biochemical changes to mesenchymal-epithelial transition (MET), thereby sensitizing CSCs to 5-FU treatment. Enrichment of CSCs, remarkable activation of tumor-promoting factors and EMT in high density co-culture highlights that the crosstalk in the tumor microenvironment plays an essential role in tumor development and progression, and this interaction appears to be mediated at least in part by TGF-b and EMT. Modulation of this synergistic crosstalk by curcumin might be a potential therapy for CRC and suppress metastasis. [Buhrmann C, Kraehe P, Lueders C, Shayan P, Goel A, Shakibaei M. Curcumin suppresses crosstalk between colon cancer stem cells and stromal fibroblasts in the tumor microenvironment: potential role of EMT. PLoS One. 2014 Sep 19;9(9):e107514.]

9. **Curcumin chemosensitizes 5-fluorouracil resistant MMR-deficient human colon cancer cells in high density cultures.** Treatment of colorectal cancer (CRC) remains a clinical challenge, as more than 15% of patients are resistant to 5- Fluorouracil (5-FU)-based chemotherapeutic regimens, and tumor recurrence rates can be as high as 50–60%. Cancer stem cells (CSC) are capable of surviving conventional chemotherapies that permits regeneration of original tumors. Therefore, we 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 curcumin significantly enhanced the effect of 5-FU on HCT116R and HCR116+ch3R cells, in contrast to 5-FU alone as evidenced by increased disintegration of colonospheres, enhanced apoptosis and by inhibiting their growth. Curcumin and/or 5-FU strongly affected MMR-deficient CRC cells in high density cultures, however MMR proficient CRC cells were more sensitive. These effects of curcumin in enhancing chemosensitivity to 5-FU were further supported by its ability to effectively suppress CSC pools as evidenced by decreased number of CSC marker positive cells, highlighting the suitability of this 3D culture model for evaluating CSC marker expression in a close to vivo setting. Our results illustrate novel and previously unrecognized effects of curcumin in enhancing chemosensitization to 5-FU-based chemotherapy on DNA MMR-deficient and their chemo-resistant counterparts by targeting the CSC subpopulation. [Shakibaei M, Buhrmann C, Kraehe P, Shayan P, Lueders C, Goel A. Curcumin chemosensitizes 5-fluorouracil resistant MMR-deficient human colon cancer cells in high density cultures. PLoS One. 2014 Jan 3;9(1):e85397.]

10. **Curcumin potentiates antitumor activity of 5-fluorouracil in a 3D alginate tumor microenvironment of colorectal cancer.** To overcome the limitations of animal-based experiments, 3D culture models mimicking the tumor microenvironment in vivo are gaining attention. Herein, we investigated an alginate-based 3D scaffold for screening of 5-fluorouracil (5-FU) or/and curcumin on malignancy of colorectal cancer cells (CRC). The potentiation effects of curcumin on 5-FU against proliferation and metastasis of HCT116 cell and its corresponding isogenic 5-FU-chemoresistant cells (HCT116R) were examined in a 3D-alginate tumor model. CRC cells encapsulated in alginate were able to proliferate in 3D-colonospheres in a vivo-like phenotype and invaded from alginate. During cultivation of cells in alginate, we could isolate 3 stages of cells, (1) alginate proliferating (2) invasive and (3) adherent cells. Tumor-promoting factors (CXCR4, MMP-9, NF-κB) were significantly increased in the proliferating and invasive compared to the adherent cells, however HCT116R cells overexpressed factors in comparison to the parental HCT116, suggesting an increase in malignancy behavior. In alginate, curcumin potentiated 5-FU-induced decreased capacity for proliferation, invasion and increased more sensitivity to 5-FU of HCT116R compared to the HCT116 cells. IC50 for HCT116 to 5-FU was 8nM, but co-treatment with 5 μM curcumin significantly reduced 5-FU concentrations in HCT116 and HCT116R cells (0.8nM, 0.1nM,

respectively) and these effects were accompanied by down-regulation of NF-κB activation and NF-κB-regulated gene products. Our results demonstrate that the alginate provides an excellent tumor microenvironment and indicate that curcumin potentiates and chemosensitizes HCT116R cells to 5-FU-based chemotherapy that may be useful for the treatment of CRC and to overcome drug resistance. [Shakibaei M, Kraehe P, Popper B, Shayan P, Goel A, Buhrmann C. Curcumin potentiates antitumor activity of 5-fluorouracil in a 3D alginate tumor microenvironment of colorectal cancer. BMC cancer. 2015 Dec;15(1):250.]

11. **Novel evidence for curcumin and boswellic acid–induced chemoprevention through regulation of miR-34a and miR-27a in colorectal cancer.** Colorectal cancer is one of the most common causes of cancer-associated mortality worldwide, but it is truly a prevent able disease. Both curcumin and boswellic acids are well established dietary botanicals with potent anti-tumorigenic properties that have been shown to modulate multiple oncogenic pathways. Recent data suggest that the chemopreventive effects of these botanicals may, in part, be mediated through regulation of key cancer-related microRNAs (miRNA) and their downstream gene targets. Here, we investigated the antitumorigenic effects of curcumin and 3 acetyl-11-keto-b-boswellic acid (AKBA) on modulation of specific cancer-related miRNAs in colorectal cancer 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 colorectal cancer cell lines, and these effects were significantly enhanced with combined treatment. Gene-expression arrays revealed that curcumin and AKBA regulated distinct cancer signaling pathways, including key cell-cycle regulatory genes. Combined bioinformatics and in silico analysis identified apoptosis, proliferation, and cell-cycle regulatory signaling pathways as key modulators of curcumin and AKBA-induced anticancer effects. It was discovered that curcumin and AKBA induced upregulation of tumor-suppressive miR-34a and down regulation of miR-27a in colorectal cancer cells. Furthermore, we demonstrated in a mouse xenograft model that both curcumin and AKBA treatments suppressed tumor growth, which corresponded with alterations in the expression of miR-34a and miR-27a, consistent with our in vitro findings. Herein, we provide novel mechanistic evidence for the chemo preventive effects of curcumin and AKBA through regulation of specific miRNAs in colorectal cancer. [Toden S, Okugawa Y, Buhrmann C, Nattamai D, Anguiano E, Baldwin N, Shakibaei M, Boland CR, Goel A. Novel evidence for curcumin and boswellic acid–induced

chemoprevention through regulation of miR-34a and miR-27a in colorectal cancer. Cancer Prevention Research. 2015 May 1;8(5):431-43.]

12. **Curcumin and major depression: a randomised, double-blind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change**. A recent randomised, double-blind, placebo controlled study conducted by the research group, provided partial support for the efficacy of supplementation with a patented curcumin extract (500 mg, twice daily) for 8 weeks in reducing depressive symptoms in people with major depressive disorder. In the present paper, a secondary, 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 Inventory of Depressive Symptomatology self-rated version ($IDS\text{-}SR_{30}$) was used as the primary depression outcome measure. Compared to placebo, 8 weeks of curcumin supplementation was associated with elevations in urinary thromboxane B2 ($p<0.05$), and substance P ($p<0.001$); while placebo supplementation was associated with reductions in aldosterone ($p<0.05$) and cortisol ($p<0.05$). Higher baseline plasma endothelin-1 ($rs= 0.587$; $p<0.01$) and leptin ($rs= 0.470$; $p<0.05$) in curcumin-treated individuals was associated with greater reductions in $IDS\text{-}SR_{30}$ score after 8 weeks of treatment. Our findings demonstrate that curcumin supplementation influences several biomarkers that may be associated with its antidepressant mechanisms of action. Plasma concentrations of leptin and endothelin-1 seem to have particular relevance to treatment outcome. Further investigations using larger samples sizes are required to elucidate these findings, as the multiple statistical comparisons completed in this study increased the risk of type I errors. [Lopresti AL, Maes M, Meddens MJ, Maker GL, Arnoldussen E, Drummond PD. Curcumin and major depression: a randomised, double-blind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change. European Neuropsychopharmacology. 2015 Jan 1;25(1):38-50.]

13. **Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colorectal cancer.** Resistance to cytotoxic chemotherapy is a major cause of mortality in colorectal cancer (CRC) patients. Chemoresistance has been linked primarily to a subset of cancer cells undergoing epithelial–

mesenchymal transition (EMT). Curcumin, a botanical with antitumorigenic properties, has been shown to enhance sensitivity of cancer cells to chemotherapeutic drugs, but the molecular mechanisms underlying this phenomenon remain unclear. Effects of curcumin and 5-fluorouracil (5FU) individually, and in combination, were examined in parental and 5FU resistant (5FUR) cell lines. We performed a series of growth proliferation and apoptosis assays in 2D and 3D cell cultures. Furthermore, we identifed and analyzed the expression pattern of a subset of putative EMT-suppressive microRNAs (miRNAs) and their downstream target genes regulated by curcumin. Chemosensitizing effects of curcumin were validated in a xenograft mouse model. Combined treatment with curcumin and 5FU enhanced cellular apoptosis and inhibited proliferation in both parental and 5FUR cells, whereas 5FU alone was ineffective in 5FUR cells. A group of EMT-suppressive miRNAs were upregulated by curcumin treatment in 5FUR cells. Curcumin suppressed EMT in 5FUR cells by downregulating BMI1, SUZ12 and EZH2 transcripts, key mediators of cancer stemness-related polycomb repressive complex subunits. Using a xenograft and mathematical models, we further demonstrated that curcumin sensitized 5FU to suppress tumor growth. We provide novel mechanistic evidence for curcumin-mediated sensitization to 5FU-related chemoresistance through suppression of EMT in 5FUR cells via upregulation of EMT-suppressive miRNAs. This study highlights the potential therapeutic usefulness of curcumin as an adjunct in patients with chemoresistant advanced CRC. [Toden S, Okugawa Y, Jascur T, Wodarz D, Komarova NL, Buhrmann C, Shakibaei M, Boland CR, Goel A. Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colorectal cancer. Carcinogenesis. 2015 Feb 4;36(3):355-67.]

14. **BCM-95 and (2-hydroxypropyl)-β-cyclodextrin reverse autophagy dysfunction and deplete stored lipids in Sap C-deficient fibroblasts**. Saposin (Sap) C deficiency is a rare variant form of Gaucher disease caused by impaired Sap C expression or accelerated degradation, and associated with accumulation of glucosylceramide and other lipids in the endo/lysosomal compartment. No effective therapies are currently available for the treatment of Sap C deficiency. We previously reported that a reduced amount and enzymatic activity of cathepsin (Cath) B and Cath D, and defective autophagy occur in Sap C-deficient fibroblasts. Here, we explored the use of two compounds, BCM-95, a curcumin derivative, and (2-hydroxypropyl)-β-cyclodextrin (HP-β-CD), to improve lysosomal function of Sap C-deficient fibroblasts.

Immunofluorescence and biochemical studies documented that each compound promotes an increase of the expression levels and activities of Cath B and Cath D, and efficient clearance of cholesterol (Chol) and ceramide (Cer) in lysosomes. We provide evidence that BCM-95 and HP-β-CD enhance lysosomal function promoting autophagic clearance capacity and lysosome reformation. Our findings suggest a novel pharmacological approach to Sap C deficiency directed to treat major secondary pathological aspects in this disorder. [Tatti M, Motta M, Scarpa S, Di Bartolomeo S, Cianfanelli V, Tartaglia M, Salvioli R. BCM-95 and (2-hydroxypropyl)-β-cyclodextrin reverse autophagy dysfunction and deplete stored lipids in Sap C-deficient fibroblasts. Human molecular genetics. 2015 Apr 29;24(15):4198-211.]

15. **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 antidepressant like activity of curcumin and its combination with fluoxetine and imipramine was studied in acute model (three doses 24, 5 and 1 h before test) of forced swimming test (FST) in glass jar and tail 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), drugs being given orally (doses for mice): Group 1 (vehicle), group 2 (curcumin 50 mg/kg), group 3 (curcumin 100 mg/kg), group 4 (fluoxetine 20 mg/kg), group 5 (imipramine 15 mg/kg), group 6 (curcumin 100 mg/kg plus fluoxetine 20 mg/kg) and group 7 (curcumin 100 mg/kg plus imipramine 15 mg/kg). Equivalent doses for rats were used. Both the acute model of FST and TST, and the chronic model of FST with water wheel showed significant antidepressant like 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 fluoxetine and imipramine ($p > 0.05$) but its addition to fluoxetine and imipramine did not improve their antidepressant activity ($p > 0.05$). Curcumin increased both the swimming and climbing behavior in FST, thus its antidepressant like activity could be due to an increase in serotonin, norepinephrine and dopamine levels in the brain. Curcumin can be a useful antidepressant especially in cases which respond to drugs having mixed effects on serotonin and catecholamines levels in the brain. [Sanmukhani J, Anovadiya A, Tripathi CB. Evaluation of antidepressant like activity of curcumin and its combination with fluoxetine and imipramine: an acute and chronic study. Acta Pol Pharm. 2011 Sep 1;68(5):769-5.]

16. **The use of an anti-inflammatory supplement in patients with chronic kidney disease.** Chronic kidney disease (CKD) is characterized by a continuous reduction in kidney function, increased inflammation, and reduced antioxidant capacity. The objective of this study was to assess the effects of a herbal supplement on systemic inflammation and antioxidant status in non-dialysis CKD patients. Sixteen patients with CKD (56.0±16.0 yrs, 171.4±11.9 cm, 99.3 ±20.2 kg) were randomly chosen to receive a herbal supplement composed of Curcuma longa and Boswellia serrata, or placebo. Plasma levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), glutathione peroxidase (GPx), and serum C-reactive protein (CRP) were measured at baseline and 8 weeks. Baseline data demonstrated elevated inflammation and low antioxidant levels. A significant time effect (p=0.03) and time x compliance interaction effect (p=0.04) were observed for IL-6. No significant differences were observed for any other variables. This study demonstrates that mild and moderate CKD is associated with chronic inflammation and low antioxidant activity. Systemic inflammation and impaired antioxidant status may be greater in CKD populations with multiple comorbidities. Curcumin and Boswellia serrata are safe and tolerable and helped to improve the levels of an inflammatory cytokine. [Moreillon JJ, Bowden RG, Deike E, Griggs J, Wilson R, Shelmadine B, Cooke M, Beaujean A. The use of an anti-inflammatory supplement in patients with chronic kidney disease. Journal of Complementary and Integrative Medicine. 2013 Jul 1;10(1):143-52.]
17. **Curcumin sensitizes pancreatic cancer cells to gemcitabine by attenuating PRC2 subunit EZH2, and the lncRNA PVT1 expression.** Development of resistance to chemotherapeutic drugs is a major challenge in the care of patients with pancreatic ductal adenocarcinoma (PDAC). Acquired resistance to chemotherapeutic agents in PDAC has been linked to a subset of cancer cells termed “cancer stem cells” (CSCs). Therefore, an improved understanding of the molecular events underlying the development of pancreatic CSCs is required to identify new therapeutic targets to overcome chemoresistance. Accumulating evidence indicates that curcumin, a phenolic compound extracted from turmeric, can overcome de-novo chemoresistance and re-sensitize tumors to various chemotherapeutic agents. However, the underlying mechanisms for curcumin-mediated chemosensitization remain unclear. The Enhancer of Zeste Homolog-2 (EZH2) subunit of Polycomb Repressive Complex 2 (PRC2) was recently identified as a key player regulating drug resistance. EZH2 mediates interaction with several long non-coding RNAs (lncRNAs) to modulate epithelial-mesenchymal transition and cancer stemness, phenomena commonly associated with drug resistance.

Here, we report the re-sensitization of chemoresistant PDAC cells by curcumin through the inhibition of the PRC2-PVT1-c-Myc axis. Using gemcitabine-resistant PDAC cell lines, we found that curcumin sensitized chemoresistant cancer cells by inhibiting the expression of the PRC2 subunit EZH2 and its related lncRNA PVT1. Curcumin was also found to prevent the formation of spheroids, a hallmark of cancer stem cells, and to down-regulate several selfrenewal driving genes. In addition, we confirmed our in vitro findings in a xenograft mouse model where curcumin inhibited gemcitabine-resistant tumor growth. Overall, this study indicates clinical relevance for combining curcumin with chemotherapy to overcome chemoresistance in PDAC. [Yoshida K, Toden S, Ravindranathan P, Han H, Goel A. Curcumin sensitizes pancreatic cancer cells to gemcitabine by attenuating PRC2 subunit EZH2, and the lncRNA PVT1 expression. Carcinogenesis. 2017 Jul 17;38(10):1036-46.]

18. **A pilot cross-over study to evaluate human oral bioavailability of BCM-95® CG (Biocurcumax™), a novel bioenhanced preparation of curcumin.** Curcumin, the bioactive component of turmeric, *Curcuma longa* has an exceptionally wide spectrum of activities including antioxidant, anti-inflammatory and anti-cancer properties, and is currently under different phases of clinical trials for various types of soft tissue cancers. However, although *in vitro* and animal studies have shown anticancer activities of curcumin for virtually all types of human cancers, its poor bioavailability in the human body has severely limited its application to these diseases. Methods to increase its oral bioavailability are a subject of intense current research. Reconstituting curcumin with the non-curcuminoid components of turmeric has been found to increase the bioavailability substantially. In the present clinical study to determine the bioavailability of curcuminoids, a patented formulation, BCM-95®CG 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 (Biocurcumax™) was about 6.93-fold compared to normal curcumin and about 6.3-fold compared to curcumin-lecithin-piperine formula. BCM-95®CG thus, has potential for widespread application for various chronic diseases. [Antony B, Merina B, Iyer VS, Judy N, Lennertz K, Joyal S. A pilot cross-over study to evaluate human oral bioavailability of BCM-95® CG (Biocurcumax™),

a novel bioenhanced preparation of curcumin. Indian journal of pharmaceutical sciences. 2008 Jul;70(4):445.]

19. **Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease.** 34 participants were randomized to either 1 gram BCM-95® curcumin, 4 grams BCM-95 curcumin, or placebo. All participants were over age 50, and had a diagnosis of probable or possible Alzheimer's disease based on the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association diagnostic criteria. Some measures were serum markers of amyloid beta, plasma isoprostanes (a measure of oxidative stress) and antioxidant status. Both 1 gram and 4 grams reduced oxidative stress and improved antioxidant status. There were more adverse effects in the placebo group than in either 1 g or 4 g BCM-95 group. There was a noted increase in serum amyloid beta in both 1 g and 4 g groups, but not placebo. The authors noted this "possibly reflected an ability of curcumin to disaggregate amyloid beta deposits in the brain, releasing the amyloid beta for circulation and disposal.". [Baum L, Lam CW, Cheung SK, Kwok T, Lui V, Tsoh J, Lam L, Leung V, Hui E, Ng C, Woo J. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. Journal of clinical psychopharmacology. 2008 Feb 1;28(1):110-3]

20. **Curcumin effects on blood lipid profile in a 6-month human study.** Pharmacological research. Studies in animals and a short-term human study have suggested that curcumin, a polyphenolic compound concentrated in the curry spice turmeric, 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 curcumin, 1 g/d curcumin, or placebo in a 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 curcumin concentration reached a mean of 490 nmol/L. The curcumin concentration was greater after capsule than powder administration. Consumption of either dose of curcumin did not significantly affect triacylglycerols, or total, LDL, and HDL cholesterol over 1 month or 6 months. However, the concentrations of plasma curcumin and serum cholesterol were positively and significantly correlated. Curcumin consumption does not appear to have a significant effect on the serum lipid profile, unless the absorbed

concentration of curcumin is considered, in which case curcumin may modestly increase cholesterol. [Baum L, Cheung SK, Mok VC, Lam LC, Leung VP, Hui E, Ng CC, Chow M, HoPC, Lam S, Woo J. Curcumin effects on blood lipid profile in a 6-month human study. Pharmacological research. 2007 Dec 1;56(6):509-14.]

21. **Bioavailability of Biocurcumax™ (BCM-095™)** Curcuminoids are the yellow colouring matter, the most active molecules of turmeric (*Curcuma longa*) one of the familiar spice possessing numerous bioactive components. But it is suggested and proved that the total curcuminoids absorb by animal system limit to 50 – 60 per cent. Biocurcumax™ (BCM-095™) is a unique blend which enhances the bioavailability of curcumin. The study described here reveals the bioavailability of Biocurcumax™ (BCM-095™) in human volunteers. [Benny M, Antony B. Bioavailability of Biocurcumax™ (BCM-095™), Spice India 2006 (Sept);11-15]

22. **Enhancing the Absorption of Curcuminoids.** Turmeric (Curcuma longa) one of the familiar spice has got number of medicinal properties such as anti-septic, anti-inflammatory, wound healing, anti-oxidant, anti-tumour etc. These properties of turmeric are attributed to the active principle, curcumin and essential oil present in the rhizome. But it is suggested and proved that only 50-60 percent of total curcumin is absorbed by animal system. Studies conducted on albino rats and results described in this paper reveal that 96-97 percent absorption of curcuminoids by mixing curcumin and standardized essential oil of turmeric. [Antony B, Benny M, Rao SB. Enhancing the Absorption of Curcuminoids, Spice India 2005(July); 23-26]

23. **Effect of a topical curcumin preparation (BIOCURCUMAX) on burn wound healing in rats.** Curcumin, a naturally occurring o-methoxyphenol derivative, has been shown to possess several biological properties including antioxidant (free radical scavenging activity), induction of detoxification enzymes and provides protection against degenerative diseases. Topical applications of compounds with free radical scavenging properties in patients have shown to improve significantly wound healing and protect tissues from oxidative damage. To assess the effect of a topical curcumin preparation on healing of partial thickness burn wounds in rats. The rats are randomly divided into four groups, comprising of six rats in each group. Partial thickness burn wounds are created by pouring hot molten wax at 80°C. Group I acts a control, Group 2 receives the standard silver sulphadiazine cream, Group 3 gets 20%

curcumin cream, and Group 4 receives the combination of the dexamethasone and curcumin cream. Parameters observed are epithelialization period and wound contraction. The percentage of wound contraction was significantly increased in the topical curcumin preparation (20%) and silver sulfadiazine group compared to control group. The mean period of epithelization was significantly reduced in topical curcumin preparation (20%) group and silver sulfadiazine group as compared to the control. Topical curcumin preparation is effective in healing burn wound and the effect was comparable to that of standard drug i.e. silver sulfadiazine. [Durgaprasad S, Reetesh R, Hareesh K, Rajput R. Effect of a topical curcumin preparation (BIOCURCUMAX) on burn wound healing in rats. Journal of Pharmaceutical and Biomedical Sciences (JPBMS). 2011;8(08).]

24. **The effect of exercise and nutritional supplementation on proinflammatory cytokine expression in young racehorses during training.** 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 postexercise inflammation. [Horohov DW, Sinatra ST, Chopra RK, Jankowitz S, Betancourt A, Bloomer RJ. The effect of exercise and nutritional supplementation on proinflammatory cytokine expression in young racehorses during training. Journal of Equine Veterinary Science. 2012 Dec 1;32(12):805-15.]

25. **Evaluation of Antiepileptic and Memory Retention Activity of Curcumin Per SE and in Combination with Antiepileptic Drugs.** Antiepileptic activity of curcumin and its combination with phenytoin and sodium valproate were studied in chronic model (14 days) of Maximal Electroshock Seizure (MES) and Pentylenetetrazole (PTZ) induced seizure respectively. Elevated plus maze test was used to study effect of drugs and/or seizures on memory retention in MES and PTZ groups. Curcumin in both doses did not show any significant effect ($P = 0.33$) on tonic extension, while curcumin 100 mg/kg significantly ($P < 0.01$) reduced clonic phase compared to vehicle control. Curcumin in 100 mg/kg dose significantly ($P < 0.001$) inhibited PTZ induced seizure. Addition of curcumin to sub therapeutic dose of sodium valproate showed synergistic effect. Curcumin did not show any effect on memory retention. Inhibition of PTZ induced seizure by curcumin could be due to effect on γ-amino butyric acid receptor (GABA) pathway and its antioxidant property. Curcumin can be effective in absence seizure alone and as add on with sodium valproate. [Anovadiya AP, Sanmukhani JJ, Vadgama VK, Tripathi CB. Evaluation of Antiepileptic and Memory Retention Activity of Curcumin Per SE and in Combination with Antiepileptic Drugs, Asian J Pharm Clin Res. 2014;6(2):145-148]

26. **Anti-inflammatory activity of BCM-95 (bio-enhanced formulation of turmeric with increased bioavailabilty) compared to Curcumin in Wistar rats.** The study was conducted to evaluate anti-inflammatory activity of bioenhanced turmeric formulation (BCM-95) and compared to commercial Curcumin formulation (Curcuminoids 95%) in Carrageenan-induced acute inflammatory model. Thirty six Wistar rats were divided into six groups-Normal control (2 ml of vehicle), Standard control (Indomethacin 10 mg/kg), 2 doses of BCM 95 (10 and 20 mg/kg) and Curcuminoids 95% (10 and 20 mg/kg). Paw volume was measured using a digital plethysmometer. Vehicle or test drugs were given to rats 30 min before carrageenan administration. Baseline paw volume reading (V0) was noted just prior to administration of 0.1 ml of 1% carrageenan to right hind paw of the rat. Test paw volume readings (Vt) were measured at 30, 60, 120, 180, 240, 300 and 360 min, after carrageenan injection. Oedema expressed as increased paw volume (vt-v0) was noted and percentage inhibition of oedema was calculated for all treatment groups. Difference between groups were analyzed with ANOVA followed by Tukey test. All treatment groups demonstrated signifcant ($p<0.05$) anti-inflammatory activity (oedema suppression) compared to normal control. Anti-inflammatory activity

of BCM 95 treated groups were comparable to standard control group except at certain time points, whereas the same activity at all-time points with Curcuminoid 95% treated groups were signifcantly less than standard control group. Percentage inhibition of paw oedema was maximum with standard control group followed by BCM 95 treated groups followed by Curcuminoid 95% treated groups. BCM 95 treated groups showed signifcant anti-inflammatory activity compared to Curcuminoid 95% treated groups. [Vinaykumar S, Rathnakar UP, Dinkar US, Priyanka K, Gaurav T, Kudgi SA, Nishith RS. Anti-inflammatory activity of BCM-95 (bio-enhanced formulation of turmeric with increased bioavailabilty) compared to Curcumin in Wistar rats. Pharmacognosy Journal. 2016;8(4).]

27. **Systematic and comprehensive investigation of the toxicity of curcuminoid-essential oil complex: A bioavailable turmeric formulation.** Curcumin, the active component present in *Curcuma longa* of the family Zingiberaceae, has a number of pharmacological effects, including potential anti-inflammatory activity. One of the major limitations of curcumin/turmeric extract is its poor absorption through the gastrointestinal tract. Several approaches have been adopted to increase the bioavailability of curcumin, including loading curcumin into liposomes or nanoparticles, complexation with phospholipids, addition of essential oils and synthesizing structural analogues of curcumin. In the present study, the toxicity and safety of one such bioavailable turmeric formulation, curcuminoid-essential oil complex (CEC), the toxicity profle of which has not been reported, were examined using *in vivo* and *in vitro*models, as per the guidelines of the Organisation for Economic Co-operation and Development. Investigations of acute toxicity study were performed in rats and mice, and the results revealed no signs and symptoms or toxicity or mortality in any of the animals at the maximum recommended dose level of 5,000 mg/kg body weight. The repeated administration of CEC for 90 days in Wistar rats at a dose of 1,000 mg/kg body weight did not induce any observable toxic effects, compared with corresponding control animals. Mutagenicity/genotoxicity investigations were also performed using a bacterial reverse mutation assay (Ames test), a mammalian bone marrow chromosome aberration test and a mammalian erythrocyte micronucleus test in mice. CEC was found to be non-mutagenic in all three mutagenic investigations. Consequently, the present study indicated that CEC elicited no toxic effects in animals or *in vitro*. Therefore, following investigations of acute toxicity, repeated dose toxicity and mutagenicity, CEC was deemed a safe, non-toxic pharmacological formulation. [Aggarwal ML, Chacko KM, Kuruvilla BT.

Systematic and comprehensive investigation of the toxicity of curcuminoid-essential oil complex: A bioavailable turmeric formulation. Molecular medicine reports. 2016 Jan 1;13(1):592-604.]

28. **Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults.** Curcumin therapy in animals has produced positive cognitive and behavioural outcomes; results of human trials, however, have been inconsistent. In this study, we report the results of a 12-month, randomised, placebo-controlled, double-blind study that investigated the ability of a curcumin formulation to prevent cognitive decline in a population of community-dwelling older adults. Individuals (n 96) ingested either placebo or 1500 mg/d BiocurcumaxTM for 12 months. A battery of clinical and cognitive measures was administered at baseline and at the 6-month and 12-month follow-up assessments. A significant time × treatment group interaction was observed for the Montreal Cognitive Assessment (repeated-measures analysis; time × treatment; F = 3·85, P < 0·05). Subsequent analysis revealed that this association was driven by a decline in function of the placebo group at 6 months that was not observed in the curcumin treatment group. No differences were observed between the groups for all other clinical and cognitive measures. Our findings suggest that further longitudinal assessment is required to investigate changes in cognitive outcome measures, ideally in conjunction with biological markers of neurodegeneration. [Rainey-Smith SR, Brown BM, Sohrabi HR, Shah T, Goozee KG, Gupta VB, Martins RN. Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults. British Journal of Nutrition. 2016 Jun;115(12):2106-13.]

29. **Effect of curcumin supplementation during radiotherapy on oxidative status of patients with prostate cancer: a double blinded, randomized, placebo-controlled study**. Curcumin is an antioxidant agent with both radiosensitizing and radioprotective properties. The aim of the present study was to evaluate the effect of curcumin supplementation on oxidative status of patients with prostate cancer who undergo radiotherapy. Forty patients treated with radiotherapy for prostate cancer were randomized to the curcumin (CG, n D 20) or placebo group (PG, n D 20). They received curcumin (total 3 g/day) or placebo during external-beam radiation therapy of up to 74 Gy. Plasma total antioxidant capacity (TAC) and activity of superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) were measured at baseline and 3 mo after radiotherapy completion. Analysis of covariance was used to

compare the variables between groups following the intervention. Serum PSA levels and MRI/MRS images were investigated. In CG, TAC significantly increased (P < 0.001) and the activity of SOD decreased (P D 0.018) after radiotherapy compared with those at baseline. In CG, however, the activity of SOD had a significant reduction (P D 0.026) and TAC had a significant increase (P D 0.014) compared with those in PG. PSA levels were reduced to below 0.2 ng/ml in both groups, 3 mo after treatment, however, no significant differences were observed between the 2 groups regarding treatment utcomes. [Hejazi J, Rastmanesh R, Taleban FA, Molana SH, Hejazi E, Ehtejab G, Hara N. Effect of curcumin supplementation during radiotherapy on oxidative status of patients with prostate cancer: a double blinded, randomized, placebo-controlled study. Nutrition and cancer. 2016 Jan 2;68(1):77-85.]

30. **A randomized double-blind placebo-controlled phase IIB trial of curcumin in oral leukoplakia.** Oral leukoplakia is a potentially malignant lesion of the oral cavity, for which no effective treatment is available. We investigated the effectiveness of curcumin, a potent inhibitor of NF-kB/COX-2, molecules perturbed in oral carcinogenesis, to treat leukoplakia. Subjects with oral leukoplakia (n = 223) were randomized (1:1 ratio) to receive orally, either 3.6 g/day of curcumin (n = 111) or placebo (n = 112), for 6 months. The primary endpoint was clinical response obtained by bi-dimensional measurement of leukoplakia size at recruitment and 6 months. Histologic response, combined clinical and histologic response, durability and effect of long-term therapy for an additional six months in partial responders, safety and compliance were the secondary endpoints. Clinical response was observed in 75 (67.5%) subjects [95% confidence interval (CI), 58.4–75.6] in the curcumin and 62 (55.3%; 95% CI, 46.1–64.2) in placebo arm (P = 0.03). This response was durable, with 16 of the 18 (88.9%; 95% CI, 67.2–96.9) subjects with complete response in curcumin and 7 of 8 subjects (87.5%) in placebo arm, demonstrating no relapse after 6 months follow up. Difference in histologic response between curcumin and placebo was not significant (HR, 0.88, 95% CI, 0.45–1.71; P = 0.71). Combined clinical and histologic response assessment indicated a significantly better response with curcumin (HR, 0.50; 95% CI, 0.27–0.92; P = 0.02). Continued therapy, in subjects with partial response at 6 months, did not yield additional benefit. The treatment did not raise any safety concerns. Treatment of oral leukoplakia with curcumin (3.6 g for six months), thus was well tolerated and demonstrated significant and durable clinical response for 6 months. [Kuriakose MA, Ramdas K, Dey B, Iyer S, Rajan G, Elango KK, Suresh A, Ravindran D, Kumar RR, Prathiba R, Ramachandran S. A

randomized double-blind placebo-controlled phase iib trial of curcumin in oral leukoplakia. Cancer Prevention Research. 2016 Aug 1;9(8):683-91.]

31. **The efficacy and safety of a combination of glucosamine hydrochloride, chondroitin sulfate and bio-curcumin with exercise in the treatment of knee osteoarthritis: a randomized, double-blind, placebo-controlled study.** Knee osteoarthritis (OA) conservative treatment aims to delay cartilage degeneration; chondroprotective agents are a valid approach in this sense. A commercially available dietary supplement, CartiJoint Forte, containing glucosamine hydrochloride (GH), chondroitin sulfate (CS) and Bio-Curcumin BCM-95®, was used in this trial.The aim of this study was to assess efficacy and safety of CartiJoint Forte combined with physical therapy in treating subjects with knee OA.A multicenter, prospective, randomized, double blind, placebo-controlled clinical trial.Outpatients referred to the Rehabilitation Departments of two University Hospitals.Fifty-three patients were randomly assigned to an experimental group (N=26) or a control group (N.=27). Experimental subjects received two tablets of CartiJoint Forte each day for 8 weeks, while those in the control group were provided with a placebo. Three subjects dropped out during the course of the study.The two groups both received 20 sessions of physical therapy during the course of the trial. Primary outcome was pain intensity, measured both at motion and at rest, using the Visual Analogue Scale (VAS). A secondary outcome was an assessment of knee function by Western Ontario and McMaster Universities Arthritis Index and Lequesne Index, knee ROM, and two inflammation markers (C-reactive protein and erythrocyte sedimentation rate). Each assessment was carried out at baseline (T0), at 8 weeks (T1) and at 12 weeks (T2).VAS at rest was found to be reduced between T0 and T1, as well as between T0 and T2 (F=13.712; P=0.0001), with no differences between groups (F=1.724; P=0.191). VAS at motion revealed a significant "group × time-check" interaction (F=2.491; P=0.032), with increasing effect of time on VAS reduction (F=17.748; P=0.0001). This was most pronounced in the experimental group at 8 weeks (F=3.437; P=0.045). The Lequesne Index showed reductions at T1 and T2 compared to T0 (F=9.535; P=0.0001), along with group effect, since the experimental group presented a lower score at T2 (F=7.091; P=0.009). No significant changes were found in the knee ROM and inflammation markers.CartiJoint Forte, added to physical therapy, may ameliorate pain and help to improve algofunctional score in knee OA patients.Treatment of knee OA with curcuminoids plus glycosaminoglycans, added to physical therapy, improves VAS at motion and Lequesne Index scores. [Sterzi S, Giordani L,

Morrone M, Lena E, Magrone G, Scarpini C, Milighetti S, Pellicciari L, Bravi M, Panni I, Ljoka C. The efficacy and safety of a combination of glucosamine hydrochloride, chondroitin sulfate and bio-curcumin with exercise in the treatment of knee osteoarthritis: a randomized, double-blind, placebo-controlled study. European journal of physical and rehabilitation medicine. 2016 Jun;52(3):321-30.]

32. **Short Report of a Preliminary Open Study of Synofit-Containing Bio-Curcumin, Greenlipped Mussel and Blackcurrant Leaf Extract in Arthritis.** The study was conducted to evaluate the potential benefit of Synofit—an association of Curcumin, *Perna canaliculus* greenmussels and blackcurrant leaf extracts. A real life open study was performed among 86 adult outpatients suffering from Fibromyalgia (n = 22), low back pain (n = 33) or knee osteoarthritis (n = 31) who accepted to take 3 tablets a day during 1 week then 2 capsules of Synofit during 2 months in addition to their conventional therapy (mainly analgesics and anti-inflammatory) and then to report their evaluation of this complementary treatment. Statistical analysis included paired t test and when possible Wilcoxon signed rank test. Accordingly, the intermediate analysis showed that already within 4 weeks of treatment, an improvement quoted as “light” was statistically reported in patients with low back pain and knee osteoarthritis but not among those with fibromyalgia on pain, physical condition, global assessment of a benefit, quality of life but not on joint stiffness (although joint stiffness considered for the whole group was statistically improved). The limited number of patients and time duration of the study and the absence of double blind controlled study do not allow concluding on the efficacy but these preliminary analyses obtained from an intermediate analysis are encouraging for further studies. [Qu J, Mélot C, Appelboom T. Short Report of a Preliminary Open Study of Synofit-Containing Bio-Curcumin, Greenlipped Mussel and Blackcurrant Leaf Extract in Arthritis. Open Journal of Rheumatology and Autoimmune Diseases. 2015 Oct 27;5(04):113.]

33. **Efficacy of curcumin, and a saffron/curcumin combination for the treatment of major depression: a randomised, double-blind, placebo-controlled study**. Several studies have supported the antidepressant effects of curcumin (from the spice turmeric) and saffron for people with major depressive disorder. However, these studies have been hampered by poor designs, small sample sizes, short treatment duration, and similar intervention dosages. Furthermore, the antidepressant effects of combined curcumin and saffron administration

are unknown. Methods: In a randomised, double-blind, placebo-controlled study, 123 individuals with major depressive disorder were allocated to one of four treatment conditions, comprising placebo, low-dose curcumin extract (250 mg b.i.d.), high-dose curcumin extract (500 mg b.i.d.), or combined low-dose curcumin extract plus saffron (15 mg b.i.d.) for 12 weeks. The outcome measures were the Inventory of Depressive Symptomatology self-rated version (IDS-SR_{30}) and Spielberger State-Trait Anxiety Inventory (STAI). The active drug treatments (combined) were associated with significantly greater improvements in depressive symptoms compared to placebo (p=.031), and superior improvements in STAI-state ($p < .001$) and STAI-trait scores (p=.001). Active drug treatments also had greater efficacy in people with atypical depression compared to the remainder of patients (response rates of 65% versus 35% respectively, p=.012). No differences were found between the differing doses of curcumin or the curcumin/saffron combination. Investigations with larger sample sizes are required to examine the efficacy of differing doses of curcumin and saffron/curcumin combination. Its effects in people with atypical depression also require examination in larger scale studies. Active drug treatments comprising differing doses of curcumin and combined curcumin/saffron were effective in reducing depressive and anxiolytic symptoms in people with major depressive disorder. [Lopresti AL, Drummond PD. Efficacy of curcumin, and a saffron/curcumin combination for the treatment of major depression: a randomised, double-blind, placebo-controlled study. Journal of affective disorders. 2017 Jan 1;207:188-96.]

34. **Effect of Infla-Kine supplementation on the gene expression of inflammatory markers in peripheral mononuclear cells and on C-reactive protein in blood.**
Chronic infammation is a predisposing factor to numerous degenerative diseases including cancer, heart failure and Alzheimer's disease. Infa-Kine is a natural supplement comprised of a proprietary blend of *Lactobacillus fermentum* extract, burdock seed (arctigenin), zinc, alpha lipoic acid, papaya enzyme and an enhanced absorption bio-curcumin complex (BCM-95®). Infa-Kine was administered twice daily to 24 health volunteers for 4 weeks. Quantitative RT-PCR was used to assess mRNA transcripts of IL-1b, IL8, IL-6, NF-κB, and TNF-α from peripheral blood mononuclear cells (PBMC). C reactive protein (CRP) was measured from serum. Additionally, quality of life questionnaires were employed to assess general feeling of well-being. Assessments were made before treatment and at conclusion of treatment (4 weeks). As compared to pre-treatment, after 4 weeks, a statistically signifcant reduction of IL8, IL-6, NF-κB, and TNF-α transcripts was observed in PBMC.

Furthermore, reduction of IL-1b transcript and serum CRP was observed but did not reach statistical signifcance. Quality of life improvements were most prevalent in muscle and joint pains. Overall, our data demonstrate that twice daily administration of Infa-Kine for 4 weeks reduces infammatory markers and quality of life in healthy volunteers. [Mikirova NA, Kesari S, Ichim TE, Riordan NH. Effect of Infla-Kine supplementation on the gene expression of inflammatory markers in peripheral mononuclear cells and on C-reactive protein in blood. Journal of translational medicine. 2017 Dec;15(1):213.]

35. **Risperidone-induced metabolic dysfunction is attenuated by Curcuma longa extract administration in mice.** Antipsychotics, such as risperidone, increase food intake and induce alteration in glucose and lipid metabolism concomitantly with overweight and body fat increase, these biological abnormalities belong to the metabolic syndrome definition (high visceral adiposity, hypertriglyceridemia, hyperglycemia, low HDL-cholesterol and high blood pressure). Curcumin is a major component of traditional turmeric (Curcuma longa) which has been reported to improve lipid and glucose metabolism and to decrease weight in obese mice. We questioned the potential capacity of curcumin, contained in Curcuma longa extract (Biocurcuma™), to attenuate the risperidone-induced metabolic dysfunction. Two groups of mice were treated once a week, for 22 weeks, with intraperitoneal injection of risperidone (Risperdal) at a dose 12.5 mpk. Two other groups received intraperitoneal injection of the vehicle of Risperdal following the same schedule. Mice of one risperidone-treated groups and of one of vehicle-treated groups were fed a diet with 0.05% Biocurcuma™ (curcumin), while mice of the two other groups received the standard diet. Curcumin limited the capacity of risperidone to reduce spontaneous motricity, but failed to impede risperidone-induced increase in food intake. Curcumin did not reduce the capacity of risperidone to induce weight gain, but decreased visceral adiposity and decreased the risperidone-induced hepatomegaly, but not steatosis. Furthermore, curcumin repressed the capacity of risperidone to induce the hepatic over expression of enzymes involved in lipid metabolism (LXRα, FAS, ACC1, LPL, PPARγ, ACO, SREBP2) and decreased risperidoneinduced glucose intolerance and hypertriglyceridemia. Curcumin decreased risperidone-induced increases in serum markers of hepatotoxicity (ALAT, ASAT), as well as of one major hepatic pro-inflammatory transcription factor (NFκB: p105 mRNA and p65 protein). These findings support that nutritional doses of curcumin contained in Curcuma longa extract are able to partially counteract the risperidoneinduced

metabolic dysfunction in mice, suggesting that curcumin ought to be tested to reduce the capacity of risperidone to induce the metabolic syndrome in human. [Auger F, Martin F, Pétrault O, Samaillie J, Hennebelle T, Trabelsi MS, Bailleul F, Staels B, Bordet R, Duriez P. Risperidone-induced metabolic dysfunction is attenuated by Curcuma longa extract administration in mice. Metabolic brain disease. 2018 Feb 1;33(1):63-77.]

36. **Curcumin and metformin-mediated chemoprevention of oral cancer is associated with inhibition of cancer stem cells.** Effective chemoprevention is critical for improving outcomes of oral cancer. As single agents, curcumin and metformin are reportedto exhibit chemopreventive properties, in vitro as well as in patients with oral cancer. In this study, the chemopreventive efficacy of this drug combination was tested in a 4-nitro quinoline-1-oxide (4NQO) induced mice oral carcinogenesis model. Molecular analysis revealed a cancer stem cell (CSC)-driven oral carcinogenic progression in this model, wherein a progressive increase in the expression of CSC-specific markers (CD44 and CD133) was observed from 8th to 25th week, at transcript (40-100-fold) and protein levels ($P \leq 0.0001$). Chemopreventive treatment of the animals at 17th week with curcumin and metformin indicated that the combination regimen decreased tumor volume when compared to the control arm (0.69+0.03 vs 6.66+2.4 mm3; $P = 0.04$) and improved overall survival of the animals ($P = 0.03$). Assessment of the molecular status showed an overall downregulation of CSC markers in the treatment arms as compared to the untreated control. Further, in vitro assessment of the treatment on the primary cells generated from progressive stages of 4NQO-induced mice tissue showed a concordant and consistent downregulation of the CSC markers following combination treatment ($P < 0.05$). Thetreatment also inhibited the migratory and self-renewal properties of these cells; the effect of which was prominent in the cultures of early dysplastic tissue ($P < 0.002$). Collectively, our observations suggest that the combination of curcumin and metformin may improve chemopreventive efficacy against oral squamous cell carcinoma through a CSC-associated mechanism. [Siddappa G, Kulsum S, Ravindra DR, Kumar VV, Raju N, Raghavan N, Sudheendra HV, Sharma A, Sunny SP, Jacob T, Kuruvilla BT. Curcumin and metformin-mediated chemoprevention of oral cancer is associated with inhibition of cancer stem cells. Molecular carcinogenesis. 2017 Nov;56(11):2446-60.]

37. **Essential turmeric oils enhance anti-inflammatory efficacy of curcumin in dextran sulfate sodium-induced colitis.** Turmeric has been used as a medicinal

herb for thousands of years for treatment of various disorders. Although curcumin is the most studied active constituents of turmeric, accumulating evidence suggests that other components of turmeric have additional anti-infammatory and anti-tumorigenic properties. Herein, we investigated anti-infammatory efcacy and associated gene expression alterations of a specifc, curcumin preparation containing essential turmeric oils (ETO-curcumin) in comparison to standard curcumin at three specifc doses (0, 5, 25 or 50 mg/kg), in an animal model of dextran sodium sulfate (DSS)-induced colitis. The present study showed that both ETO and standard curcumin treatments provided protection against DSS-induced infammation. However, ETO-curcumin improved disease activity index (DAI) dose-dependently, while the anti-infammatory efcacy of standard curcumin remained constant, suggesting that ETO-curcumin may provide superior anti-infammatory efcacy compared to standard curcumin. Gene expression analysis revealed that anti-infammatory cytokines including IL-10 and IL-11 as well as FOXP3 were upregulated in the colon by ETO-curcumin. Collectively, these fndings suggest that the combined treatment of curcumin and essential turmeric oils provides superior protection from DSS-induced colitis than curcumin alone, highlighting the antiinfammatory potential of turmeric. [Toden S, Theiss AL, Wang X, Goel A. Essential turmeric oils enhance anti-inflammatory efficacy of curcumin in dextran sulfate sodium-induced colitis. Scientific reports. 2017 Apr 11;7(1):814.]

38. **Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study.** The aim of this clinical trial was to assess the efficacy and safety of curcuminoid complex extract from turmeric rhizome with turmeric volatile oil (CuraMed®) and its combination with boswellic acid extract from Indian frankincense root (Curamin®) vs placebo for the treatment of 40- to 70-year-old patients with osteoarthritis (OA). The effects of CuraMed® 500-mg capsules (333 mg curcuminoids) and Curamin® 500-mg capsules (350 mg curcuminoids and 150 mg boswellic acid) taken orally three times a day for 12 weeks in 201 patients was investigated in a three-arm, parallel-group, randomized, double-blinded, placebo-controlled trial. Primary outcome efficacy measures included OA physical function performance-based tests, the WOMAC recommended index of joint pain, morning stiffness, limitations of physical function, and the patients' global assessment of disease severity. Favorable effects of both preparations compared to placebo were observed after only 3 months of continuous treatment. A significant effect of Curamin®

compared to placebo was observed both in physical performance tests and the WOMAC joint pain index, while superior efficacy of CuraMed vs placebo was observed only in physical performance tests. The effect size compared to placebo was comparable for both treatment groups but was superior in the Curamin® group. The treatments were well tolerated. Twelve-week use of curcumin complex or its combination with boswellic acid reduces pain-related symptoms in patients with OA. Curcumin in combination with boswellic acid is more effective. Combining Curcuma longa and Boswellia serrata extracts in Curamin® increases the efficacy of OA treatment presumably due to synergistic effects of curcumin and boswellic acid. [Haroyan A, Mukuchyan V, Mkrtchyan N, Minasyan N, Gasparyan S, Sargsyan A, Narimanyan M, Hovhannisyan A. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. BMC complementary and alternative medicine. 2018 Dec;18(1):7.]

39. **Suppression of proliferation and invasive behavior of human metastatic breast cancer cells by dietary supplement BreastDefend. Integrative cancer therapies.** The study was to evaluate the effect of the dietary supplement BreastDefend (BD) on the proliferation and invasive behavior of highly metastatic human breast cancer cells in vitro. Cell proliferation and cytotoxicity of BD 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 were 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, and 17.5 µg/mL for 24, 48, and 72 hours, respectively. The inhibition of proliferation was mediated by the upregulation expression of *CCNG1*, *CHEK1*, *CDKN1C*, *GADD45A*, and *E2F2*, whereas BD downregulated 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 downregulation of expression of CXCR4 in breast cancer cells treated with BD. *Conclusion:* BD inhibits proliferation and invasive behavior of the highly metastatic human breast cancer cells in vitro. BD may have a therapeutic potential for prevention or treatment of highly metastatic

breast cancers. [Jiang J, Wojnowski R, Jedinak A, Sliva D. Suppression of proliferation and invasive behavior of human metastatic breast cancer cells by dietary supplement BreastDefend. Integrative cancer therapies. 2011 Jun;10(2):192-200.]

40. **Suppression of growth and invasive behavior of human prostate cancer cells by ProstaCaid™: Mechanism of activity.** Since the use of dietary supplements as alternative treatments or adjuvant therapies in cancer treatment is growing, a scientifc verifcation of their biological activity and the detailed mechanisms of their action are necessary for the acceptance of dietary supplements in conventional cancer treatments. In the present study we have evaluated the anti-cancer 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 purifed vitamin C, vitamin D3, selenium, quercetin, citrus bioflavonoid complex, β sitosterolzinc, lycopene, α lipoic acid, boron, berberine and 3.3'-diinodolymethane (DIM). We show that PC treatment resulted in the inhibition of cell proliferation of the highly invasive human hormone refractory (independent) PC-3 prostate cancer cells in a dose- and timedependent 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 metastatic 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 PC-3 cells. In conclusion, the dietary supplement PC is a promising natural complex with the potency to inhibit invasive human prostate cancer. [Jiang J, Eliaz I, Sliva D. Suppression of growth and invasive behavior of human prostate cancer cells by ProstaCaid™: Mechanism of activity. International journal of oncology. 2011 Jun 1;38(6):1675-82.]

41. **ProstaCaid induces G2/M cell cycle arrest and apoptosis in human and mouse androgen-dependent and-independent prostate cancer cells..**The anticancer effects of ProstaCaid, a novel integrative blend of vitamins, minerals, multiherb

extracts, and derivatives, were tested in human and mouse androgen–dependent (AD) and –independent (AI) prostate cancer cell lines. ProstaCaid shows growth inhibitory effects on both human and mouse AD prostate cancer cells (LNCaP and CASP 2.1) and AI prostate cancer cells (PC3 and CASP 1.1) in a dose-/time-dependent manner. Consistently, long-term treatment with ProstaCaid also reduced colony formation capacities of prostate cancer 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 chemopreventive and therapeutic agent for both AD and, more importantly, AI prostate cancer. [Yan J, Katz AE. ProstaCaid induces G2/M cell cycle arrest and apoptosis in human and mouse androgen-dependent and-independent prostate cancer cells. Integrative cancer therapies. 2010 Jun;9(2):186-96.]

42. **Comparative bioavailability of curcumin, turmeric and Biocurcumax™ in traditional vehicles using non-everted rat intestinal sac model.** The bioavailability of curcumin from turmeric, Biocurcumax 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 turmeric and Biocurcumax than from plain curcumin. These studies strongly suggest that curcumin may be consumed as turmeric/Biocurcumax in lipophilic vehicles instead of plain curcumin for maximum beneficial effects. [Maheshwari M. Comparative bioavailability of curcumin, turmeric and Biocurcumax™ in

traditional vehicles using non-everted rat intestinal sac model. Journal of Functional Foods. 2010 Jan 1;2(1):60-5.]

43. **Clinical Evaluation Of A Herbal Formulation, Rhulief™, In The Management Of Knee Osteoarthritis.** 28 subjects with diagnosed osteoarthritis of the knee were randomized to a 500 mg blend BCM-95 curcumin and Bospure® Boswellia twice a day or to the prescription drug celecoxib (one brand name is Celebrex®) 100 mg twice a day. Symptom scoring and clinical evaluation yielded superior results on pain relief and distance walked for the BCM- 95 and Bospure blend compared to celecoxib. BCM-95 and Bospure equaled celecoxib on joint flexibility. No serious adverse effects noted. [Antony B, Kizhakedath R, Benny M, Kuruvilla Bt. Clinical evaluation of a herbal formulation, Rhulief™, In the Management of Knee Osteoarthritis. Osteoarthritis and Cartilage 2011 Sep 1 (Vol. 19, Pp. S145-S146).

44. **Effect of Biocurcumax TM Curcumin (BCM-95) On Treatment of Moderate Chronic Periodontitis.** Controlling inflammation is a major approach in periodontal
treatments, but scaling and root planing are not always effective enough. Curcumin is anti-inflammatory and can adjust inflammatory reactions and its efficacy and immunity is proven. The present research aimed at evaluating the potential of Curcumin BCM-95 in treatment of patients with chronic periodontitis. In a double blind clinical trial, the clinical parameters including, Gingival Sulcus Bleeding Index (GSBI), Loe and Silness Gingival Index (GI), Probing Pocket Depth (PPD), and Clinical Attachment Level (CAL) were recorded at the beginning of the study, at week 6, and month 4. In case group, patients with moderate chronic periodontitis who had no systemic disease with at least one periodontal pocket with 4-6mm depth in each quadrant and bleeding on probing were chosen. After scaling and root planing, the patients took 2 Curcumin oral capsules per day for 4 weeks. The patients in the control group were given placebos. The effect of time was found to be significant in PPD, GI, CAL, and GSBI. Moreover, significant differences were seen between PPD average measurements before medication, at first follow up, and second follow-up ($P<0.05$). But, in GI, GSBI, and CAL the group effect was not significant. In other words, the reduction was seen in these parameters in both groups but they were not significant. The effect of Biocurcumax TM Curcumin (BCM-95) was significant in treatment of moderate chronic periodontitis in PPD between the two groups which reduced this parameter. [Amoian B, Ehsani H, Moghadamnia A, Dabagh Satari F, Ehsani H. Effect of Biocurcumax TM

Curcumin (BCM-95) On Treatment of Moderate Chronic Periodontitis. Journal of Mazandaran University of Medical Sciences. 2018 Mar 15;27(158):45-55.]

45. **Role of curcumin as an adjuvant in treatment of advanced head and neck squamous cell carcinoma.** Chemoradiation forms the major line of treatment in advanced head and neck squamous cell carcinoma, but the benefit of chemotherapeutic agents is at the expense of various toxicities. Curcumin has demonstrated promising results in in-vivo and in-vitro studies as a radiosensitiser. The objective of the study was to determine the role of curcumin as an adjuvant in patients undergoing chemo radiation for advanced head and neck cancers. Study involved 21 patients who underwent chemo radiotherapy for advanced head and neck cancers. They were randomized into two groups. Group A received 500 mg of curcumin while, Group B received placebo along with chemoradiation. The response was assessed using RECIST criteria at three months post treatment using contrast enhanced computerized tomography scan. Overall 58.3% patients had partial response and 41.7% patients had stable disease in group A. In group B, 33.3% patients had a partial response and 66.6% patient had a stable disease. Patients receiving curcumin along with chemoradiation had a marginal decrease in tumour volume and 58.3% patients had partial response and 41.7% had stable disease. A statistical significance could not be achieved due to lack of stage-match controls. Further studies are required to validate the role of curcumin as an adjuvant in the treatment of head and neck squamous cell carcinomas. [Arun P, Sagayaraj A, Mohiyuddin SMA, Santhosh D. Role of curcumin as an adjuvant in treatment of advanced head and neck squamous cell carcinoma. Int J Otorhinolaryngol Head Neck Surg 2018;4:1388-93.]

46. **(a) Evaluation of hepatoprotective activity of combination of Phyllanthus niruri and Curcuma longa extracts in wistar rats.** Hepatoprotective activity of combination of *Phyllanthus niruri PN)* and *Curcuma longa(CL)* extract was evaluated against carbon tetrachloride(CCl_4) induced liver damage. Combination of *PN+CL* extract at a dose of 400mg/kg, orally was coadministered with CCl_4 (0.5 mg/kg i.p) to rats for 7 days. On 8th day serum enzyme levels such as AST, ALT, ALP, TB were determined. Thiopentone induced sleeping time is estimated as an indirect index of functionality of liver. Liver tissue was used to estimate antioxidants such as MDA, GST levels and for histopathological assessment. There was a significant increase in serum enzyme levels and duration of thiopentone induced sleep time in CCl4 treated rats. Coadministration of *PN+CL* extract combination with CCl_4 significantly

prevented the rise in serum enzyme levels and normalize the duration of thiopentone induced sleep time. Combination of *PN +CL* produced significant reduction and increase in MDA & GST liver levels respectively. Histological section of liver in animals treated with CCl4 showed centrilobular area of necrosis with derangement in hepatic architecture. *PN+CL* administration prevented these deleterious changes, histological section of liver in rats treated with *PN+CL* showed normal hepatic parenchyma. Combination of *PN+CL* extract showed significant hepatoprotection against CCl4 induced liver damage. [Adiga S, Vinay BS, Kamath S, Gaonkar B, Panda A, Rao KM, Bairy KL. Evaluation of hepatoprotective activity of combination of Phyllanthus niruri and Curcuma longa extracts in wistar rats. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2012 Jul 1;3(3):1260-8.]

46.(b) **Hepatoprotective activity of combination of Phyllanthus niruri and Curcuma longa extracts against ethanol induced toxicity in wistar rats**. Alcohol is an important substance with addictive potential. Alcohol is metabolised in the liver. Free radicals generated during the metabolism of alcohol is responsible for hepatic damage. Options available for treatment of alcohol induced liver disease was inadequate in modern medicine. *Phyllanthus niruri* and *Curcuma longa* have been shown to have hepatoprotective activity. Hence this study was undertaken to evaluate the effects of *Phyllanthus niruri* and *Curcuma longa* in combination to prevent alcohol induced hepatotoxicity. Evaluation was done by comapring the levels of liver enzymes, bilirubin, antioxidants, thiopentone induced sleeping time and liver hisotpathology in various groups of albino rats after administration of ethanol. Treatment with extracts of *Phyllanthus niruri* and *Curcuma longa* caused a significant reduction in liver enzymes, bilirubin levels and increase in antioxidants. The results of our study indicate that combination of *Phyllanthus niruri* and *Curcuma longa* possess significant hepatoprotective activity against alcohol induced liver damage. [Vinay BS, Adiga S, Kamath S, Rao KM, Avin S. Hepatoprotective activity of combination of Phyllanthus niruri and Curcuma longa extracts against ethanol induced toxicity in wistar rats. International Journal of Pharma and Bio Sciences. 2016;7(1):P12-8.]

47. **Curcumin Inhibits Polycomb Repressive Complex 2 through lncRNA-PVT1 and Enhances Gemcitabine Sensitivity in Chemoresistant Pancreatic Cancer.** Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies, and a major cause of PDAC-associated mortality is acquisition of resistance to chemotherapy. Curcumin is a phenolic compound extracted

from turmeric, and is known for its potent anti-inflammatory, anti-oxidative and anti-tumorigenic properties. Accumulating evidence suggests that curcumin can overcome *de-novo* chemoresistance and re-sensitize tumors to various chemotherapeutic drugs. Recently, polycomb repressive complex 2 (PRC2) was reported to be involved in drug resistant through interaction with several long non-coding RNAs (lncRNAs). Our data provide previously unrecognized evidence for curcumin-induced sensitization to gemcitabine, through co-modulation of PRC2 and PVT1 in PDAC. These data highlight the potential adjunctive therapeutic role for curcumin together with conventional chemotherapeutic drugs in patients with PDAC. [Yoshida K, Toden S, Weng W, Shigeyasu K, Han H, Becerra C, Boland CR, Goel A. Su2060 Curcumin Inhibits Polycomb Repressive Complex 2 through lncRNA-PVT1 and Enhances Gemcitabine Sensitivity in Chemoresistant Pancreatic Cancer. Gastroenterology. 2016 Apr 1;150(4):S624.]

48. **Impact of a 3-weeks randomized double-blind cross-over study curuminoid supplementation on endotoxemia, inflammatory markers, and lipid profiles in healthy overweight and obese adults.** Postprandial endotoxaemia (increased bacterial lipopolysaccharide [LPS] level in the circulation) is associated to the increase of pro-inflammatory markers after intake of high-fat high-calorie meals . Endotoxaemia is a potential driver for chronic low-grade inflammation, linked to non-communicable chronic diseases. Curcumin (turmeric) has potential anti-inflammatory and hypolipidemic properties; and was shown to attenuate the effect of LPS-induced endotoxaemia in rats . The aim of this study was to investigate whether curcuminoid supplementation affected postprandial endotoxaemia, inflammatory markers, and lipid profiles in humans. Healthy volunteers (n = 16, 50 % men and 50 % women, aged 19–43 y, BMI 25–44 kg/m2 , fat mass 19–53 %) participated in a double-blinded, placebo-controlled, cross-over study (4 weeks wash-out period). Participants were randomized to 1 capsule per day, curcuminoids (380 mg) or placebo, for three weeks. Postprandial endotoxaemia was induced by single high-fat high-calorie meal intake (929 kcal, 65 g fat, 63 %E). Blood samples were collected before and after each leg of the study. Endotoxaemia markers (sCD14 & LBP) and inflammatory markers (CRP, TNF-α, IL-6, IL-1β, and IL-10) were measured with immunoassays; lipids were measured colorimetrically. Two participants dropped-out. There was no change in LBP for either trial leg. Subgroup analysis however indicated a 22 % decrease in LBP in volunteers with very high fat mass (n = 5) after leg A (p = 0·02). No differences were seen in CRP level after either leg, with large inter-individual variability (36·4–1028·3 ng/mL).

sCD14 decreased after both legs (leg A, p = 0·015; leg B, p = 0·019). There were no effects on TNF-α, IL-6, and IL-1β. HDL level (before high-fat meal) was significantly higher after leg A (p = 0·01) with no different after the meal. No other effects were seen on total cholesterol, LDL, and triglycerides. HDL is the main lipoprotein removing LPS from the circulation, transporting LPS to the hepatocytes for clearance (4). Thus increased HDL level could be of benefit to reduce LPS and inhibit subsequent inflammatory responses. Assessing LPS level in plasma will give a better understanding of this effect. [Nuraiza M, Edwards CA, Combet E. Impact of a 3-weeks randomized double-blind cross-over study curuminoid supplementation on endotoxemia, inflammatory markers, and lipid profiles in healthy overweight and obese adults. Proceedings of the Nutrition Society. 2016;75(OCE3).]

49. **Curcumin inhibits cancer-associated fibroblast-driven prostate cancer invasion through MAOA/mTOR/HIF-1α signaling.** Cancer-associated fbroblasts (CAFs) are key determinants in the malignant progression of cancer, supporting tumorigenesis and metastasis. CAFs also mediate epithelial to mesenchymal transition (EMT) in tumor cells and their achievement of stem cell traits. Curcumin has recently been found to possess anticancer activities via its effect on a variety of biological pathways involved in cancer progression. In this study, we found that CAFs could induce prostate cancer cell EMT and invasion through a monoamine oxidase A (MAOA)/mammalian target of rapamycin (mTOR)/hypoxia-inducible factor-1α (HIF-1α) signaling pathway, which exploits reactive oxygen species (ROS) to drive a migratory and aggressive phenotype of prostate carcinoma cells. Moreover, CAFs was able to increase CXC chemokine receptor 4 (CXCR4) and interleukin-6 (IL-6) receptor expression in prostate cancer cells. However, curcumin abrogated CAF-induced invasion and EMT, and inhibited ROS production and CXCR4 and IL-6 receptor expression in prostate cancer cells through inhibiting MAOA/mTOR/HIF-1α signaling, thereby supporting the therapeutic effect of curcumin in prostate cancer. [Du Y, Long Q, Zhang L, Shi Y, Liu X, Li X, Guan B, Tian Y, Wang X, Li L, He D. Curcumin inhibits cancer-associated fibroblast-driven prostate cancer invasion through MAOA/mTOR/HIF-1α signaling. International journal of oncology. 2015 Dec 1;47(6):2064-72.]

50. **ProstaCaid™ inhibits tumor growth in a xenograft model of human prostate cancer.** We have recently demonstrated that the dietary supplement ProstaCaid™ (PC) inhibits growth and invasive behavior of PC-3 human prostate cancer cells *in vitro*. In the present study, we evaluated toxicity and

whether PC suppresses growth of prostate cancer in a xenograft model of human prostate cancer cells implanted in mice. Here, we show that an oral administration of PC (100, 200 and 400 mg/kg) did not affect body weight or activity of liver enzymes (ALT, AST) and did not show any sign of toxicity in liver, spleen, kidney, lung and heart tissues in mice. In addition, PC treatment resulted in the inhibition of tumor volumes (1024.6±378.6 vs. 749.3±234.3, P<0.001) in a xenograft model of prostate cancer with human hormone refractory (independent) PC-3 prostate cancer cells. Moreover, qRT-PCR analysis demonstrated signifcant upregulation of expression of *CDKN1A* (p21) and inhibition of expression of *IGF2*, *NR2F2* and *PLAU* (uPA) genes by an oral administration of PC in prostate cancer xenografts. Our study demonstrates that the concentrations of the dietary supplement ProstaCaid tested did not show signs of toxicity, and its oral application has signifcant anticancer activity *in vivo* and can be considered as an alternative treatment for prostate cancer patients. [Jiang J, Loganathan J, Eliaz I, Terry C, Sandusky GE, Sliva D. ProstaCaid™ inhibits tumor growth in a xenograft model of human prostate cancer. International journal of oncology. 2012 May 1;40(5):1339-44.]

51. **BreastDefend™ prevents breast-to-lung cancer metastases in an orthotopic animal model of triple-negative human breast cancer**. It was recently demonstrated that a natural dietary supplement BreastDefend (BD), which contains extracts from medicinal mushrooms (*Coriolus versicolor, Ganoderma lucidum, Phellinus linteus*), medicinal herbs (S*cutellaria barbata, Astragalus membranaceus, Curcuma longa*), and purifed biologically active nutritional compounds (diindolylmethane and quercetin), inhibits proliferation and metastatic behavior of MDA-MB-231 invasive human breast cancer cells *in vitro*. In the present study, we evaluated whether BD suppresses growth and breast-to lung cancer metastasis in an orthotopic model of human breast cancer cells implanted in mice. Oral application of BD (100 mg/kg of body weight for 4 weeks) by intragastric gavage did not affect body weight or activity of liver enzymes and did not show any sign of toxicity in liver, spleen, kidney, lung and heart tissues in mice. Moreover, BD signifcantly decreased the change in tumor volume over time compared to the control group (p=0.002). BD treatment also markedly decreased the incidence of breast-to-lung cancer metastasis from 67% (control) to 20% (BD) (p<0.05) and the number of metastases from 2.8 (0.0, 48.0) in the control group to 0.0 (0.0, 14.2) in the BD treatment group (p<0.05). Finally, anti-metastatic activity of BD *in vivo* was further confrmed by the downregulation of expression of *PLAU* (urokinase plasminogen activator, uPA) and *CXCR4* (C-X-C chemokine receptor-4) genes

in breast tumors. In conclusion, BD may be considered as a biological therapeutic agent against invasive breast cancers. [Jiang J, Thyagarajan-Sahu A, Loganathan J, Eliaz I, Terry C, Sandusky GE, Sliva D. BreastDefend™ prevents breast-to-lung cancer metastases in an orthotopic animal model of triple-negative human breast cancer. Oncology reports. 2012 Oct 1;28(4):1139-45.]

52. **Curcumin supplementation mitigates NASH development and progression in female Wistar rats.** Curcumin, a naturally occurring plant polyphenolic compound, may have beneficial effects in nonalcoholic steatohepatitis (NASH) development. We examined whether curcumin supplementation could be used in both prevention and treatment of NASH with fibrosis. Female Wistar rats were provided ad libitum access to a "western diet" (WD) high in fat (43% kcal), sucrose (29% kcal), and cholesterol (2% w/v), as well as 15% fructose drinking water. Intraperitoneal CC14 injections (0.5 mL/kg) were also administered at weeks 1, 2, 4, and 6 to accelerate development of a NASH with fibrosis phenotype. Rats were randomized to four groups (n = 9–12/group) and fed ad libitum: (1) WD for 8-weeks (8WD), (2) WD enriched with curcumin for 8-weeks (8WD+C; 0.2% curcumin, BCM-95, DolCas Biotech) to assess prevention, (3) WD for 12-weeks (12WD), (4) WD for 8-weeks followed by 4-weeks WD+C (12WD+C) to assess treatment. Curcumin prevention (8WD vs. 8WD+C) attenuated ($P < 0.05$) histological liver inflammation, molecular markers of fibrosis (Col1a1 mRNA) and a serum marker of liver injury (AST). Curcumin treatment (12WD vs. 12WD+C) reduced ($P < 0.05$) hepatocellular inflammation, steatosis, NAFLD Activity Scores, and serum markers of liver injury (AST, ALP). Moreover, curcumin treatment also increased hepatic pACC/ACC, ApoB100, and SOD1 protein, and decreased hepatic FGF-21 levels; whereas, curcumin prevention increased hepatic glutathione levels. Both curcumin prevention and treatment reduced molecular markers of hepatic fibrosis (Col1a1 mRNA) and inflammation (TNF-a, SPP1 mRNA). Curcumin supplementation beneficially altered the NASH phenotype in female Wistar rats, particularly the reversal of hepatocellular inflammation. [Cunningham RP, Moore MP, Moore AN, Healy JC, Roberts MD, Rector RS, Martin JS. Curcumin supplementation mitigates NASH development and progression in female Wistar rats. Physiological reports. 2018 Jul;6(14):e13789.]

53. **Oral Bioavailability of BCM-95® in Dogs.** This study looked specifically at bioavailability in dogs for veterinary purposes. Curcuminoids, the biologically active components of tumeric, have been shown to have high antioxidant, and

anti-inflammatory activity. Both in vitro and in vivo studies on model systems in multiple species have demonstrated a wide range of effects that support the use of curcumin in a wide range of conditions. However, these applications are constrained by the relatively poor bioavailability of curcumin. A comparison was made in dogs of a standard commercial curcumin extract and a unique highly bioavailable enhanced formulation of BCM-95 curcumin (reported as the veterinary NMXCC-95 designation). Two groups of 3 dogs, weighing 12–15 kg were dosed with 2 gram equivalents of curcumin either as curcumin powdered extract or NMXCC95™ following a 12 hour fast. After a one week washout dogs received the other formulation. Plasma curcumin levels were determined for 0–8 hr samples by HPLC method. The standard curcumin extract had a shorter Tmax compared to the NXMCC95™ formulation (1.5 hrs vs 3.17 hrs), but the enhanced formulation reached a 3-fold higher Cmax (296.4 vs 98.6 ng/g) and a 7-fold higher AUC over 8 hrs (1381 vs 199 nghr/g). Furthermore the plasma levels with NMXCC95™ remained elevated at 8 hrs (107.162.7 ng/g) while levels from standard curcumin extract returned close to zero (6.38.2 ng/g). These data show that the enhanced formulation of curcumin NMXCC95™ has a substantially higher bioavailability in dogs than standard powdered curcumin extract and has the potential to serve as an effective control of conditions with an underlying inflammatory basis. [Antony B, Butchin RK, Griffin DW. Bioavailability of a novel, bioenhanced preparation in dogs. Poster Presentation. 2009 ACVIM Forum/Canadian VMA Convention: June 3-6, 2009; Montréal, Québec, Canada.]

54. **A combination of curcumin and oligomeric proanthocyanidins offer superior anti-tumorigenic properties in colorectal cancer.** Combining anti-cancer agents in cancer therapies is becoming increasingly popular due to improved efcacy, reduced toxicity and decreased emergence of resistance. Here, the hypothesis was that dietary agents such as oligomeric proanthocyanidins (OPCs) and curcumin cooperatively modulate cancer-associated cellular mechanisms to inhibit carcinogenesis. By a series of *in vitro* assays in colorectal cancer cell lines, we showed that the anti-tumorigenic properties of the OPCs-curcumin combination were superior to the efects of individual compounds. By RNA-sequencing based geneexpression profling in six colorectal cancer cell lines, we identifed the cooperative modulation of key cancer-associated pathways such as DNA replication and cell cycle pathways. Moreover, several pathways, including protein export, glutathione metabolism and porphyrin metabolism were more efectively modulated by the combination

of OPCs and curcumin. We validated genes belonging to these pathways, such as HSPA5, SEC61B, G6PD, HMOX1 and PDE3B to be cooperatively modulated by the OPCs-curcumin combination. We further confrmed that the OPCs-curcumin combination more potently suppresses colorectal carcinogenesis and modulated expression of genes identifed by RNA-sequencing in mice xenografts and in colorectal cancer patient-derived organoids. Overall, by delineating the cooperative mechanisms of action of OPCs and curcumin, we make a case for the clinical co-administration of curcumin and OPCs as a treatment therapy for patients with colorectal cancer. [Ravindranathan P, Pasham D, Balaji U, Cardenas J, Gu J, Toden S, Goel A. A combination of curcumin and oligomeric proanthocyanidins offer superior anti-tumorigenic properties in colorectal cancer. Scientific reports. 2018 Sep 14;8(1):13869.]

55. **Curcumin downregulates expression of opioid-related nociceptin receptor gene (OPRL1) in isolated neuroglia cells.** Curcumin (CC) exerts polyvalent pharmacological actions and multi-target effects, including pain relief and anti-nociceptive activity. In combination with *Boswellia serrata* extract (BS), curcumin shows greater efficacy in knee osteoarthritis management, presumably due to synergistic interaction of the ingredients. The aim of the study was to elucidate the molecular mechanisms underlying the analgesic activity of curcumin and its synergistic interaction with BS. Gene expression profling by transcriptome-wide mRNA sequencing in human T98G neuroglia cells treated with CC (Curamed), BS, and the combination of CC and BS (CC-BS; Curamin), followed by interactive pathways analysis of the regulated genes was performed. Treatment with CC and with CC-BS selectively downregulated opioid-related nociceptin receptor 1gene (*OPRL1*) expression by 5.9-fold and 7.2-fold, respectively. No changes were detected in the other canonical opioid receptor genes: *OPRK1, OPRD1*, and *OPRM1*. Nociceptin reportedly increases the sensation of pain in supra-spinal pain transduction pathways. Thus, CC and CC-BS may downregulate *OPRL1*, consequently inhibiting production of the nociception receptor NOP, leading to pain relief. In neuroglia cells, CC and CC-BS inhibited signaling pathways related to opioids, neuropathic pain, neuroinflammation, osteoarthritis, and rheumatoid diseases. CC and CC-BS also downregulated ADAM metallopeptidase gene *ADAMTS5* expression by 11.2-fold and 13.5-fold, respectively. *ADAMTS5* encodes a peptidase that plays a crucial role in osteoarthritis development via inhibition of a corresponding signaling pathway. It is reported for the first time that CC and CC-BS act as nociceptin receptor antagonists, selectively downregulating

opioid-related nociceptin receptor 1 gene (*OPRL1*) expression, which is associated with pain relief. BS alone did not affect *OPRL1* expression, but rather appears to potentiate the effects of CC via multiple mechanisms, including synergistic interactions of molecular networks. [Seo EJ, Efferth T, Panossian A. Curcumin downregulates expression of opioid-related nociceptin receptor gene (OPRL1) in isolated neuroglia cells. Phytomedicine. 2018 Nov 15;50:285-99.]

56. **The effects of curcumin supplementation on liver enzymes, lipid profile, glucose homeostasis, and hepatic steatosis and fibrosis in patients with non-alcoholic fatty liver disease.** Nonalcoholic fatty liver disease (NAFLD) is a major global health problem. The most common cause of death in these patients is due to cardiovascular disorders. The aim of this study was to examine the effects of curcumin supplementation on cardiovascular risk factors in patients with NAFLD. In this randomized, placebo-controlled, clinical trial, fifty two patients with NAFLD were randomly assigned to receive life style recommendations plus either 1500 mg curcumin or placebo for 12 weeks. Anthropometric indices, blood lipid profile, insulin resistance, as well as hepatic steatosis and fibrosis scores were measured at the beginning and the end of the study, and compared between and within groups. Hepatic fibrosis, serum cholesterol, glucose and alanin aminotransferase (ALT) reduced significantly only in curcumin group ($p < 0.05$). Anthropometric indices, blood lipid profile, insulin resistance, and hepatic steatosis decreased significantly in both groups ($p < 0.05$), without any significant difference between two groups.The results showed that daily intake of 1500 mg curcumin plus weight loss is not superior to weight loss alone in amelioration of cardiovascular risk factors in patients with NAFLD. Further studies with different dosages of curcumin are needed to be able to conclude about the effects of this dietary supplement on cardiovascular risk factors and NAFLD characteristics. [Saadati S, Hatami B, Yari Z, Shahrbaf MA, Eghtesad S, Mansour A, Poustchi H, Hedayati M, Aghajanpoor-pasha M, Sadeghi A, Hekmatdoost A. The effects of curcumin supplementation on liver enzymes, lipid profile, glucose homeostasis, and hepatic steatosis and fibrosis in patients with non-alcoholic fatty liver disease. European journal of clinical nutrition. 2019 Mar;73(3):441.]

57. **Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study.** The purpose of this study was to compare the efficacy and safety of curcumin with those of diclofenac in the treatment of knee osteoarthritis (OA). In this randomized, open-label, parallel,

active controlled clinical study, 139 patients with knee OA were randomly assigned to receive either a curcumin 500-mg (BCM-95®) capsule three times daily or a diclofenac 50-mg tablet two times daily for 28 days. Patients underwent assessment at baseline and days 7, 14, and 28. The main outcome measure was severity of pain using visual analogue scale score at days 14 and 28. Knee Injury and Osteoarthritis Outcome Score (KOOS) (at days 14 and 28), anti-flatulent effect (at day 7), anti-ulcer effect, weight-lowering effect, and patient's and physician's global assessment of therapy at day 28 were included as secondary outcome measures. Safety after treatment was evaluated by recording adverse events and laboratory investigation. At days 14 and 28, patients receiving curcumin showed similar improvement in severity of pain and KOOS scale when compared with diclofenac, and the difference was not statistically significant. At day 7, the patients who received curcumin experienced a significantly greater reduction in the number of episodes of flatulence compared with diclofenac ($P < 0.01$). At day 28, a weight-lowering effect ($P < 0.01$) and anti-ulcer effect ($P < 0.01$) of curcumin were observed. None of the patients required H2 blockers in the curcumin group, and 19 patients required H2 blockers in the diclofenac group (0% versus 28%, respectively; $P < 0.01$). Adverse effects were significantly less in the curcumin group (13% versus 38% in the diclofenac group; $P < 0.01$). Patient's and physician's global assessment of therapy was similar in the two treatment groups. Curcumin has similar efficacy to diclofenac but demonstrated better tolerance among patients with knee OA. Curcumin can be an alternative treatment option in the patients with knee OA who are intolerant to the side effects of non-steroidal anti-inflammatory drugs. [Shep D, Khanwelkar C, Gade P, Karad S. Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study. Trials. 2019;20(1):214.]

58. **The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes.** Diabetes mellitus is one of the most common and important metabolic diseases in human. Curcumin, which is a natural polyphenol found in turmeric, can be used in treatment of diabetes complications for its antidiabetic, anti-inflammatory, and antioxidant properties. In this double-blind randomized clinical trial, 44 patients with Type 2 diabetes randomly assigned to curcumin or placebo group. Patients consumed either 1,500-mg curcumin or placebo daily for 10 weeks. Anthropometric measurements were measured at baseline and at the end of the study. Serum concentrations of triglyceride (TG), total

cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and adiponectin were determined after 12-hr fasting at the beginning and end of study. The mean serum level of TG decreased in curcumin group compared with baseline (109 ± 36 vs. 124 ± 36; $p < 0.05$). At the end of study, the mean concentration of high-sensitivity C-reactive protein decreased in the curcumin group compared to the control (2.9 ± 2.9 vs. 3.4 ± 4.2; $p < 0.05$). The mean serum concentration of adiponectin increased (64 ± 3 vs. 63 ± 4; $p < 0.05$) in the treatment group compared with the placebo at the end of the study. The results of the current study indicate that curcumin consumption may reduce diabetes complications through decreasing TG level as well as indicators of inflammation. [Adibian M, Hodaei H, Nikpayam O, Sohrab G, Hekmatdoost A, Hedayati M. The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. Phytotherapy Research. 2019 Mar 12.]

59. **Evaluation of Antinociceptive Activity of Bcm95 and Bospure® in Rodents.** The analgesic activity of BCM95, BosPure®and its formulations in different ratios in rodents is evaluated. The antinociceptive effect of test drugs were investigated in mice and rats using two models: writhing test and formalin test. Ten groups were studied, each group consisting of 6 animals, Group I to X received: 2% gum acacia, Aspirin /Morphine s.c (formalin test), BCM95, BosPure®, Crude boswellia extract, BCM95:BosPure® 1:1, BCM95:BosPure®3:1, BCM95:BosPure®1:3, BCM95 + BosPure® + Soy, BCM95 + BosPure® micronised orally respectively 45 min before the experiment. Solution of 0.6% acetic acid was injected i.p to the mice, placed individually in the glass beakers to record the number of writhes. In formalin test model wistar rats (150-200 g) were injected with 50 ul of a 5% (v/v) solution of formalin into the sub plantar region of the right hind paw and the number of flinches in initial phase and second phase was recorded. At all the doses the test drugs produced a significant inhibition of writhing ($V = 6$; $P < 0.01$) compared to control. In formalin test all the test groups showed significant reduction in number of flinches in the second phase when compared to control ($V = 6$; $P < 0.01$) similar to analgesics with peripheral action like NSAIDs. Conclusions: BCM95, BosPure® and its formulations in different ratios possess antinociceptive activity in both the models. BCM95: BosPure® in 1:1 ratio showed better analgesic activity than other test groups in both models. [Sahana D Acharya, RS Nishith, BS Nischal, UP Rathnakar, Sheetal Ullal, Ashok K Shenoy. Evaluation of Antinociceptive Activity of Bcm95 and

Bospure® in Rodents. Indian Journal of Pharmacology, December 2013, Volume 45, Supplement S187.]

60. **The effect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes.** Diabetes mellitus is a common metabolic disorders in human and affect a lot of people around the world. Curcumin is a component of turmeric and in many studies therapeutic effects such as anti-hypertensive, antihyperlipidemia, anti-hyperglycemia for this substance are shown. The aim of this study was to investigate the effect of curcumin supplementation on anthropometric indices glycemic control and oxidative stress in overweight patients with type 2 diabetes. In this randomized, double-blind, placebo-controlled trial, 53 participants with type 2 diabetes were divided randomly into the experimental and control groups to receive either 1500 mg curcumin or placebo capsule three times in a day for 10 weeks. Supplementation with curcumin in type 2 diabetes compare to placebo causes a signifcant changes in mean weight (-0.64±0.22 vs. 0.19±0.37 $p < 0.05$), body mass index (BMI) (0.3±0.03 vs. 0.1±0 $p < 0.05$), waist circumference (WC) (-1.2±0.4 vs. -0.43±0.11 $p < 0.05$) and fasting blood sugar (FBS) (-7±2 vs. 3±0.2 $p < 0.05$) but did not show any diference for hemoglobin A1c (HbA1c), insulin, malondialdehyde (MDA), total antioxidant capacity (TAC), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and pancreatic B cell function (HOMA-B) at end of study. This study indicated that daily administration of 1500 mg curcumin has positive efects in reducing fasting blood glucose and weight in patients with type 2 diabetes. [Hodaei H, Adibian M, Nikpayam O, Hedayati M, Sohrab G. The effect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes: a randomized, double-blind clinical trial. Diabetology & metabolic syndrome. 2019 Dec;11(1):41.]

61. **Effect of curcumin supplementation on serum expression of select cytokines and chemokines in a female rat model of nonalcoholic steatohepatitis.** It is recently reported that curcumin supplementation in a metabolically (i.e., Western diet [WD]) and chemically (i.e., CCl4) induced female rat model of non-alcoholic steatohepatitis (NASH) was associated with lower liver pathology scores and molecular markers of inflammation. This occurred when curcumin was given during induction of disease (preventative arm; 8-week WD with or without curcumin [8WD + C vs. 8WD]) as well as when given after disease development (treatment arm; 12-week WD with or without curcumin during

weeks 9–12 [12WD + C vs. 12WD]). Herein, the findings from that study was extended by determining the effects of curcumin supplementation on cytokine/chemokine expression in serum collected from these same rats. 24 cytokines/chemokines were assayed. IL-2 (+ 80%) and IL-13 (+ 83%) were greater with curcumin supplementation in the prevention arm. IL-2 (+ 192%), IL-13 (+ 87%), IL-17A (+ 81%) and fractalkine (+ 121%) were higher while RANTES was lower (– 22%) with curcumin supplementation in the treatment arm ($p < 0.05$ for all). RANTES concentrations also correlated significantly with hepatic pathology scores of inflammation (r = 0.417, $p = 0.008$). Select serum cytokines/chemokines were affected with curcumin supplementation in this female rat model of NASH. Moreover, curcumin's effect(s) on RANTES and its association with liver disease pathogenesis and progression may warrant further investigation. [Pickich MB, Hargrove MW, Phillips CN, Healy JC, Moore AN, Roberts MD, Martin JS. Effect of curcumin supplementation on serum expression of select cytokines and chemokines in a female rat model of nonalcoholic steatohepatitis. BMC research notes. 2019 Dec;12(1):1-7]

62. **Comparing different non-invasive methods in assessment of the effects of curcumin on hepatic fibrosis in patients with non-alcoholic fatty liver disease.** The aim of this study was to examine the effects of curcumin supplementation on hepatic fibrosis using different fibrosis assessment methods. Nonalcoholic fatty liver disease (NAFLD) may progress to hepatic fibrosis. Detection of hepatic fibrosis should be measured by liver biopsy, which is an invasive method. Thus, some non-invasive methods are suggested. Hepatic fibrosis was evaluated in forty six patients with NAFLD before and three months after supplementation with 1.5 gram curcumin or placebo. Methods of assessments included fibroscan, and calculating non-invasive marker panel including FIB-4 (Fibrosis4), NFS (NAFLD fibrosis score), APRI (AST (Aspartate amino transferase) Platelet Ratio Index), and BARD (body mass index, AST/ALT (Alanine aminotransferase ratio, diabetes). Fibrosis score was reduced significantly after curcumin supplementation using fibroscan ($p<0.01$), FIB-4 ($p<0.05$) and APRI ($p<0.05$) tests, while fibrosis score did not change significantly using BARD and NFS methods ($p>0.05$). Results revealed that fibroscan, FIB-4, and APRI are similar in assessment of hepatic fibrosis changes after curcumin supplementation. [Saadati S, Hekmatdoost A, Hatami B, Mansour A, Zahra Z, Hedayati M, Sadeghi A. Comparing different non-invasive methods in assessment of the effects of curcumin on hepatic fibrosis in patients with non-alcoholic fatty liver disease. Gastroenterology and hepatology from bed to bench. 2018;11(Suppl 1):S8.]

63. **Curcumin and inflammation in non-alcoholic fatty liver disease: a randomized, placebo controlled clinical trial.** The aim of the present study was to evaluate the effects of curcumin supplementation on inflammatory indices, and hepatic features in patients with non-alcoholic fatty liver disease (NAFLD). Fifty patients with NAFLD were randomized to receive lifestyle modification advice plus either 1500 mg curcumin or the same amount of placebo for 12 weeks. Curcumin supplementation was associated with significant decrease in hepatic fibrosis ($p < 0.001$), and nuclear factor-kappa B activity ($p < 0.05$) as compared with the baseline. Hepatic steatosis and serum level of liver enzymes, and tumor necrosis-α (TNF-α) significantly reduced in both groups ($p < 0.05$). None of the changes were significantly different between two groups. Our results indicated that curcumin supplementation plus lifestyle modification is not superior to lifestyle modification alone in amelioration of inflammation. [Saadati S, Sadeghi A, Mansour A, Yari Z, Poustchi H, Hedayati M, Hatami B, Hekmatdoost A. Curcumin and inflammation in non-alcoholic fatty liver disease: a randomized, placebo controlled clinical trial. BMC gastroenterology. 2019 Dec;19(1):133.]

64. **Role of turmeric extract in minimising mucositis in patients receiving radiotherapy for head and neck squamous cell cancer: a randomised, placebo-controlled trial.** The aim of the study was to determine the role of turmeric extract in reducing mucositis in patients undergoing radiotherapy for head and neck cancer. Sixty-one patients who underwent radiotherapy were included in the study and randomised into groups A and B. Patients in group A received 500 mg of turmeric extract (BCM95) thrice daily, while patients in group B received placebo until radiotherapy completion. All patients were assessed for oral mucositis on a weekly basis during treatment and two months post-treatment using the National Cancer Institute Common Terminology Criteria for Adverse Events and World Health Organization criteria. Both groups had a similar grade of mucositis in first two weeks of treatment. The severity of mucositis was progressive in the control group, with four patients developing grade 3 mucositis by week four. In group A, however, the majority of patients (73.3 per cent) had grade 1 mucositis after four weeks of treatment. The difference was statistically significant from the third week onwards ($p < 0.001$). Turmeric extract reduces the incidence and severity of radiation-induced mucositis, which can benefit patients undergoing radiation for head and neck cancer. [Arun P, Sagayaraj A, Azeem Mohiyuddin SM, Santosh D. Role of turmeric extract in minimising mucositis in patients

receiving radiotherapy for head and neck squamous cell cancer: a randomised, placebocontrolled trial. J Laryngol Otol 2020;1–6.]

65. **Evaluation of the articular cartilage in the knees of rats with induced arthritis treated with curcumin.** This study was designed to evaluate the anti-inflammatory effects of a curcumin treatment on the knee of rats with induced osteoarthritis. Fifteen adult rats were used and divided in three groups: the osteoarthritis group (OAG), control group (CG–without induction of osteoarthritis), and curcumin-treated osteoarthritis group (COAG). Osteoarthritis was induced in the right knee of rats in the OAG and COAG by administering an intra-articular injection of 1 mg of zymosan. Fourteen days after induction, 50 mg/kg curcumin was administered by gavage daily for 60 days to the COAG. After the treatment period, rats from all groups were euthanized. Medial femoral condyles were collected for light microscopy and immunohistochemical staining. The expression of SOX-5, IHH, MMP-8, MMP-13, and collagen 2 (Col2) was analyzed. The COAG exhibited an increase in the number of chondrocytes in the surface and middle layers compared with that of the OAG and CG, respectively. The COAG also showed a decrease in the thicknesses of the middle and deep layers compared with those of the OAG, and an increase in Col2 expression was observed in all articular layers (surface, middle, and deep) in the COAG compared with that in the OAG. SOX-5 expression was increased in the surface and deep layers of the COAG compared with those in the OAG and CG. Based on the results of this study, the curcumin treatment appeared to exert a protective effect on cartilage, as it did not result in an increase in cartilage thickness or in MMP- 8 and MMP-13 expression but led to increased IHH, Col2, and SOX-5 expression and the number of chondrocytes. [Nicoliche T, Maldonado DC, Faber J, Silva MCPd (2020) Evaluation of the articular cartilage in the knees of rats with induced arthritis treated with curcumin. PLoS ONE 15(3): e0230228]

66. **Natural agents inhibit colon cancer cell proliferation and alter microbial diversity in mice.** The current study was undertaken to investigate the effect of differentially formulated polyphenolic compound Essential Turmeric Oil-Curcumin (ETO-Cur), and Tocotrienol-rich fraction (TRF) of vitamin E isomers on colorectal cancer (CRC) cells that produce aggressive tumors. Combinations of ETO-Cur and TRF were used to determine the combinatorial effects of ETO-Cur and TRF-mediated inhibition of growth of CRC cells in vitro and HCT- 116 cells xenograft in SCID mice. 16S rRNA gene sequence profiling was performed to determine the outcome of gut microbial communities in mice

feces between control and ETO-Cur-TRF groups. Bacterial identifications were validated by performing SYBR-based Real Time (RT) PCR. For metagenomics analysis to characterize the microbial communities, multiple software/tools were used, including Quantitative Insights into Microbial Ecology (QIIME) processing tool. We found ETO-Cur and TRF to synergize and that the combination of ETO-Cur-TRF significantly inhibited growth of HCT-116 xenografts in SCID mice. This was associated with a marked alteration in microbial communities and increased microbial OTU (operation taxonomic unit) number. The relative abundance of taxa was increased and the level of microbial diversity after 34 days of combinatorial treatment was found to be 44% higher over the control. Shifting of microbial family composition was observed in ETO-Cur-TRF treated mice as evidenced by marked reductions in Bacteroidaceae, Ruminococcaceae, Clostridiales, Firmicutes and Parabacteroids families, compared to controls. Interestingly, during the inhibition of tumor growth in ETO-Cur treated mice, probiotic Lactobacillaceae and Bifidobacteriaceae were increased by 20-fold and 6-fold, respectively. The relative abundance of anti-inflammatory Clostridium XIVa was also increased in ETO-Cur-TRF treated mice when compared with the control. Our data suggest
that ETO-Cur-TRF show synergistic effects in inhibiting colorectal cancer cell proliferation in vitro and in mouse xenografts in vivo, and might induce changes in microbial diversity in mice. [Farhana L, Sarkar S, Nangia-Makker P, Yu Y, Khosla P, Levi E, et al. (2020) Natural agents inhibit colon cancer cell proliferation and alter microbial diversity in mice. PLoS ONE 15(3): e0229823]

67. **Efficacy and safety of combination of curcuminoid complex and diclofenac versus diclofenac in knee osteoarthritis: a randomized trial.** The aim of the srudy was to compare the efficacy and safety of combination of curcuminoid complex and diclofenac vs diclofenac alone in the treatment of knee osteoarthritis (OA). In this randomized trial, 140 patients of knee OA received either curcuminoid complex 500mg (BCM-95) with diclofenac 50mg 2 times daily or diclofenac 50mg alone 2 times daily for 28 days. Patients were assessed at baseline, day 14 and day 28. Primary efficacy measures were Knee injury and OA outcome score (KOOS) subscale at day 14 and day 28. Anti-ulcer effect and patient-physician's global assessment of therapy at day 28 were included as secondary endpoints. Safety after treatment was evaluated by recording adverse events and laboratory investigations. Both treatment groups showed improvement in primary endpoints at each evaluation visit. Patients receiving curcuminoid complex plus diclofenac

showed significantly superior improvement in KOOS subscales, viz. pain and quality of life at each study visit (P<.001) when compared to diclofenac. Less number of patients required rescue analgesics in curcuminoid complex plus diclofenac group (3%) compared to diclofenac group (17%). The number of patients who required histamine 2 (H2) blockers was significantly less in curcuminoid complex plus diclofenac group compared to diclofenac group (6% vs 28%, respectively; P<.001). Adverse effects were significantly less in curcuminoid complex plus diclofenac group (13% vs 38% in diclofenac group; P<.001). Patient's and physician's global assessment of therapy favored curcuminoid complex plus diclofenac than diclofenac. Combination of curcuminoid complex and diclofenac showed a greater improvement in pain and functional capacity with better tolerability and could be a better alternative treatment option in symptomatic management of knee OA. [Shep D, Khanwelkar C, Gade P, Karad S. Efficacy and safety of combination of curcuminoid complex and diclofenac versus diclofenac in knee osteoarthritis: a randomized trial. Medicine 2020;99:16(e19723]

68. **A Randomized Controlled Trial Of Curcumin And Diclofenac Combination In Knee Osteoarthritis.** The objective of the study was to evaluate pain relief and safety of the combination of curcumin and diclofenac versus diclofenac alone in the treatment of knee osteoarthritis (OA). 140 patients of knee OA meeting inclusion criteria were randomized to receive either curcumin 500 mg with diclofenac 50 mg twice daily or diclofenac 50 mg tablet alone twice daily for 28 d. Patients were assessed at baseline, Day 14 and Day 28. Primary efficacy measure was severity of pain (Visual Analogue Scale) at day 14 and day 28. Safety after treatment was evaluated by recording side effects and laboratory investigations. Patients receiving curcumin plus diclofenac showed significantly superior improvement in severity of pain at each study visit (p<0.001) when compared to diclofenac. Adverse effects were significantly less in curcumin plus diclofenac group (p<0.001). Combination of curcumin and diclofenac showed a significant improvement in pain on the basis of VAS when compared to diclofenac which may be due to synergistic effect between curcumin and diclofenac. [Shep D, Khanwelkar C, Gade P, Karad S. A Randomized Controlled Trial Of Curcumin And Diclofenac Combination In Knee Osteoarthritis. Int J Curr Pharm Sci [Internet]. 2019nov.15 [Cited 2020may4];11(6):111-4. DOI: http://dx.doi.org/10.22159/ijcpr.2019v11i6.36355]

69. **The Feasibility and Efficacy of a Brief Integrative Treatment for Adults With Depression and/or Anxiety: A Randomized Controlled Trial.** The aim of this study was to investigate the efficacy and suitability of a brief integrative intervention, Personalized Integrative Therapy (PI Therapy), for the treatment of adult depression and/or anxiety. In this 6-week, 3-arm, parallel-group, randomized trial, PI Therapy delivered alone or with nutritional supplements (PI Therapy þ Supps) was compared to cognitive behavior therapy (CBT) in 48 adults with depression and/or anxiety. All treatments were delivered as a 1-day workshop plus 6 weeks of reminder phone text messages to reinforce topics and skills covered in the workshop. Affective symptoms decreased significantly and to the same extent in all 3 conditions. At the end of treatment, 33% to 58% of participants reported levels of depressive symptoms in the normal range, and 50% to 58% reported nonclinical levels of anxiety. Compared to CBT and PI Therapy, PI Therapy þ Supps was associated with significantly greater improvements in sleep quality. These findings suggest that a brief integrative intervention with or without supplements was comparable to CBT in reducing affective symptoms in adults with depression and/or anxiety. However, sleep quality improved only in the PI Therapy þ Supps condition. These findings will require replication with a larger cohort. [Lopresti AL, Smith SJ, Metse AP, Foster T, Drummond PD. The feasibility and efficacy of a brief integrative treatment for adults with depression and/or anxiety: a randomized controlled trial. Journal of evidence-based integrative medicine. 2020 Jul 7;25:2515690X20937997.]

70. **Neuroprotective Effect of Turmeric Extract in Combination with Its Essential Oil and Enhanced Brain Bioavailability in an Animal Model.** The study evaluated the neuroprotective effect and pharmacokinetic profile of turmeric extract and their metabolites in the blood and brain in an aluminum-induced neurotoxic animal model. Methods. Swiss albino mice received turmeric extract (TE), TE-essential oil combination (TE+EO) at doses of 25 and 50 mg/kg/day orally, vehicle (control), and a positive control group. Neurotoxicity was induced by injecting aluminum chloride (40 mg/kg/day, i.p.), and the effect of the intervention was studied for 45 days. The pharmacokinetic and behavioral biochemical markers of brain function and brain histopathological changes were evaluated. Results. The AUC 0-t showed a 30.1 and 54.2 times higher free curcumin concentration in plasma with 25 mg/kg and 50 mg/kg of TE+EO vs. TE, respectively. The concentration of free curcumin in the brain was 11.01 and 13.71- fold higher for 25 mg/kg and 50 mg/kg of TE+EO vs. TE, respectively. Aluminum impairs spatial learning and memory, which was

significantly reversed with TE+EO by 28.6% (25 mg/kg) and 39.4% (50 mg/kg). In the elevated plus maze test, 44.8% (25 mg/kg) and 67.1% (50 mg/kg) improvements were observed. A significant reduction in aluminum-induced lipid peroxidation was observed. Also, the levels of glutathione, acetylcholinesterase, and catalase were improved with TE+EO. Damage to the hippocampal pyramidal cells was averted with TE+EO. Conclusion. The neuroprotective and antioxidant response confirms the benefits of TE+EO against aluminum-induced neurotoxicity. The presence of free curcumin and its metabolites in the brain and plasma establishes its improved bioavailability and tissue distribution. Therefore, the benefits of TE +EO could be harnessed in neurodegenerative diseases. [Banji D, Banji OJ, Srinivas K. Neuroprotective Effect of Turmeric Extract in Combination with Its Essential Oil and Enhanced Brain Bioavailability in an Animal Model. BioMed Research International. 2021 Jan 27;2021.]

71. **Synofit Premium in Refractory Low Back Pain: A Retrospective Observational Study.** In this retrospective observational study, information about pain and quality of life was collected for analysis from medical records of 85 patients with chronic low back pain who were treated for 3 months with Synofit® Premium (2 - 3 capsules daily), a liquid mixture of green-lipped mussel from New Zealand, blackcurrant leaf, and curcuma extract. Within the first 6 weeks of therapy, a significant clinical benefit was observed for relief from pain, need for pain-relieving drugs, and the interference of pain with personal care and lifting. This benefit was more pronounced at 3 months. The mixture was well tolerated without significant side effects. Adherence was estimated to be “good” to “very good.” Patients assessed global improvement and efficacy as “sufficient” to “good.” Based on this study, the mode of action of Synofit® Premium appears mainly to be analgesic, as reported by patients, and allows them to reduce the consumption of other pain-relieving substances and improve their quality of life. In conclusion, Synofit® Premium holds potential as a promising candidate alternative therapy for relief of low back pain and likely other painful rheumatic conditions, with almost no or minor side effects. [Qu J, Mélot C, Appelboom T. Synofit Premium in Refractory Low Back Pain: A Retrospective Observational Study. Open Journal of Rheumatology and Autoimmune Diseases. 2017;7(02):120.]

72. **A novel cancer preventative botanical mixture, TriCurin, inhibits viral transcripts and the growth of W12 cervical cells harbouring extrachromosomal or integrated HPV16 DNA.** The phytochemical mixture TriCurin (curcumin,

epigallocatechin gallate (EGCG) and resveratrol) eliminates human papillomavirus (HPV) (+) cancer cells in vitro and in vivo. In this study, we further evaluate TriCurin. The activity of TriCurin and its individual compounds was assayed on W12 cells, derived from a cervical precancer containing episomal and integrated HPV16 DNA, using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays, microscopy and reverse transcription-polymerase chain reaction (RT-PCR), and on HeLa cells by gene expression analysis. The stability and toxicity of TriCurin microemulsion were tested in an organotypic cervical tissue model. TriCurin and its individual compounds inhibit the growth of W12 cells, episomal, type 1 and 2 integrants; the relative order of activity is TriCurin, EGCG, curcumin, or resveratrol. RT-PCR shows that TriCurin activates p53 and suppresses HPV16 mRNAs E1, E2, E4, E6 and E7 at 24 h in W12 cells. Gene expression analysis shows that TriCurin activates pro-apoptotic genes and represses anti-apoptotic genes in HeLa cells. TriCurin in a microemulsion is stable and non-toxic to cervical tissue. The combination of TriCurin and tanshinone IIA exhibits additional synergy against HeLa cells. TriCurin, and the combination of TriCurin with tanshinone IIA, are effective against HPV (+) cells. The phytochemical mixture, in the microemulsion-based cream, is a promising therapeutic for the prevention and treatment of cervical cancer. [Einbond LS, Zhou J, Wu HA, Mbazor E, Song G, Balick M, DeVoti JA, Redenti S, Castellanos MR. A novel cancer preventative botanical mixture, TriCurin, inhibits viral transcripts and the growth of W12 cervical cells harbouring extrachromosomal or integrated HPV16 DNA. British Journal of Cancer. 2021 Mar;124(5):901-13.].

73. **Bioavailable turmeric extract for knee osteoarthritis: a randomized, non-inferiority trial versus paracetamol.** The purpose of the study was to compare the efficacy and safety of bioavailable turmeric extract versus paracetamol in patients with knee osteoarthritis (OA). In this randomized, non-inferiority, controlled clinical study, patients of knee OA were randomized to receive bioavailable turmeric extract (BCM-95®) 500 mg capsule two times daily or paracetamol 650 mg tablet three times daily for 6 weeks. The primary outcome measure was Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale. The secondary outcome measures were WOMAC total, WOMAC stiffness, and WOMAC physical function scores. Responder analysis of individual patients at different levels (≥ 20%, ≥ 50%, and ≥ 70%) for WOMAC score was calculated. TNF alpha and CRP levels were evaluated and adverse events (AE) were also recorded. Seventy-one and seventy-three knee OA patients, respectively in bioavailable turmeric extract and

paracetamol groups, completed the study. Non-inferiority (equivalence) test showed that WOMAC scores were equivalent in both the groups (p value < 0.05) in all the domains within the equivalence limit defined by effect size (Cohen's d) of 0.5 whereas CRP and TNF-α were better reduced with turmeric extract than paracetamol. After 6 weeks of treatment, WOMAC total score, pain, stiffness, and function scores got a significant improvement of 23.59, 32.09, 28.5, and 20.25% respectively with turmeric extract. In the turmeric extract group, 18% of patients got more than 50% improvement and 3% of patients got more than 70% improvement in WOMAC pain and function/ stiffness score and none of the patients in the paracetamol group met the criteria. CRP and TNF-α got significantly reduced (37.21 and 74.81% respectively) in the turmeric extract group. Adverse events reported were mild and comparatively less in the turmeric extract group (5.48%) than in the paracetamol group (12.68%). The results of the study suggest that bioavailable turmeric extract is as effective as paracetamol in reducing pain and other symptoms of knee osteoarthritis and found to be safe and more effective in reducing CRP and TNF-α. [Singhal S, Hasan N, Nirmal K, Chawla R, Chawla S, Kalra BS, Dhal A. Bioavailable turmeric extract for knee osteoarthritis: a randomized, non-inferiority trial versus paracetamol. Trials. 2021 Dec;22(1):1-1.]

74. **Verapamil/Curcumin treatment attenuates the behavioral alterations observed in Williams Syndrome mice by regulation of MAPK pathway and Microglia overexpression.** The study investigated the progression of behavioral deficits present in CD (complete deletion) mice, a rodent model of Williams-Beuren syndrome (WBS), a rare neurodevelopmental disorder without any effective treatments. The test compounds curcumin, verapamil and a combination of both were given as chronic treatments. These compounds have been proven to have beneficial effects over different cognitive aspects of various murine models and thus, may have neuroprotective effects in WBS. Treatment was administered orally dissolved in drinking water. A set of behavioral tests demonstrated the efficiency of combinatorial treatment. Some histological and molecular analyses were performed to analyze the effects of treatment and its underlying mechanism in CD mice. Behavioral improvement correlates with the molecular recovery of several affected pathways regarding MAPK signaling, in tight relation with the control of synaptic transmission. Moreover, CD mice showed an increased activated microglia density in different brain regions, which was prevented by treatment. Therefore, results show that treatment prevented behavioral deficits by recovering altered gene expression in cortex

of CD mice, reducing activated microglia and normalizing Bdnf expression levels. These findings unravel the mechanisms underlying the beneficial effects of this novel treatment on behavioral deficits observed in CD mice, and suggest that the combination of curcumin and verapamil could be a potential candidate to treat the cognitive impairments in WBS patients. [Paula Ortiz-Romero, Gustavo Egea1, Luis A Pérez-Jurado, Victoria Campuzano. Verapamil/Curcumin treatment attenuates the behavioral alterations observed in Williams Syndrome mice by regulation of MAPK pathway and Microglia over expression. doi: https://doi.org/10.1101/2021.02.01.429086]

75. **Anti-SASP and anti-inflammatory activity of resveratrol, curcumin and b-caryophyllene association on human endothelial and monocytic cells.** The study investigated both the anti senescence associated secretory phenotype (SASP) and anti-inflammatory activities of a nutritional supplement, namely FenoxidolTM, composed of turmeric extract bioCurcumin (bCUR), Polydatin (the natural glycosylated precursor of Resveratrol-RSV), and liposomal b-caryophyllene (BCP), in two human cellular models, such as the primary endothelial cell line, HUVECs and the monocytic cell line, THP-1. Replicative and Doxorubicin-induced senescent HUVECs, both chosen as cellular models of SASP, and lipopolysaccharides (LPS)-stimulated THP-1, selected as a model of the inflammatory response, were treated with the three single natural compounds or with a combination of them (MIX). In both senescent HUVEC models, MIX treatment significantly reduced IL-1b and IL-6 expression levels and p16ink4a protein, and also increased SIRT1 protein level, as well as downregulated miR-146a and miR-21 expression, two of the so-called inflamma-miRNAs, more effectively than the single compounds. In THP-1 cells stimulated with LPS, the MIX showed a significant effect in decreasing IL-1b, IL-6, TNF-a, and miR-146a expression levels and Caspase-1 activation, in association with an up-regulation of SIRT1 protein, compared to the single compounds. Overall, results suggest that the three analysed compounds can have a combined effect in restraining SASP in senescent HUVECs as well as the inflammatory response in LPS-stimulated THP-1 cells. [Giulia Matacchione, Felicia Gurau, Andrea Silvestrini, Mattia Tiboni, Luca Mancini, Debora Valli, Maria Rita Rippo, Rina Recchioni, Fiorella Marcheselli, Oliana Carnevali, Antonio Domenico Procopio, Luca Casettari, Fabiola Olivieri. Anti-SASP and anti-inflammatory activity of resveratrol, curcumin and b-caryophyllene association on human endothelial and monocytic cells. Biogerontology, https://doi.org/10.1007/s10522-021-09915-0.]

76. **Curcugreen Treatment Prevented Splenomegaly and Other Peripheral Organ Abnormalities in Mouse Models of Alzheimer's Disease.** Metabolic dysfunction and immune disorders are common in Alzheimer's disease (AD). The mechanistic details of these epiphenomena in AD are unclear. Here, we have investigated whether a highly bioavailable curcuminoid formulation, Curcugreen (CGR), can prevent abnormalities in peripheral organs of two mouse models of AD. Eighteen- and 24-month-old male and female 3xTg and 5xFAD mice were treated with CGR (100 mg/kg) for 2 months, orally. Cytoarchitectural changes of spleen, liver, kidney and lungs were studied by H&E stain. Apoptotic death was confirmed by TUNEL staining. Amyloid deposition, pTau levels, proinflammatory, anti inflammatory and cell death/survival markers were studied by Western blots. Curcugreen reduced the observed splenomegaly (3xTg) and degeneration of spleen, granulomatous inflammation in the kidney, hepatic sinusoidal disorganization, hepatocellular hypertrophy, inflammation of the central hepatic vein, infiltration and swelling of lung tissues, and apoptotic death in all these areas in both 3xTg and 5xFAD mice. Similarly, CGR decreased amyloid deposition, pTau, proinflammatory markers, cell loss and decrements in anti-inflammatory markers in both 3xTg and 5xFAD mice. Peripheral organ abnormalities and inflammatory responses in AD were ameliorated by curcuminoid treatment. [Manna, J.; Dunbar, G.L.; Maiti, P. Curcugreen Treatment Prevented Splenomegaly and Other Peripheral Organ Abnormalities in 3xTg and 5xFAD Mouse Models of Alzheimer's Disease. Antioxidants 2021, 10, 899.]

77. **The effect of curcumin and zinc co-supplementation on glycemic parameters in overweight or obese prediabetic subjects.** Management of prediabetes is a critical step to prevent type-2 diabetes. Curcumin and zinc have been studied as an antioxidant, anti-inflammatory, and antidiabetic agents. In this clinical trial, 84 subjects were randomized into curcumin (500 mg), zinc (30 mg), zinc and curcumin, and placebo groups for 90 days. At the baseline and the end of the study, the outcomes (fasting plasma glucose (FPG), 2-hour postprandial glucose (2hpp), HbA1C, insulin, insulin sensitivity (IS), insulin resistance (IR), β-cell function (BCF), weight, body mass index (BMI), dietary intake, and physical activity (PA)) were measured. A hypocaloric diet and PA were recommended for all subjects. In total, 82 subjects completed the study. After the intervention, dietary intake, PA, weight, and BCF% did not show a significant difference among the groups. However, subjects taking only zinc and zinc and curcumin groups experienced decreased BMI compared to the placebo ($p = .01$ and .007, respectively). The three treated groups had improved FPG ($p = .01$), 2hpp

(p = .003), HbA1C (p = .004), insulin (p = .001), IS% (p = .001), and IR (p < .001) compared to the placebo. Based on these results, zinc and curcumin supplementation exerted a beneficial effect on several key glycemic parameters. [Majid Karandish, Hassan Mozaffari-Khosravi , Seyed Mohammad Mohammadi , Bahman Cheraghian , Maryam Azhdari. The effect of curcumin and zinc co-supplementation on glycemic parameters in overweight or obese prediabetic subjects: A phase 2 randomized, placebo-controlled trial with a multi-arm, parallel-group design. Phytother Res. 2021 Apr 23. doi: 10.1002/ptr.7136.]

78. **A Randomized, Placebo-Controlled Study to Evaluate the Effect of Bio-Enhanced Turmeric Formulation on Radiation-Induced Oral Mucositis.** Oral mucositis is the most common toxicity of chemoradiotherapy treatment of head and neck cancers. The present study was performed to evaluate the effect of a researched turmeric formulation on oral mucositis in patients receiving chemoradiotherapy for oral cancer. This randomized double-blinded placebo-controlled trial included 60 patients with oral cancer who had undergone radical surgery. Patients were equally randomized into 3 arms. Bio-enhanced turmeric formulation (BTF) capsules (low dose [1 g/day] or high dose [1.5 g/day]) or placebo was administered daily for 6 weeks with concurrent chemoradiotherapy. Study endpoints included the impact of the treatment on chemoradiotherapy-induced oral mucositis along with dysphagia, oral pain, dermatitis, and weight loss. The incidence of grade 3 toxicity of oral mucositis, oral pain, dysphagia, and dermatitis was significantly lower in patients who received BTF than placebo. Twenty-five and 20% patients in BTF 1 g/day (p = 0.011) and 1.5 g/day (p = 0.004) arms, respectively, developed grade 3 oral mucositis compared to 65% patients in the placebo arm. Thirty-five and 30% patients in BTF 1 g/day (p = 0.027) and 1.5 g/day (p = 0.011) arms, respectively, developed grade 3 oral pain compared to 70% patients in the placebo arm. Twenty-five and 20% patients in BTF 1 g/day (p = 0.025) and 1.5 g/day (p = 0.010) arms, respectively, developed grade 3 dysphagia compared to 60% patients in the placebo arm. Ten and 5% patients in BTF 1 g/day (p = 0.114) and 1.5 g/day (p = 0.037) arms. respectively, developed grade 3 dermatitis compared to 30% patients in the placebo arm. Patients under BTF supplementation experienced significantly less weight loss and greater compliance with treatment than placebo. BTF (BCM-95®) can significantly reduce chemoradiotherapy-induced severe oral mucositis, dysphagia, oral pain, and dermatitis in oral cancer patients. [Tej Prakash Soni, Anil Kumar Gupta, Lalit Mohan Sharma, Harish Singhal, Shantanu Sharma, Ravindra Singh

Gothwal; A Randomized, Placebo-Controlled Study to Evaluate the Effect of Bio-Enhanced Turmeric Formulation on Radiation-Induced Oral Mucositis; PMID: 34161952; ORL J Otorhinolaryngol Relat Spec. 2021 Jun 23;1-11. doi: 10.1159/000516577]

79. **Curcuma longa and Boswellia Serrata for improving functional status in osteoarthritis patients: From bench to bedside evidences.** The management of osteoarthritis (OA) represents a real challenge. Curcumin is a highly pleiotropic molecule with an excellent safety profile. Some previous studies showed the extract of Curcuma longa and Boswellia Serrata(CB extract) is a promising potential as therapeutic interventions against OA. This study aimed to measure the effectiveness and safety of CB extract for improving functional status in patients with OA. A randomized controlled trial (RCT) in OA patients. The treatment used in this trial were CB extract (350 mg of Curcuma longa and 150 mg Boswellia Serrata) and NSAID (400 mg ibuprofen or 50 mg diclofenac sodium). Subjects were randomized to 3 different group (Group 1: CB extract and NSAID; group 2: CB extract; group 3: NSAID). Each subject would be followed up 3 times: baseline (visit I), 2 weeks after baseline (visit II), and 4 weeks after baseline (visit III). The measurement of functional status with WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index). There were 105 osteoarthritis patients. Seven subjects were lost to follow up and three subjects were excluded from the study due to medication side effect. Ninety-five subjects (group 1: 36; group 2: 29, group 3: 30) remained for complete analysis. Delta (Δ) WOMAC score defined as the result of subtraction between WOMAC score at visit I and WOMAC score at visit III. Group 1 showed the greatest reduction of WOMAC score after 4 weeks of treatment (ΔWOMAC = 12.08 ± 18.6). Group 3 has the least WOMAC score reduction (ΔWOMAC = 6.9 ± 16). There was no statistical difference of ΔWOMAC score between groups (p = 0.367). There were no statistical difference of the prevalence of AE between groups at the visit II (p: 0.119) and at the visit III (p: 0.767). CB extract is effective and safe for improving functional status in OA patients. [Rizaldy Taslim Pinzon, Vincent Ongko Wijaya; Curcuma longa and Boswellia Serrata for improving functional status in osteoarthritis patients: From bench to bedside evidences; Asian Journal of Medical Sciences, Sep-Oct 2019, Vol 10, Issue 5; DOI: 10.3126/ajms.v10i5.24918]

80. **Antidiabetic effect of bio-enhanced preparation of turmeric in streptozotocin-nicotinamide induced type 2 diabetic Wistar rats.** Poor oral bioavailability of curcumin, the active ingredient in turmeric, has limited its therapeutic use in

various diseases including diabetes mellitus (DM). The present study was aimed at evaluating and comparing the antidiabetic activity as well as pharmacokinetic profile of two turmeric extracts. Rats were divided into seven groups (n=6) including Normal control (NC), Diabetic control (DC), two standard control groups- Glibenclamide (GLIB) 5 mg/kg and Metformin (MET) 500 mg/kg, two bio-enhanced turmeric extract (BTE) treated groups (BTE-30 (30 mg/kg), BTE-60 (60 mg/ kg)) and one regular turmeric extract treated (RTE) group RTE-30 (30 mg/kg). Treatment was given orally for 30 days. Streptozotocin (60 mg/kg) and Nicotinamide (110 mg/kg) were administered intraperitoneally to induce diabetes. Fasting blood glucose (FBG), oral glucose tolerance test at 60 min and 120 min (OG1 and OG2) were analysed at baseline and at the end of study on Day 29. FBG, fasting serum insulin, and concentration of curcumin and its derivatives present in pancreas were analysed at the end of study on Day 30. Turmeric extract treated groups showed significant ($p < 0.05$) blood glucose lowering effect, when compared with DC group. FBG, OG1 and OG2 readings were found significantly ($p < 0.05$) higher in RTE-30 treated group when compared with BTE-30 treated groups. Turmeric extracts showed improved beta-cell function, insulin sensitivity and decreased insulin resistance. BTE-30 had more pancreatic bioavailability of curcumin than RTE-30. Turmeric extracts demonstrated an antidiabetic effect in streptozotocin-nicotinamide induced type 2 diabetic Wistar rats. BTE extract was found to be an effective agent as compared to RTE in controlling hyperglycemia. [Vinay Kumar Sayeli, Ashok K. Shenoy; Antidiabetic effect of bio-enhanced preparation of turmeric in streptozotocin-nicotinamide induced type 2 diabetic Wistar rats; Journal of Ayurveda and Integrative Medicine 12 (2021) 474-479; https://doi.org/10.1016/j.jaim.2021.04.010]

81. **Potential Therapeutic Effects of Curcuma longa extract in Patients with Osteoarthritis: A Randomized Controlled Trial.** Osteoarthritis (OA) is the most common degenerative joint disorder in the elderly and a major public health problem in worldwide. Non-steroidal anti-inflammatory drug (NSAID) is a common medication given in OA patients, but its use was limited due to many side effects. Previous studies showed that Curcuma Longa extracts may exhibit benefic effects in the treatment of OA. To determine the effective and safety of Curcuma Longa extracts for reducing pain in patients with osteoarthritis. A randomized controlled trial (RCT) in OA patients. Subjects were randomized to 3 different group. Group I: CB extract (350 mg of Curcuma longa and 150 mg Boswellia serrata) and NSAID (400 mg ibuprofen or 50 mg diclofenac sodium), group II: CB extract, group III: NSAID. Each subject would

be followed up 3 times: baseline, second weeks, fourth weeks after baseline. The pain severity was measured using visual analogue scale (VAS). The analysis is intention to treat based. There were 105 subjects enrolled at the study. Subjects were dominated by female (80%) with mean aged 63 years. Ninety-five subjects (group I: 36; group II: 29, group III: 30) remained for complete analysis. Group I showed the greatest reduction of VAS score after the second and fourth weeks of treatment (more than 50%). Group III has the least VAS score reduction after fourth weeks from baseline. There was statistically different of VAS score reduction between groups ($P<0.001$). The most frequent AE were reported from subjects in group III. CB extract is effective and safe for reducing pain in OA patients. [Rizaldy Taslim Pinzon, Fransiscus Buwana; Potential Therapeutic Effects of Curcuma longa extract in Patients with Osteoarthritis: A Randomized Controlled Trial; J. Pharm. Sci. & Res. Vol. 11(11), 2019, 3628-3633]

82. **A Randomized Controlled Trial of Curcuma Longa and Boswellia Serrata Extract in Osteoarthritis.** Chronic pain is the major complaint in subjects with osteoarthritis (OA). Non- steroid anti inflammatory drug (NSAID) is still the drug of choice in Indonesia to treat OA patients. The prolonged consumption of NSAID may lead to many adverse events (AE). Some previous studies showed the extract of Curcuma longa and Boswellia serrata is a promising potential as therapeutic interventions against OA. This study aimed to evaluate the effectiveness and safety of CB extract to relieve symptoms in patients with OA. This was a randomized controlled trial (RCT) in OA patients. The treatment used in this trial were CB extract (350 mg of Curcuma longa and 150 mg Boswellia serrata) and NSAID (400 mg ibuprofen or 50 mg diclofenac sodium). Subjects were randomized to 3 different groups (Group 1: CB extract and NSAID; group 2: CB extract; group 3: NSAID). Each medication was taken two times per day for four weeks. Paracetamol tablet 500 mg gave to each subject as a rescue medication. Each subject would be followed up three times: baseline (visit I), two weeks after baseline (visit II), and four weeks after baseline (visit III). The measurement was using WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index). There were 105 subjects at the beginning of the study dominated by a female with mean aged 63 years and have osteoarthritis with KL grade II. Seven subjects were lost to follow up, and three subjects excluded from the study due to adverse event. Ninety-five subjects (group 1: 36; group 2: 29, group 3: 30) remained for complete analysis. Delta (Δ) WOMAC score defined as the result of subtraction between WOMAC score at a visit I and WOMAC score at visit III. The highest mean of

the WOMAC score was in group 1. However, group 1 showed the greatest reduction of WOMAC score after four weeks of treatment (ΔWOMAC = 12.08 ± 18.6). Group 3 has the least WOMAC score reduction (ΔWOMAC = 6.9 ± 16). There was no statistically different ΔWOMAC score between groups (p = 0.367). The highest consumption of rescue medication was in group 3, whereas the least consumption was in group 2. There was no statistical different of rescue medication consumption between groups (p: 0.346). Group 3 was the most frequently group with reported AE, whereas group 2 has the least reported AE. There were no statistically difference from the prevalence of AE between groups at the visit II (p: 0.119) and the visit III (p: 0.767). CB extract is effective for OA treatment and also has a better safety profile compared to NSAID. [Rizaldy Taslim Pinzon, Rosa De Lima Renita Sanyasi, Esdras Ardi Pramudita & Septian Dewi Periska; A Randomized Controlled Trial of Curcuma Longa and Boswellia Serrata Extract in Osteoarthritis; Global Journal of Medical Research (H) Volume XIX, Issue III, Version I , Year 2019]

83. **The benefit of Curcuma longa and Boswellia serrata to improve quality of life in osteoarthritis patients: a randomized controlled trial.** Quality of life (QoL) can be affected by chronic pain in osteoarthritis (OA). Previous studies showed that combination of Curcuma longa (CL) and Boswellia serrata (BS) extract (CB extract) are promising for alternative treatment for pain in OA. This study aimed to measure the benefit of CB extract to improve QoL in patients with OA. This was a randomized controlled trial (RCT) in OA patients. Subjects were randomized to 3 different group (Group 1: CB extract (350 mg of CL and 150 mg BS) and NSAID (400 mg ibuprofen or 50 mg diclofenac sodium); group 2: CB extract; group 3: NSAID). Each medication was taken two times per day for 4 weeks. QoL measured using 5Q-5D-5L that include five dimensions in 5Q-5D: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, with 5 levels of severity. There were 105 subjects at baseline. After 4 weeks of study, remained 95 subjects. The most common problem in group 1, 2, and 3 was pain (n=23, n=8, n=15 respectively). The improvement of level of severity in group 1 after 4 weeks of treatment was significant in mobility problems (p=0.002), pain/discomfort (p<0.001), and anxiety/depression (p=0.008). A significant improvement was only seen in usual activity problems (p=0.013) in group 2. The decrease of level of severity in usual activity problems (p=0.034), pain/discomfort (p=0.005), and anxiety/depression (p=0.018) in group 3 were also statistically significant. CB extract was beneficial to improve QoL in OA patients with a less side effect compared to NSAID. [Rizaldy Taslim Pinzon, Rosa De Lima Renita Sanyasi,

Esdras Ardi Pramudita, Septian Dewi Periska; The benefit of Curcuma longa and Boswellia serrata to improve quality of life in osteoarthritis patients: a randomized controlled trial; International Journal of Research in Orthopaedics; 2019 Nov;5(6):1005-1014; DOI: http://dx.doi.org/10.18203/issn.2455-4510. IntJResOrthop20194807]