

Efficacy and Safety of Meriva[®], a Curcumin-phosphatidylcholine Complex, during Extended Administration in Osteoarthritis Patients

Gianni Belcaro; Maria Rosaria Cesarone; Mark Dugall; Luciano Pellegrini; Andrea Ledda; Maria Giovanna Grossi; Stefano Togni; Giovanni Appendino

Giovanni Appendino – Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università del Piemonte Orientale, Novara, Italy.
Correspondence address: Università del Piemonte Orientale, Dipartimento di Scienze Chimiche Alimentari, Farmaceutiche e Farmacologiche, Via Bovio, 6 - 28100 Novara, Italy
Email: appendino@pharm.unipmn.it

Gianni Belcaro – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

Maria Rosaria Cesarone – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

Mark Dugall – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

Luciano Pellegrini – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

Andrea Ledda – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

Maria Giovanna Grossi – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

Stefano Togni – Indena S.p.A., Viale Ortles 12, Milano, Italy

Abstract

In a previous three-month study of Meriva[®], a proprietary curcumin-phosphatidylcholine phytosome complex, decreased joint pain and improvement in joint function were observed in 50 osteoarthritis (OA) patients. Since OA is a chronic condition requiring prolonged treatment, the long-term efficacy and safety of Meriva were investigated in a longer (eight months) study involving 100 OA patients. The clinical end points (Western Ontario and McMaster Universities [WOMAC] score, Karnofsky Performance Scale Index, and treadmill walking performance) were complemented by the evaluation of a series of inflammatory markers (interleukin [IL]-1 β , IL-6, soluble CD40 ligand [sCD40L], soluble vascular cell adhesion molecule (sVCAM)-1, and erythrocyte sedimentation rate [ESR]). This represents the most ambitious attempt, to date, to evaluate the clinical efficacy and safety of curcumin as an anti-inflammatory agent. Significant improvements of both the clinical and biochemical end points were observed for Meriva compared to the control group. This, coupled with an excellent tolerability, suggests that Meriva is worth considering for the long-term complementary management of osteoarthritis. (*Altern Med Rev* 2010;15(4):337-344)

Introduction

Curcumin is the yellow pigment of turmeric (*Curcuma longa* L.), the most popular spice in Indian cuisine and a major ingredient of curry powders.¹ Turmeric has a long history of medicinal use, especially to treat inflammation,² and many of its traditional uses have been mechanistically validated in cellular systems as well as in animal models of disease. Indeed, with almost 3,000 preclinical investigations, curcumin is one of the best investigated botanical constituents in the biomedical literature.² These studies have

demonstrated that curcumin acts as a master switch of inflammation by acting at the level of pro-inflammatory enzymes (cyclooxygenases [COX] and lipoxygenases) and inflammatory transcription factors (nuclear factor-kappaB [NF- κ B] and signal transducer and activator of transcription 3 [STAT3]) and their genomic expression.³ Most of the beneficial effects of curcumin are suggested by epidemiological studies, supported by studies in animal models, and extrapolated from *in vitro* studies, but not validated clinically.² This paradoxical situation is due to the poor stability of curcumin, which is highly unstable at intestinal pH (half-life at pH 7 <10 min),⁴ and low oral absorption. Plasma concentrations barely reach 50 ng/mL of phase II metabolites (glucuronides and sulfates) after oral administration of dosages as high as 12 g/day.⁴ Once in the plasma, however, curcumin enjoys a surprising stability and even permeability to tissues hard to reach like the brain.⁴

Similar to most dietary phenolics, curcumin is sparingly water and lipid soluble. It has polar groups (two phenolic hydroxyls and one enolic hydroxyl) that can interact via hydrogen bonds and polar interactions with a complementary group, like the polar heads of phospholipids.^{5,6} Phenolics show a high affinity for biological membranes and, once complexed with phospholipids, are embedded into a lipid matrix that, while shielding them from hydrolytic degradation, can lead to an increased cellular uptake by capitalizing on the rapid exchange of phospholipids between biological membranes and the extracellular fluids. These principles are the basic tenets of the phytosome strategy to improve the bioavailability of phenolics and have now been successfully

applied to curcumin,^{5,6} a patented complex with phosphatidylcholine (Meriva®). Capitalizing on very promising results in terms of improved hydrolytical stability (unpublished), human pharmacokinetics,^{5,7} and a previous OA clinical study,⁸ this study investigated the long-term efficacy and safety of this curcumin phytosome in the management of osteoarthritis, a condition in need of novel therapeutic options.⁹

Osteoarthritis is the leading cause of physical disability and impairment in life quality for millions of elderly people, both in industrialized and in developing countries, and its dramatic influence on healthcare costs is likely worsened because of the aging population and current epidemic of obesity.¹⁰ An effective cure for osteoarthritis remains elusive. Typically, osteoarthritis is managed with palliative measures that focus on symptom reduction – lifestyle modification (weight loss and exercise) and analgesics providing the primary treatments.^{11,12} Despite the serious adverse effects associated with long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), these compounds remain the most widely used treatment option for OA. Given this scenario, it is not surprising that OA is the leading medical condition for which people use alternative therapies.¹³

A recent three-month registry study (n=50) demonstrated Meriva improved symptoms and joint function in OA patients, as assessed by the Western Ontario and McMaster Universities (WOMAC) score and the treadmill walking performance, respectively.⁸ The current study was performed to evaluate the long-term efficacy and safety of Meriva in OA. This larger (n=100), eight-month study extended the end points of the previous study to include a series of biochemical markers of inflammation (interleukin [IL]-1β, IL-6, soluble CD40 ligand [sCD40L], soluble vascular cell adhesion molecule [sVCAM]-1, erythrocyte sedimentation rate [ESR]) of general relevance for inflammatory conditions.^{14,15} This study is the most extensive, to date, to evaluate the clinical efficacy of curcumin as an anti-inflammatory agent.³

Material and Methods

Subjects

The study enrolled 100 patients with osteoarthritis, confirmed by x-ray analysis. Patients were recruited using the database of the San Valentino vascular screening project,

an epidemiological study mainly following the evolution of asymptomatic cardiovascular atherosclerosis. Subjects were considered eligible for the study when they fulfilled the criteria for primary knee osteoarthritis (grade 1 or 2) according to the American Rheumatism Association. These patients participated in an open, product evaluation registry for the complementary management of osteoarthritis. Patients were informed about the aim of the study and treatment procedure according to the Declaration of Helsinki and provided informed consent. Patients were informed that they could leave the study at any time and were allowed to medicate with NSAIDs during the eight-month trial. Two groups of subjects with symptomatic osteoarthritis were defined: Group A was managed using the “best available treatment”

Key words: curcumin, osteoarthritis, Meriva, arthritis, inflammation, joint, phytosome, turmeric, NSAIDs, anti-inflammatory, curcuma

Table 1. Karnofsky Performance Scale Index

Able to carry on normal activity and to work; no special care needed	100	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or do active work
	60	Requires occasional assistance, but is able to care for most personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Deceased

as defined by the patient's general practitioner and specialists; and Group B used best available treatment plus Meriva. For clinical homogeneity, the primary location of osteoarthritis was one or both knees.

Inclusion Criteria

Primary osteoarthritis in one or both knees was diagnosed by x-ray investigation. Subjects had mild-to-moderate pain not adequately or completely controlled with anti-inflammatory drugs. They were required to perform the treadmill walking test and to understand all questions from the WOMAC questionnaire.¹⁶

Exclusion Criteria

Exclusion criteria were cardiovascular disease requiring drug treatment, diabetes, body mass index >25, severe metabolic disorders, surgery or arthroscopy within three months prior to inclusion, any oncological condition, or severe bone or joint deformation or condition making the patient unable to walk. Pregnancy, breast feeding, and planned conception were also exclusion criteria.

Measurements

Evaluation of Functional Impairment

The Karnofsky Performance Scale Index was used to classify patients as to their functional impairment. The Karnofsky Performance Scale Index can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the functional impairment (Table 1).¹⁷

Evaluation of Signs/Symptoms of Osteoarthritis

The WOMAC questionnaire was applied to describe and rate the symptoms of OA.¹⁶ The status of OA signs/symptoms was evaluated by the investigator together with the patient at inclusion and after eight months of treatment.

Evaluation of Physical Performance

Patients were trained to perform the treadmill test in two tutorials. Performance was evaluated by the treadmill test at a speed of 3 km/hour and an inclination of 10 percent. The total distance that could be covered without pain was noted at the beginning and end of the trial.

Evaluation of Associated Treatments Needed to Manage Osteoarthritis

A diary was kept to record the use of any drug prescribed by the patient's physician, the use of

which was free (with only a warning not to use an excess of treatment).

Evaluation of Costs and Side Effects

The treatment and other costs (including work disruption and hospital admission) occurring during the trial period were recorded in a specific file.

Laboratory Testing

At baseline, a heparinized venous blood specimen was collected and deep frozen; after completion of the eight-month investigation, blood was drawn again. The oxidative stress status of patients was investigated by quantifying direct reactive oxygen metabolites (D-ROM) using the Free Radical Analytical System (FRAS; Diacron, Grosseto, Italy). In brief, the assay estimates hydroperoxides in a small blood sample (20 µL) after incubation in buffer solution together with a chromogenic agent. Photometric analysis provides oxidative stress status in Carr units, with 1 Carr unit corresponding to 80 µg H₂O₂/dL. Values above 300 Carr units suggest oxidative stress. IL-1β, IL-6, sCD40L, and sVCAM-1 (inflammatory markers) were determined by enzyme-linked immunosorbent assay (Millipore; Billerica, MA).

Materials

Meriva (developed by Indena, S.p.A.) tablets were prepared by Sigmar Italia S.p.A. (Almè, Italy). The treatment consisted of two 500-mg tablets daily, one after breakfast and one after dinner (1,000 mg/day, corresponding to 200 mg curcumin/day). The composition of the test material was a natural curcuminoid mixture (20%), phosphatidylcholine (40%), and microcrystalline cellulose (40%). The composition of the curcuminoid mixture was 75-percent curcumin, 15-percent demethoxycurcumin, and 10-percent bisdemethoxycurcumin.

Statistical Analysis

The variations of results (i.e., walking distance) were considered parametric. Non-parametric observations (e.g., WOMAC score) were evaluated using the analysis of variance (ANOVA with the Bonferroni correction). Considering possible intra-individual and inter-individual data variations, completion of the entire follow-up period by at least 40 subjects in each group was required. This number was defined – on the basis of our previous study – in order to overcome spontaneous variability and temporal variations. OA and its related signs/symptoms, even in conditions of

relative stability, may have a spontaneous degree of variability associated with periods of improvement. Clinical variations in signs/symptoms, walking distance, and the Karnofsky scale may be due to different clinical and non-clinical (e.g., environmental or climatic) factors, including individual, psychological, and drug-related elements.

Results

In a previous three-month pilot study, 50 patients suffering from mild-to-moderate knee osteoarthritis received either the “best available treatment” or the “best available treatment and Meriva.” Pain sensation, joint stiffness, and physical function improved significantly with Meriva, as judged by WOMAC scores. Furthermore, a significant improvement of mobility, measured under controlled conditions on a treadmill, was also observed.⁸ Blood samples at baseline and after completion of the three-month trial demonstrated a statistically significant reduction of C-reactive protein (CRP) levels in the subgroup with elevated CRP treated with Meriva.^{8,14}

In the current study, the treatment group (n=50) and the control group (n=50) did not differ in respect to Karnofsky Performance Scale Index (Table 2),¹⁷ age, male-to-female ratio, overall WOMAC score, or performance on the treadmill test (Table 3). Five patients in the treatment group and six patients in the control group left the study for non-medical reasons, including moving or work problems. The results of the Karnofsky Performance Scale Index are presented in Table 2. Meriva significantly improved the Karnofsky Scale (from 73.3 at inclusion to 92.2 at the completion of the study), with no significant improvements in the control group.

WOMAC scores are presented in Table 4. Scores for pain dropped significantly (p<0.05) following Meriva administration from 16.6 to 7.3, with no significant effects in the control group. The scores for stiffness in the treatment group were reduced significantly from 7.4 to 3.2 (p<0.05), while scores for the control group remained substantially unchanged after eight months. The scores for physical function in the Meriva group were significantly

Table 2. Variations of Karnofsky Performance Scale Index (median and range)

	Inclusion	After 8 months
Treatment	73.3 (57-79.4)	92.2 (88-100)*
Control	74.2 (58-83)	81 (71-86.3)

*p<0.05

Table 3. Patient Characteristics at Inclusion

Patient Data	Treatment Group	Control Group
Age (years)	43.6 SD 5.5	44.2 SD 6
Male/female ratio	23/27	28/22
Mean global WOMAC score	81.2	79.6
Treadmill test mean distance achieved*	77.3 meters (15-188)	82.3 meters (19-210)

*8 km/h with an inclination of 10%

Table 4. Change of Mean WOMAC Scores after Eight Months of Treatment

WOMAC items	Treatment Group		Control Group	
	Enrollment	8 months	Enrollment	8 months
Pain	16.6	7.3	16	15.2
Stiffness	7.4	3.2	6.6	6.7
Physical functions	56.6	22.8	55.2	46.9
Total	80.6	33.3	77.8	68.8

Table 5. Alterations in WOMAC Social and Emotional Function

WOMAC items	Treatment Group		Control Group	
	Enrollment	8 months	Enrollment	8 months
Social functions	24.4	10.3	23.8	21.9
Emotional functions	33.9	10.2	33.1	33.9

Table 6. Results of Treadmill Test (median and range)

	Treatment Group		Control Group	
	Enrollment	8 months	Enrollment	8 months
Distance	77.3 meters (15-188)	344.4 meters (113-478)*	82.3 meters (19-210)	156 meters (46-383)*

The treadmill test was performed with the treadmill at the speed of 3 km/hour, with an inclination of 10%.

*p<0.05

Table 7. Changes in Inflammatory Markers

	Treatment Group		Control Group	
	Enrollment	8 months	Enrollment	8 months
sCD40L (ng/mL)	2.47	1.39*	2.34	2.46
IL-1 β (pg/mL)	0.88	0.31*	0.92	0.89
IL-6 (pg/mL)	1.38	1.01*	1.36	1.39
sVCAM-1 (ng/mL)	644	456*	652	641
ESR (mm/hr)	35.23	26.3*	37.59	36.63

*p<0.05 versus values at enrollment

reduced, from 56.6 to 22.8 during the course of the study ($p<0.05$), while the improvement in the control group was not significant. The global WOMAC score decreased significantly following Meriva treatment, from 80.6 to 33.3; while in the control group the decrease from 77.8 to 68.8 was statistically insignificant. Negative effects on social function caused by osteoarthritis decreased significantly in the treatment group ($p<0.05$), but not in the control group (Table 5). The well-being of patients was significantly enhanced ($p<0.05$) in the treatment group, as reflected in scores for emotional function (Table 5), while in the control group there was only a marginal improvement. In conclusion, all WOMAC scores improved significantly ($p<0.05$) after eight months treatment, compared to baseline as well as to the control group.

Table 6 illustrates the results of the exercise (treadmill) tests (median and range). The treadmill (at a speed of 3 km/hour, with a 10% inclination) indicates an improvement of 345 percent from the baseline initial distance ($p<0.05$) after eight months, compared to an 89-percent increase in the controls. This represents a statistically significant difference between the improvement in the treatment group compared to the control group ($p<0.05$). In other words, Meriva treatment produced a 3.87-times greater improvement in physical performance than the control group (best treatment available).

Table 7 illustrates the results of sCD40L, IL-1 β , IL-6, sVCAM-1, and ESR. Following treatment for eight months, Meriva induced a statistically significant reduction of all markers of inflammation. Conversely, the control group had only marginal and nonsignificant effects on all parameters. There were no other hematological changes noted.

Table 8 illustrates other observations noted in the study. Most relevant is the decreased (63%) use of NSAIDs and other painkillers (acetaminophen 2 g/day or celecoxib 200 mg/day as needed by the patients in either group and according to physicians' recommendations) in the treatment group compared to 12 percent

Table 8. Other Observations (median decrease after eight months)

	Treatment Group	Control Group
Decrease in use of NSAIDs/painkillers	63.4%	8%
Decrease in gastrointestinal complications	66.7%	12.4%
Decrease in use of other drugs/treatments	42.4%	7.4%
Decrease in management costs	63.5%	3.7%
Decrease in distal edema	69%	1.7%
Decrease in hospital admissions, consultation, and tests	44.6%	2.6%
Specific decrease in non-drug treatment (e.g., physiotherapy), costs due to other complications, new consultations, tests, etc.	46.6%	5.5%

*p<0.05 versus values at enrollment

in controls ($p<0.05$). This was accompanied by a decrease in gastrointestinal complaints by 38 percent in Meriva patients compared to 15 percent in controls ($p<0.05$) (presumably, due to decreased use of NSAIDs and the reported GI-protective effect of curcumin). The decrease in use of other medications or treatments was 38 percent in treatment subjects versus 11 percent in controls ($p<0.05$). The global decrease in management costs was 49 percent in Meriva patients compared to three percent (not significant) in controls (difference between groups: $p<0.05$).

The median decrease in distal edema was 65 percent versus five percent in controls ($p<0.05$). The presence of edema in these patients is mainly associated with a combination of inflammation, forced reduced activity (caused by pain on motion), and relative impaired limb mobility altering the venous pump function and venous return, particularly of the lower limbs. Hospital admissions, consultation, imaging, and instrumental tests decreased (median) 38 percent ($p<0.05$) in the treatment group compared with a six percent (not significant) decrease in controls (difference between groups: $p<0.05$). The specific decrease in

non-drug treatment (i.e., physiotherapy) costs due to different types of complications, new consultations, or blood tests was 44 percent ($p<0.025$) in Meriva patients compared with eight percent (not significant) in controls (the difference between the two groups was significant: $p<0.05$).

Discussion

Curcumin is one of the most extensively investigated natural products,¹⁻³ and its broad spectrum of preclinical activity and low oral toxicity suggest benefit for the treatment of a host of inflammatory conditions. However, few successful clinical studies of curcumin have been reported³ because of its poor oral bioavailability. Unrealistically high dosages (>10 g/day) are often required to achieve plasma concentrations corresponding to those suggested by the preclinical studies.⁴ To overcome these issues, a phytosome was developed, complexing curcumin with phosphatidylcholine.¹⁸ In the wake of studies showing promising data for hydrolytic stabilization at physiological pH (unpublished), approximately 20-fold improvement of oral absorption compared to non-complexed curcumin in animal¹⁹ and human⁷ pharmacokinetic

studies, and nutrigenomic veterinarian evidence of anti-inflammatory activity,²⁰ clinical studies on Meriva were commenced,⁸ focusing on OA because of the strong rationale for the use of curcumin in this condition.²¹

The hallmark of OA is an imbalance between inflammatory and anti-inflammatory signaling in chondrocytes and synovial cells, with an abnormal activation of cytokine cascades and an overproduction of inflammatory mediators.^{11,12,21} The up-regulation of inflammatory cytokines like IL-1 β and tumor necrosis factor-alpha leads to a decrease in collagen synthesis and, by activation of matrix metalloproteinases (MMPs), to a corresponding increase in collagen degradation, with further up-regulation of mediators and effectors like IL-8, IL-6, prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS).^{11,12,21} Remarkably, curcumin can regulate in a beneficial fashion the activity of all the major inflammatory players involved in OA.²¹

OA, as a chronic disease, requires continuous treatment. However, while there is no shortage of effective pharmacological treatments for OA, they cannot be used continuously because of severe side effects (e.g., gastrointestinal problems with NSAIDs and hypercorticosteroidism with corticosteroids).^{11,12} It was therefore critical to evaluate the efficacy and safety profile of Meriva over a longer treatment time than the initial three-month evaluation;⁸ this was the rationale for the present study. No attempt to evaluate the clinical efficacy of curcumin as an anti-inflammatory agent in studies of this duration, enrollment, and diversity of end-points has previously been reported.³ Also, the low dosage employed (1 g Meriva, corresponding to 200 mg/day curcumin) has few clinical precedents,¹⁻³ but was validated in a previous study⁸ and supported by a human pharmacokinetic study that confirmed the >20-fold increase of bioavailability for Meriva compared to uncomplexed curcumin observed in a previous animal study.⁷

In this trial, positive results were obtained for all end-points evaluated. Thus, after eight months of continuous use of 1 g/day Meriva, the WOMAC score for OA symptoms decreased by more than 50 percent, while the treadmill test showed an overall three-fold increase in walking distance compared to the control group. The objective and subjective clinical outcomes were substantiated by interesting findings in the biochemical evaluation of inflammatory status and oxidative stress in patients in the treatment group. The significant decrease of all

inflammatory markers measured suggests that the clinical improvements observed have a clear mechanistic basis that validates previous *in vitro* observations of curcumin on joint cells.

The improvement of physical function and quality of life evidenced in the WOMAC questionnaires deserve comment. Patients were able to engage more in social activities, reportedly feeling markedly “in a better mood.” Pain and osteoarthritis symptoms are known to limit social interactions, and any improvement in these conditions is likely to have a socio-emotional effect. It is, however, interesting to note that preclinical investigations have also suggested a direct antidepressive effect of curcumin.²²

A somewhat related observation could be made in regard to the marked reduction of NSAID-associated gastrointestinal problems in the treatment group. This might be related to a reduced use of these drugs, to the known gastrointestinal protective effects of curcumin,¹ or to a combination of both. Finally, the cost effectiveness associated with the use of Meriva is also worth noting.

Conclusions

Meriva is an effective and safe agent for the complementary management of osteoarthritis, leading to better disease control, a decreased use of NSAIDs, and an overall improvement in quality of life. Although no direct comparison study of Meriva versus NSAIDs has been conducted,^{1,23-26} the decreased use of these drugs observed in the treatment group provides a rationale for evaluating whether the biochemical improvement in the inflammatory status associated with Meriva could eventually translate to a phase out of NSAID use, at least for mild-to-moderate OA. Studies with an even larger population and longer treatment period are needed to confirm these findings and evaluate the efficacy and safety of Meriva in a head-to-head comparison with NSAIDs. Nevertheless, our study exemplifies the potential of combining traditional knowledge and modern science to provide dietary ingredients that can stand the litmus test of modern medical evaluation in terms of safety and efficacy.

Acknowledgement

We are grateful to Sigmar Italia S.p.A. (Almè, Italy) for providing the Meriva tablets used in this investigation.

Conflict of Interest

S. Togni is a manager and G. Appendino is a consultant at Indena S.p.A., the company producing Meriva.

References

- Goel A, Kunnumakkara AJ, Aggarwal BB. Curcumin as “curcumin”: from kitchen to clinic. *Biochem Pharmacol* 2008;75:787-809.
- Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol Sci* 2009;30:85-94.
- Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: a review of preclinical and clinical research. *Altern Med Rev* 2009;14:141-153.
- Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm* 2007;4:807-818.
- Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenolics: the silymarin, curcumin, green tea, and grape seed extracts. *Altern Med Rev* 2009;14:226-246.
- Semalty A, Semalty M, Rawat MS, Franceschi F. Supramolecular phospholipids-polyphenolics interactions: the PHYTOSOME® strategy to improve the bioavailability of phytochemicals. *Fitoterapia* 2010;81:306-314.
- Cuomo J, Dixon ES, Dern A, et al. Comparative bioavailability of unformulated curcumin and a curcumin-phosphatidylcholine complex. Manuscript submitted for publication to *J Nat Prod*.
- Belcaro G, Cesarone MR, Dugall M, et al. Product evaluation registry of Meriva®, a curcumin-phosphatidylcholine complex, for the complementary management of osteoarthritis. *Panminerva Med* 2010;52:55-62.
- Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137-162.
- Felson DT, Zhang Y, Anthony JM. Weight loss reduces the risk of symptomatic knee osteoarthritis in women. The Framingham Study. *Ann Intern Med* 1992;116:535-539.
- Goldring MB, Goldring SR. Osteoarthritis. *J Cell Physiol* 2007;213:626-634.
- Krasnokutsky S, Samuels J, Abramson SB. Osteoarthritis in 2007. *Bull NYU Hosp Joint Dis* 2007;65:222-228.
- Resch KL, Hill S, Ernst E. Use of complimentary therapies by individuals with ‘arthritis’. *Clin Rheumatol* 1997;16:391-395.
- Sharif M, Shepstone L, Elson CJ, et al. Increased serum C reactive protein may reflect events that precede radiographic progression in osteoarthritis of the knee. *Ann Rheum Dis* 2000;59:71-74.
- Pearle AD, Scanzello CR, George S, et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. *Osteoarthritis Cartilage* 2007;15:516-523.
- Baron G, Tubach F, Ravaud P, et al. Validation of a short form of the Western Ontario and McMaster Universities Osteoarthritic Index function subscale in hip and knee osteoarthritis. *Arthritis Rheum* 2007;57:633-638.
- Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncology* 1984;2:187-193.
- Giori A, Franceschi F. European Patent Application EP1837030
- Marczylo TH, Vershoyle RD, Cooke DN, et al. Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine. *Cancer Chemother Pharmacol* 2007;60:171-177.
- Farinacci M, Gasparido B, Colitti M, Stefanon B. Dietary administration of curcumin modifies transcriptional profile of genes involved in inflammatory cascade in horse leukocytes. *Ital J Anim Sci* 2009;8:84-86.
- Henrotin Y, Clutterbuck AL, Allaway D, et al. Biological actions of curcumin on articular chondrocytes. *Osteoarthritis Cartilage* 2010;18:141-149.
- Kulkarni S, Dhir A, Akula KK. Potentials of curcumin as an antidepressant. *ScientificWorldJournal* 2009;9:1233-1241.
- Deodhar SD, Sethi R, Srimal RC. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). *Indian J Med Res* 1980;71:632-634.
- Satoskar RR, Shah SJ, Shenoy SG. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. *Int J Clin Pharmacol Ther Toxicol* 1986;24:651-654.
- Kuptniratsaikul Thanakhumtorn S, Chinswangwatanakul P, Wattanamongkonsil L, Thamlikitkul V. Efficacy and safety of *Curcuma domestica* extracts in patients with knee osteoarthritis. *J Alt Compl Med* 2009;15:891-897.
- Badria FA, El-Farahaty Shabana AA, Hawas SA, El-Batoty F. Boswellia-curcumin preparation for treating knee osteoarthritis. *Alt Compl Ther* 2002;341-348.