


MERIVA®
BIOAVAILABLE CURCUMIN

Proprietary delivery form
of curcumin

.....
Clinically supported in
terms of efficacy and
safety

.....
Validated for improved
oral absorption by a
human PK study


Meriva®

Curcuma longa L.

■ Curcumin is the yellow pigment of turmeric (*Curcuma longa L.*), the most popular spice of the Indian cuisine and a major ingredient of curry powders. The dietary intake of curcumin in asian countries can reach much as 200 mg/die.^[1]

In the UK population the mean and maximum reported use levels of curcumin have been estimated, combining the use of curcumin from naturally occurring curcumin in foods (turmeric as spice and in curry powder) and from its use as a food colour, of over 50 mg/die and 210 mg/die respectively in the adult population.^[2]

Turmeric has a long history of medicinal use in India, and the large conditions it can address make it a veritable panacea.^[3] Modern cellular studies on curcumin have validated most of its indications in traditional medicine, even expanding the potential of curcumin to genetic diseases typical of Caucasian.^[3]

Indeed, with almost 4000 pre-clinical investigations, curcumin is one of the best studied products of the whole biomedical literature. As a result, curcumin has emerged as a master switch of inflammation, with both a direct and a genomic activity on pro-inflammatory enzymes, inflammatory transcription factors and inflammatory cytokines.^[4]

Despite these promising findings, little clinical evidence of efficacy has so far been reported for curcumin, and most of its beneficial effects are suggested by epidemiological studies, supported by studies in animal models, extrapolated from studies *in vitro*, but not yet validated clinically.^[4]

Meriva® - bioavailable curcumin

Meriva® is a patented delivery form of curcumin.^[5] Curcumin and soy lecithin are formulated in a 1:2 weight ratio, and two parts of microcrystalline cellulose are then added to improve flowability, with an overall content of curcumin of in the final product of around 20%.

Meriva® is based on Indena's Phytosome® strategy to improve the bioavailability of compounds like polyphenolics and triterpenoid acids, that are normally characterized by poor solubility both in water and in organic solvents.^[6,7]

Curcumin, just like most dietary phenolics, is sparingly soluble both in water and in oily solvents, but shows polar groups (two phenolic hydroxyl and one enolic hydroxyl) that can interact via hydrogen bondings and polar interactions with complementary groups, like the polar heads of phospholipids. Thus, soy lecithin has a highly polarized head, with the negative charge of a phosphate group and the positive charge of the choline ammonium group, and can complex a variety of poorly soluble phenolics, including curcumin.^[6,7]

Phenolics as curcumin, show a high affinity for biological membranes, and, once complexed with phospholipids, are embedded into a lipidic matrix that, while shielding them from hydrolytic degradation, can capitalize on the rapid exchange of phospholipids between biological membranes and the extracellular fluids, shuttling it into biological membranes and increasing its cellular captation.^[6,7]

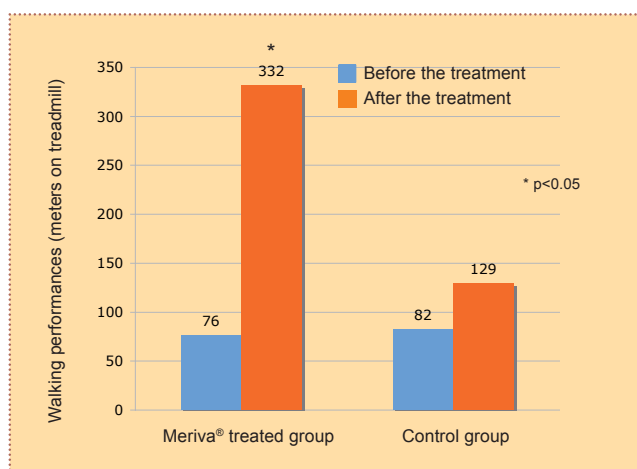
Clinical studies on Meriva® as anti-inflammatory

According to the Framingham Cohort (USA), 25% of people in their 60s and 50% in their 80s show radiographic osteoarthritic changes,^[9] and age, female sex, obesity, occupational knee-bending, physical labour, and joint trauma have all been identified as risk factors. The use of Meriva® for osteoarthritis is based on the capacity of this compound to interrupt pro-inflammatory signaling and increase anti-oxidant levels. Preclinical and clinical evidence suggests that chronic degenerative conditions are better addressed by a multi-targeted, rather than by a mono-targeted, therapy, and agents that modulate multiple cellular targets, like curcumin, have a great potential for the management of these pathologies.

Meriva® and the complementary management of osteoarthritis (OA): walking performances and WOMAC score

Meriva® was evaluated for its efficacy in 50 patients affected by osteoarthritis (X-ray OA diagnosis confirmation).^[9]

The disease symptoms were evaluated by the WOMAC score; mobility was studied by walking performance on the treadmill and the overall inflammatory status was assessed by measurements of C-reactive protein plasma concentration (as a marker for inflammation). The trial was conducted over a three months' period, and the patients were randomly divided into two groups receiving respectively Meriva® 1 g/die (in two separate administrations) and the "best available treatment", or the "best available treatment" alone, as defined by the patients' general practitioners or specialists. The treadmill performance (10% inclination, 3 Km/h speed) showed an improvement of 201% of the initial walked distance at two months, and a further improvement (+44%) at three months from the beginning of the study. These positive results were complemented by secondary end-points, namely the decrease in painkillers use (63% in the Meriva® group vs 12% in the treatment group) and the decrease in gastrointestinal complications (38% in Meriva® vs 15% in controls ($p < 0.05$)).



Effect of Meriva® on the improvement of symptoms associated osteoarthritis: walking performance (treadmill).

Overall, the management costs in the Meriva® group decreased by 49% compared to a non significant 3% decrease for the control group.

In a second study,^[10] the activity of Meriva® for the complementary treatment of osteoarthritis was further confirmed in a larger and longer (8 months) investigation, that enrolled 100 patients and was, otherwise, methodologically similar to the previous one, including the dosage (1 g/die of Meriva®, corresponding to 200 mg curcumin/die in two separate administrations).

The results showed that the Meriva®-treated group enjoyed a statistically significant reduction in all primary clinical end-points, the Western Ontario and McMaster Universities

(WOMAC) score (decreased from 80.6 to 33.2), the Karnofsky Performance Scale (improved from 73.3 to 92.2), and the treadmill walking performance test.

These results were complemented by the evaluation of a series of inflammatory markers wider than the one considered in the first study (interleukin [IL]-1b, IL-6, soluble CD40 ligand [sCD40L], soluble vascular cell adhesion molecule (sVCAM)-1, and erythrocyte sedimentation rate [ESR]) that also showed a marked reduction in the Meriva® treated group. Conversely, no significant variation was observed in the "best available treatment" control group.

WOMAC items	Treated with Meriva® group		Control group	
	Enrollment	after 8 months	Enrollment	after 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

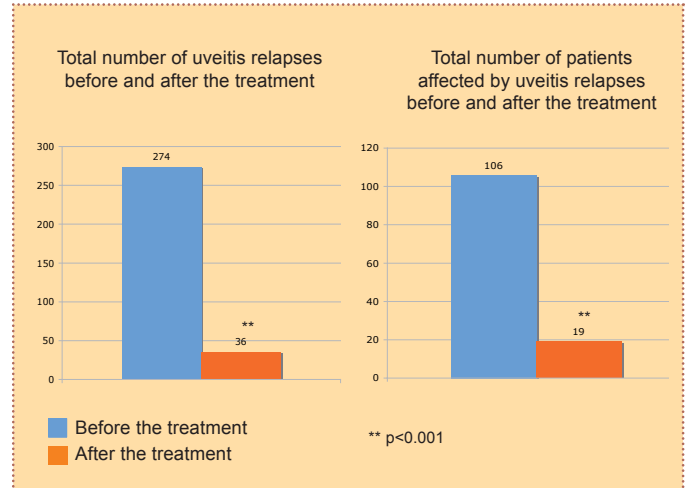
Effect of Meriva® on the change of Mean WOMAC Score after eight months of treatment.

Meriva® for uveitis and chronic eye-inflammation^[11]

A trial on 106 patients affected by chronic anterior uveitis relapsing since at least 2 years was carried out.

A 1.2 g/die dosage of Meriva® was administered (two separate admin. per day) for at least twelve months, complementing the therapy already in course.

86% of patients in the Meriva® group enjoyed a subjective improvement of the overall well being after only 4/6 weeks, with a remarkable reduction in relapses number. Also the number of patients affected by uveitis relapses decreased by over 80%. This suggests that Meriva®, in association to standard treatment, is useful in reducing the ocular problems related to chronic inflammation of the inner eye. These results qualify Meriva® as a safe ingredient with a strong potential even in poorly vascularized tissues like the ocular bulb.



Effect of Meriva® on uveitis relapses frequency.

Meriva® and diabetic angiopathy^[12]

In another registry study, 50 diabetic patients were treated with Meriva® (1g/die) to evaluate a possible reduction of the endothelial damage related to oxidative stress. Patients, whose disease was manageable without insulin and only with oral antidiabetics were divided in two groups.

The first one received Meriva® for 4 weeks while the second group was used as a control. The presence and evolution of diabetic microangiopathy was measured instrumentally (laser doppler flowmetry, pO₂) and observationally (evaluation of edema at the foot), after 4 weeks of treatment, the Meriva® group showed an amelioration of all the parameters investigated, as well as a general amelioration of the quality of life, as measured by the Karnofsky scale.

		Inclusion	4 weeks	P
LFD Flux	Curcum	3.32;0.8 flux units	2.35;0.72	<0.022
	Controls	3.33;0.7	3.2;1	ns
VAR	Curcum	23.4% (12-39.5)	39.7 (15-44.4)	<0.05
	Controls	24.1(13-44.4)	24.6 (12-42)	ns
Tc-PO ₂	Curcum	42.6;7.4 mmHg	49.3;4.4	<0.02
	Controls	43.1;4.3	42.3;4.4	ns
EDEMA (0-3)	Curcum	2.22;1.2	1.53;1.33	<0.025
	Controls	2.23;0.7	2.2;0.8	ns
KARNOFSKY SCALE	Curcum	84.2;8.8	89.6;4.8	<0.05
	Controls	85.8;7.2	83.5;3.7	ns

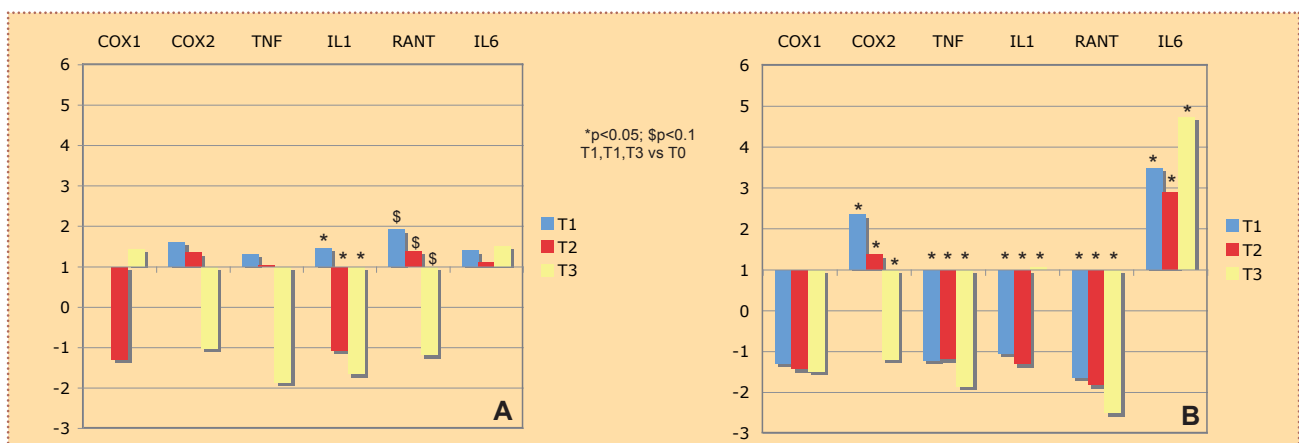
Microcirculatory measurements (VAR = venoarteriolar response), edema and the Karnofsky scale.

Meriva® and inflammation in vivo^[13]

In a study on mares and foals affected by degenerative joints disease Meriva® was able to downregulate the expression of a series of cytokines, enzymes and transcription factors involved in inflammation. Meriva® was administered for 15 days, and gene expression was compared with the initial state at days 4, 8 and 15 from the beginning of the treatment. In mares, curcumin inhibited the expression of COX-2,

TNF- α , IL-1 β , IL-1RN and IL-6, with special significance being observed for IL-1 β and IL-6. In foals, curcumin significantly inhibited the expression of COX-2, TNF- α , IL-1 β , IL1RN and IL-6.

These results underline the nutritional potential of curcumin as a natural anti-inflammatory aid for treating osteoarthritis also in animals.



Effect of Meriva® on the expression level (n-fold) of a set of genes of the inflammatory cascade in mares (A) and foals (B).

Pharmacokinetics

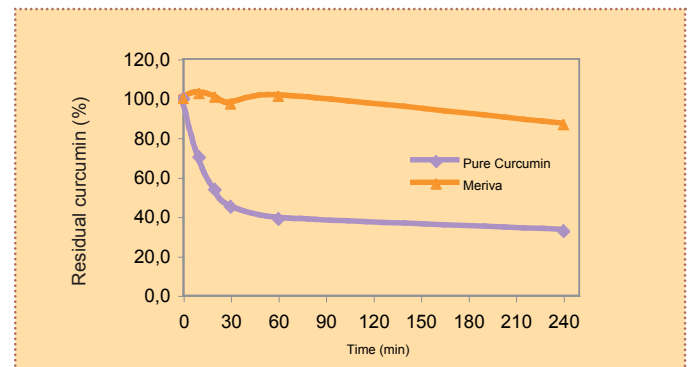
Despite acting on numerous molecular targets, little clinical evidence of efficacy has so far been reported for curcumin, and most of its beneficial effects are suggested by epidemiological studies, supported by studies in animal models or extrapolated from studies *in vitro*, but not yet validated clinically.^[4] This paradoxical situation is due to the poor druggability of curcumin. Indeed, monomolecular curcumin is highly instable at intestinal pH (having a half-life shorter than 10 min at pH 7), and curcumin has a dimly low oral absorption, characterized by plasma concentrations that barely overcome 50 ng/mL after administration of dosages as high as 12 g/die.^[14]

The Meriva® solution

Hydrolytical stability

A comparative study^[15] on the hydrolytical stability of unformulated pure curcumin and Meriva® showed that, while the half-life of unformulated pure curcumin at pH 7.2 (phosphate buffer) was shorter than 10 minutes, under the same conditions curcumin as Meriva® was still 82% unscathed after 240 minutes (almost 4 hours) at this pH value.

Similar results were obtained at pH 8, where at 30 minutes, degradation of unformulated curcumin and curcumin as Meriva® were 88% and 20%, respectively.



Curcumin degradation as monomolecular curcumin and Meriva® at 37° C in pH buffer at 7.2.

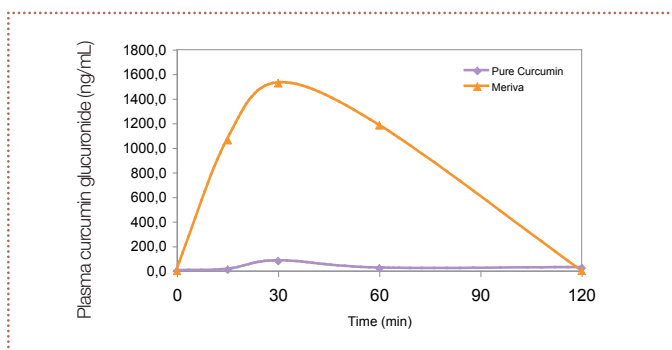
Pharmacokinetic studies

A high oral load of unformulated curcumin (340 mg/Kg) and an amount of Meriva® of 1.8 g/Kg, (corresponding to 340 mg/Kg of curcumin), were administered by oral gavage to Male Wistar rats.^[16] The presence of curcumin and metabolites was evaluated at 15, 30, 60 and 120 minutes after administration in plasma, liver and intestinal mucosa. In accordance with previous studies, 99% of curcumin was present in plasma as glucuronides, with the remaining 1% being curcumin sulphate and free curcumin. Formulation with phospholipids led to a marked (over 20-fold) increase in the concentration of plasma curcumin (essentially glucuronides).

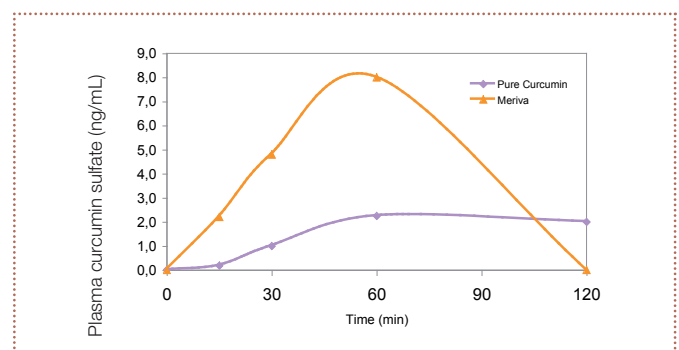
^a AUC was calculated using WinNonLin and employing a non-compartmental model

	Unformulated Curcumin (Cmax (nM))	Meriva® Cmax (nM)	Unformulated Curcumin AUC (µg•min/ml) ^a	Meriva® AUC (µg•min/ml) ^a
Free curcumin	6.5 ± 4.5	33.4 ± 7.1	4.8	26.7
Curcumin glucuronide	225 ± 0.6	4420 ± 292	200.7	4764.7
Curcumin sulphate	7.5 ± 11.5	21.2 ± 3.9	15.5	24.8

Estimated plasma peak levels (Cmax), time of peak levels (Tmax) and AUC values for unformulated curcumin and Meriva®.



Plasma levels of curcumin glucuronide in rats which had received curcumin or Meriva® by oral gavage. Curcumin conjugated metabolite concentrations were estimated using the curcumin calibration curve.



Plasma levels of curcumin sulfate in rats which had received curcumin or Meriva® by oral gavage. Curcumin conjugated metabolite concentrations were estimated using the curcumin calibration curve.

The Phytosome[®] advantage: clinical validation

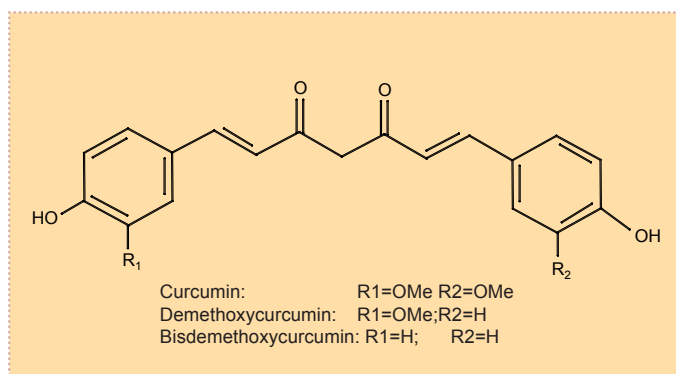
Commercial curcumin is a mixture of three curcuminoids, monomolecular curcumin, demethoxycurcumin, and bisdemethoxycurcumin, in a ca. 75:15:10 ratio. In a comparative pharmacokinetic study in humans,^[17] the absorption of each single curcuminoid present in commercial curcumin was compared between two dosages of Meriva[®] (1.0 and 1.9 g, corresponding to 209 and 376 mg of curcuminoids respectively) and one dosage of the corresponding unformulated curcuminoid mixture (1.8 g). The overall increase of curcuminoid absorption from Meriva[®] was ca. 29-fold (27-fold for the low dosage, 31-fold for the high dose). The increase of curcuminoid absorption was ca 20-fold for monomolecular curcumin, but 50 to 60 fold higher for demethoxycurcumin and bisdemethoxycurcumin, with demethoxycurcumin, and not curcumin, being the major plasma curcuminoid with both dosages of Meriva[®]. Remarkably, demethoxycurcumin is more potent than curcumin in many anti-inflammatory assays. The improved absorption, and possibly also a better plasma curcuminoid profile, might underlie the clinical efficacy of Meriva[®] at doses significantly lower than unformulated curcuminoid mixtures.

CURCUMINOIDS	MERIVA [®]		CURCUMIN (REFERENCE)		RELATIVE ABSORPTION*
	AUC (ng/mL)	Cmax (ng/mL)	AUC (ng/mL)	Cmax (ng/mL)	
Curcumin	538.0 ± 130.7	50.3 ± 12.7	122.5 ± 29.3	9.0 ± 2.8	19.2
Demethoxycurcumin	655.0 ± 195.7	134.6 ± 40.6	55.8 ± 15.5	4.2 ± 1.1	68.3
Bisdemethoxycurcumin	142.2 ± 58.2	24.9 ± 8.1	24.6 ± 10.3	2.1 ± 0.8	56.8
TOTAL CURCUMINOIDS	1336.0 ± 357.1	206.9 ± 54.9	202.8 ± 53.8	14.4 ± 4.2	31.5

*Normalized AUCs, expressed in ng/mL (plasma) x h/mg ingested, were divided by the AUC value of the reference to calculate the relative absorption values.

Chemistry

The natural components of the turmeric extracts are not only monomolecular curcumin (that in its pure form is more conveniently obtained by synthesis rather than by isolation), but also two minor components: bisdemethoxycurcumin and demethoxycurcumin, accounting for about 15 and about 10% respectively.^[3]

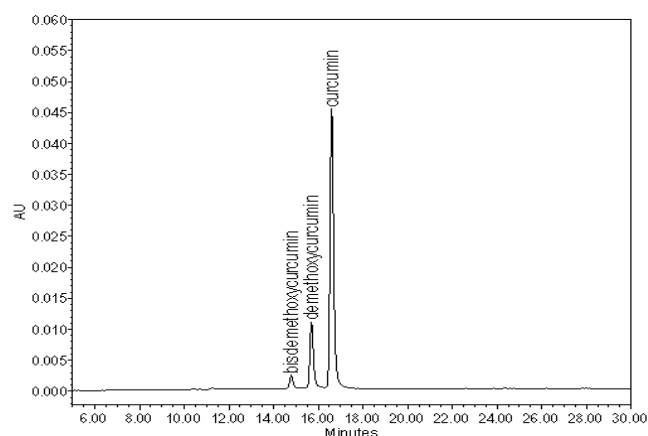


The composition of Meriva[®] reflects the most typical ratio between the three components. Recent researches indicate that the commixture of curcumin (monomolecular) and demethoxycurcumin, which is the natural status of natural curcumin, is more stable at the same

conditions than monomolecular curcumin alone, suggesting that demethoxycurcumin acts as a stabilizing agent of curcumin.^[18]

Additional findings^[19] indicate that both demethoxycurcumin and bisdemethoxycurcumin had a stabilizing effect on monomolecular curcumin in a dose-effect relationship.

This, together with the Phytosome[®] technology, act in improving the stability and the bioavailability of natural curcumin.



HPLC chromatogram of natural curcumin, displaying the three major components: monomolecular curcumin (curcumin), demethoxycurcumin and bisdemethoxycurcumin.

Concluding remarks

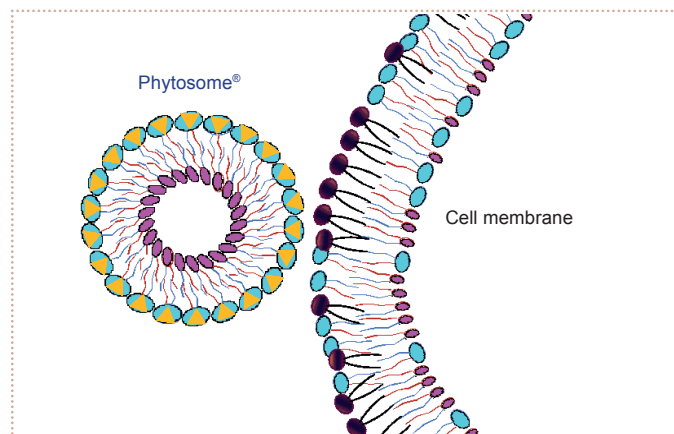
Meriva[®], a patented Phytosome[®] delivery form of curcumin with soy lecithin^[5] has been shown to increase the hydrolytical stability of curcumin and to increase the oral absorption of curcuminoids by near 30 folds.^[16]

By embedding curcumin into a lipophilic phospholipid environment, curcumin is shielded from water-triggered degradation while, at the same time, the rapid exchange of phospholipids between biological membranes and the extracellular fluids can shuttle it into biological membranes, boosting its cellular captation.

The improved oral bioavailability of curcumin as Meriva[®] has been translated into clinical efficacy for the treatment of inflammatory conditions at dosages significantly lower than those associated to uncomplexed curcumin, with ongoing clinical studies also for other conditions (Alzheimer's disease, liver protection and chemoprevention) where a solid mechanistic rationale and pre-clinical rationale and pre-clinical evidence of efficacy exists for curcumin.

Just like curcumin, Meriva[®] is characterized by a remarkable

safety. Apart from animal data (LD50 >2 g/Kg in rats), no side-effects were observed when Meriva[®] was administered at 1.2 g/die to over 100 volunteers for 18 months.^[10]



Representation of a Phytosome[®] approaching a cell membrane. The affinity of the two structures shuttles the active ingredient into the cell membrane.

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