Curcumin is the yellow pigment of turmeric (Curcuma longa L.), the most popular spice in Indian cuisine and a major ingredient of curry powders. The dietary intake of curcumin in Asian countries can reach much as 200 mg/day.[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, at over 50 mg/day and 210 mg/day, respectively, in the adult population.[2] Turmeric has a long history of traditional medicinal use in India to address many conditions. Modern cellular studies on curcumin have validated most of its traditional uses and the potential to address natural life conditions typical in Western peoples.[3] Indeed, with almost 4000 pre-clinical investigations, curcumin is one of the best studied natural products of the whole biomedical literature. As a result, curcumin has emerged as a master switch of addressing the natural inflammation response function, with both a direct and a genomic activity on relevant enzymes, transcription factors and 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.[5]

Meriva® - bioavailable curcumin

Meriva® is a patented delivery form of curcumin. 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 be formulated with a variety of poorly soluble phenolics, including curcumin.[6,7] Phenolics as curcumin, show a high affinity for biological membranes, and, once formulated with phospholipids, are embedded into a lipidic matrix that 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 Use

Clinical studies on Meriva® to address the natural inflammatory response process

According to the Framingham Cohort (USA), 25% of people in their 60s and 50% in their 80s show changes in bone health by radiography, and age, female sex, overweight, occupational knee-bending, physical labour, and joint challenges have all been identified as risk factors. The use of Meriva® for bone health is based on the capacity of this compound to interrupt inflammatory response signaling and increase anti-oxidant levels. Preclinical and clinical evidence suggests that bone health is better supported by a multi-targeted, rather than by a mono-targeted, approach, and agents that modulate multiple cellular targets, like curcumin, have a great potential for the management of these conditions.

Meriva® and the complementary management of bone health: walking performances and WOMAC score

Meriva® was evaluated for its efficacy in 50 individuals affected by bone health challenge (X-ray diagnosis confirmation). The symptoms were evaluated by the WOMAC score; mobility was studied by walking performance on the treadmill and the overall inflammatory response function was assessed by measurements of C-reactive protein plasma concentration. The trial was conducted over a three months’ period, and the individuals 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 individuals’ 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 supplemental therapy 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).

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, the activity of Meriva® for the maintenance of bone health was further confirmed in a larger and longer (8 months) investigation, that enrolled 100 partecipants and was, otherwise, methodologically similar to the previous one, including the dosage (1 g/day of Meriva®, corresponding to 200 mg curcumin/day in two separate administrations). The results showed that the Meriva® group enjoyed a statistically significant reduction in all primary clinical endpoints, 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 response function 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.

<table>
<thead>
<tr>
<th>WOMAC items</th>
<th>Enrolled</th>
<th>after 8 months</th>
<th>Enrolled</th>
<th>after 8 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>pain</td>
<td>16.6</td>
<td>7.3</td>
<td>16</td>
<td>15.2</td>
</tr>
<tr>
<td>stiffness</td>
<td>7.4</td>
<td>3.2</td>
<td>6.6</td>
<td>6.7</td>
</tr>
<tr>
<td>physical functions</td>
<td>56.6</td>
<td>22.8</td>
<td>55.2</td>
<td>46.9</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>80.6</strong></td>
<td><strong>33.3</strong></td>
<td><strong>77.8</strong></td>
<td><strong>68.8</strong></td>
</tr>
</tbody>
</table>

Effect of Meriva® on the change of Mean WOMAC Score after eight months of treatment.
**Meriva® and challenges to the eye’s middle layer**

A trial on 106 subjects whose eye middle layer was challenged and relapsing since at least 2 years was carried out. A 1.2 g/day dosage of Meriva® was administered (two separate admin. per day) for at least twelve months, complementing the treatment already in course. 86% of subjects in the Meriva® group enjoyed a subjective improvement of the overall well being after only 4/6 weeks, with a remarkable reduction in challenges. Also the number of subjects with challenges decreased by over 80%. In a recent pilot study, the daily use of 1 g/day of Meriva®, associated with the standard treatment, has shown to ameliorate the visual acuity, supporting healthy vision. These results qualify Meriva® as a safe ingredient with a strong potential even in poorly vascolarized tissues like the ocular bulb.

**Meriva® and healthy blood vessel function**

In another registry study,[13] 50 subjects prone to blood vessel challenge were treated with Meriva® (1g/day) to evaluate its ability to support healthy blood vessels. Participants 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 endothelial challenge was measured instrumentally (laser doppler flowmetry, pO2) and observationally (evaluation of 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. Furthermore, in a previous reported pilot study,[14] 38 subjects prone to blood vessel challenge were administered with 1 g/day of Meriva (in addition to the standard management plan) for at least 4 weeks. Compared to the control group (n=39), following the standard management plan alone, the Meriva® group showed a statistically significant improvement in the vessel response (p<0.05) and the decrease in the score of the peripheral vessel challenge (p<0.05).

**Meriva® and the natural inflammation response function in vivo and in humans**

In a study on mares and foals,[14] Meriva® was able to downregulate the expression of a series of cytokines, enzymes and transcription factors involved in the natural inflammation response. 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-1β, IL-1RN and IL-6, with special significance being observed for IL-1β and IL-6. In foals, curcumin significantly inhibited the expression of COX-2, TNF-α, IL-1β, IL1RN and IL-6. In a recent genomic study,[15] on dogs, the differential modulation of inflammation response markers by Meriva® and another agent was investigated. Meriva® (40 mg/Kg/day, corresponding to 8 mg/Kg/day of curcumin) or another agent (4 mg/Kg/day) were administered to two groups of 6 JC dogs for 20 days. Gene expression was compared with a control group of 6 dogs at the beginning (T0) and at the end of the study (T20). At the beginning of the study, the two experimental groups of dogs showed the differential expression of 475 (other agent arm) and 498 (Meriva® arm) genes compared to the control group. These genes could be broadly defined as pro-inflammatory response markers. Both curcumin and the other agent could significantly attenuate the expression of this genomic signature, since at the end of the study only 173+ (other agent arm) and 141 (Meriva® arm) genes were differentially expressed compared to the control group. From a genomic standpoint, Meriva® outperformed the other agent, since important genes underlying the production of iκB and IL18 were modulated only by Meriva®. Compared to the other agent, Meriva® could downregulate the inflammatory response pathway mediated by TNFα, macrophage proliferation and fibrinolysis. Taken together, these provide a genomic rationale for the use of Meriva® for the complimentary support of joint health, an indication validated by human clinical studies. A recent registry study,[16] on 61 subjects evaluated Meriva® efficacy in supporting healthy prostate function compared to the best standard management (BSM) available. Signs and symptoms were evaluated using the International Prostate Symptom Score (IPSS). A first group of 33 subjects were administered with BSM in association with Meriva® at the dosage of 500 mg/day for at least 24 weeks, while the remaining 28 volunteers (control group) were administered with only BSM. All IPSS scores and quality of life improved in both groups, while in the Meriva® arm were significantly better than in the BSM-only group (p<0.05 for IPSS and p<0.01 for quality of life). All these results underline the nutritional potential of curcumin as a natural ingredient to support the body’s inflammation response function.
**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.\(^\text{[19]}\) 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).

<table>
<thead>
<tr>
<th>Unformulated Curcumin</th>
<th>Meriva®</th>
<th>Unformulated Curcumin</th>
<th>Meriva®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cmax (nM)</strong></td>
<td><strong>Cmax (nM)</strong></td>
<td><strong>AUC (µg·min/ml)</strong></td>
<td><strong>AUC (µg·min/ml)</strong></td>
</tr>
<tr>
<td>FREE CURCUMIN</td>
<td>6.5 ± 4.5</td>
<td>33.4 ± 7.1</td>
<td>4.8</td>
</tr>
<tr>
<td>CURCUMIN GLUCURONIDE</td>
<td>225 ± 0.6</td>
<td>4420 ± 292</td>
<td>200.7</td>
</tr>
<tr>
<td>CURCUMIN SULPHATE</td>
<td>7.5 ± 11.5</td>
<td>21.2 ± 3.9</td>
<td>15.5</td>
</tr>
</tbody>
</table>

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

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**Meriva® and sports nutrition**

In a randomized, placebo-controlled, single-blinded study,\(^\text{[17]}\) 20 healthy and moderately active subjects received 1g Meriva® or a placebo twice daily, 48 hours prior to a downhill running test, the day of the test, and 24 hours after the test, for an overall 4 day treatment.

The end point was the evaluation of delayed onset muscle soreness (DOMS), that is the muscular discomfort and stiffness that develops after unaccustomed or strenuous exercise, with soreness being felt most strongly 24 to 72 hours after the exercise.

Muscle soreness was quantified by magnetic resonance imaging, laboratory tests, and histologic analyses on muscle samples obtained 48 hours after the test. The intensity of discomfort was also evaluated. Participants were asked to indicate the location of pain on a drawing representing the lower limbs, and to rank pain intensity on a 0-4 point scale, where 0=no pain, 4=disabling pain when descending or climbing stairs.

The observation from the study suggests that curcumin as Meriva® can be beneficial to attenuate exercise-induced DOMS, and larger studies could provide statistical significance also for parameters like the histological evaluation of muscle that only showed a trend to improvement in this pilot study.

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.\(^\text{[4]}\) This paradoxical situation is due to the poor absorbability of curcumin. Indeed, monomolecular curcumin is highly instable at intestinal pH (having a half-life shorter that 10 min at pH 7), and curcumin has a dismal low oral absorption, characterized by plasma concentrations that barely overcome 50 ng/mL after administration of dosages as high as 12 g/day.\(^\text{[18]}\)
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,[23] 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 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.

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.[21] Additional findings[22] 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 bioavailability of natural curcumin.

**The Phytosome® advantage: clinical validation**

<table>
<thead>
<tr>
<th>CURCUMINOIDS</th>
<th>AUC (ng/mL)</th>
<th>Cmax (ng/mL)</th>
<th>AUC (ng/mL)</th>
<th>Cmax (ng/mL)</th>
<th>RELATIVE ABSORPTION*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>538.0 ± 130.7</td>
<td>50.3 ± 12.7</td>
<td>122.5 ± 29.3</td>
<td>9.0 ± 2.8</td>
<td>19.2</td>
</tr>
<tr>
<td>Demethoxycurcumin</td>
<td>655.0 ± 195.7</td>
<td>134.6 ± 40.6</td>
<td>55.8 ± 15.5</td>
<td>4.2 ± 1.1</td>
<td>68.3</td>
</tr>
<tr>
<td>Bisdemethoxycurcumin</td>
<td>142.2 ± 58.2</td>
<td>24.9 ± 8.1</td>
<td>24.6 ± 10.3</td>
<td>2.1 ± 0.8</td>
<td>56.8</td>
</tr>
<tr>
<td>TOTAL CURCUMINOIDS</td>
<td>1336.0 ± 357.1</td>
<td>206.9 ± 54.9</td>
<td>202.8 ± 53.8</td>
<td>14.4 ± 4.2</td>
<td>31.5</td>
</tr>
</tbody>
</table>

*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.

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.[24]
Meriva®, a patented Phytosome® delivery form of curcumin with soy lecithin has been shown to increase the oral absorption of curcuminoids by nearly 30 fold. By embedding curcumin into a lipophilic phospholipid environment, 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 addressing the natural inflammatory response function at dosages significantly lower than those associated to unformulated curcumin, with ongoing clinical studies also for other conditions where a solid mechanistic 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/day to over 100 volunteers for 18 months.

Concluding remarks

References