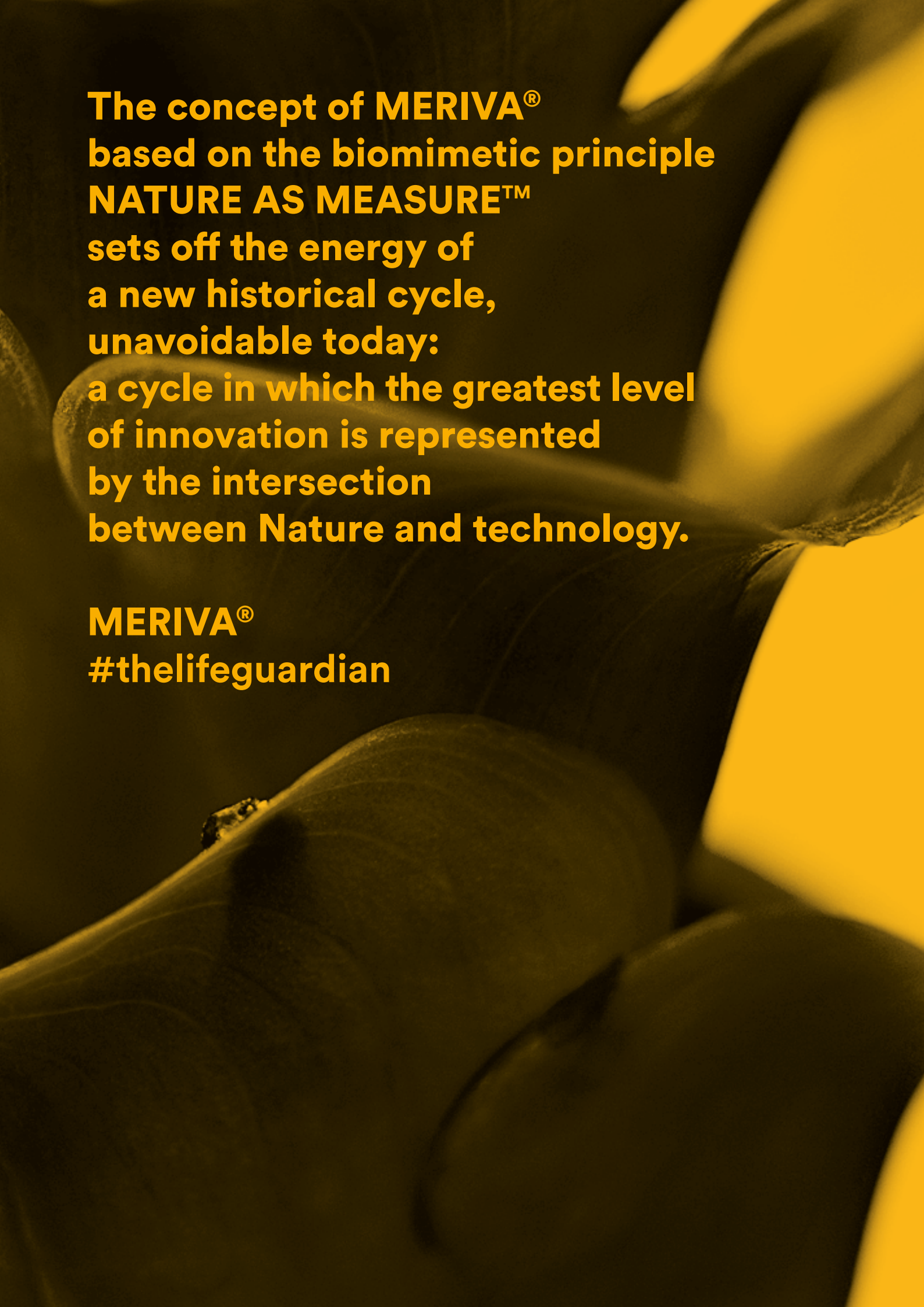


Meriva[®] Curcumin Phytosome[®]

Low-level chronic inflammation. Pioneering a contemporary approach to turmeric.





**The concept of MERIVA®
based on the biomimetic principle
NATURE AS MEASURE™
sets off the energy of
a new historical cycle,
unavoidable today:
a cycle in which the greatest level
of innovation is represented
by the intersection
between Nature and technology.**

**MERIVA®
#thelifeguardian**

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Executive summary

MERIVA® Curcumin Phytosome® is a product that, **thanks to its characteristics, can represent a reference model for a new type of relationship between the active biological components of turmeric, namely curcuminoids, and the maintenance of our lives.**

The MERIVA® concept is based on a **biomimetic scientific approach [*bios = life; mimesis = imitation*]**. Observing Nature in all its forms and exploiting its beneficial effects on the lab bench has been INDENA's commitment for almost a century.

The Indena Phytosome®, which is the basis of MERIVA®, IS THE ONLY DELIVERY SYSTEM OF BOTANICAL DERIVATIVES IN THE WORLD that can claim a 100% foodgrade composition. The application of the biomimetic principle NATURE AS MEASURE™ places this formulation out of the fierce and conceptually reductive competition on the increase of bioavailability levels. MERIVA® is much more: it optimizes bioabsorption levels [NATURE AS MEASURE™] according to the 3 basic parameters of EFFECTIVENESS, TOLERABILITY OVER TIME, SAFETY.



The clinical and scientific evidence gathered since 2005 grants MERIVA® the role of THE LIFE GUARDIAN™ for the entire course of our lives, since silent chronic inflammation is one of the great challenges of our time.

The clinically validated human dose resulting from over 30 clinical studies is 1g, corresponding to 200mg of curcuminoids. Such studies have not only demonstrated the effectiveness of MERIVA®, but also provided valuable insights into the extremely high tolerability profile of the ingredient in the long term.

Sensitivity, scientific expertise, biomimetic science and critical thinking were the pillars that made the development of MERIVA® Curcumin Phytosome® approach possible, exploring new potentials and supporting its customers towards new futures.

The biomimetic approach of INDENA

A close-up photograph of several yellow flower petals, likely from a sunflower, set against a dark background. The petals are in sharp focus, showing their texture and vibrant yellow color. The lighting is dramatic, highlighting the edges and veins of the petals.

The magic word is to mimic. But to mimic what?

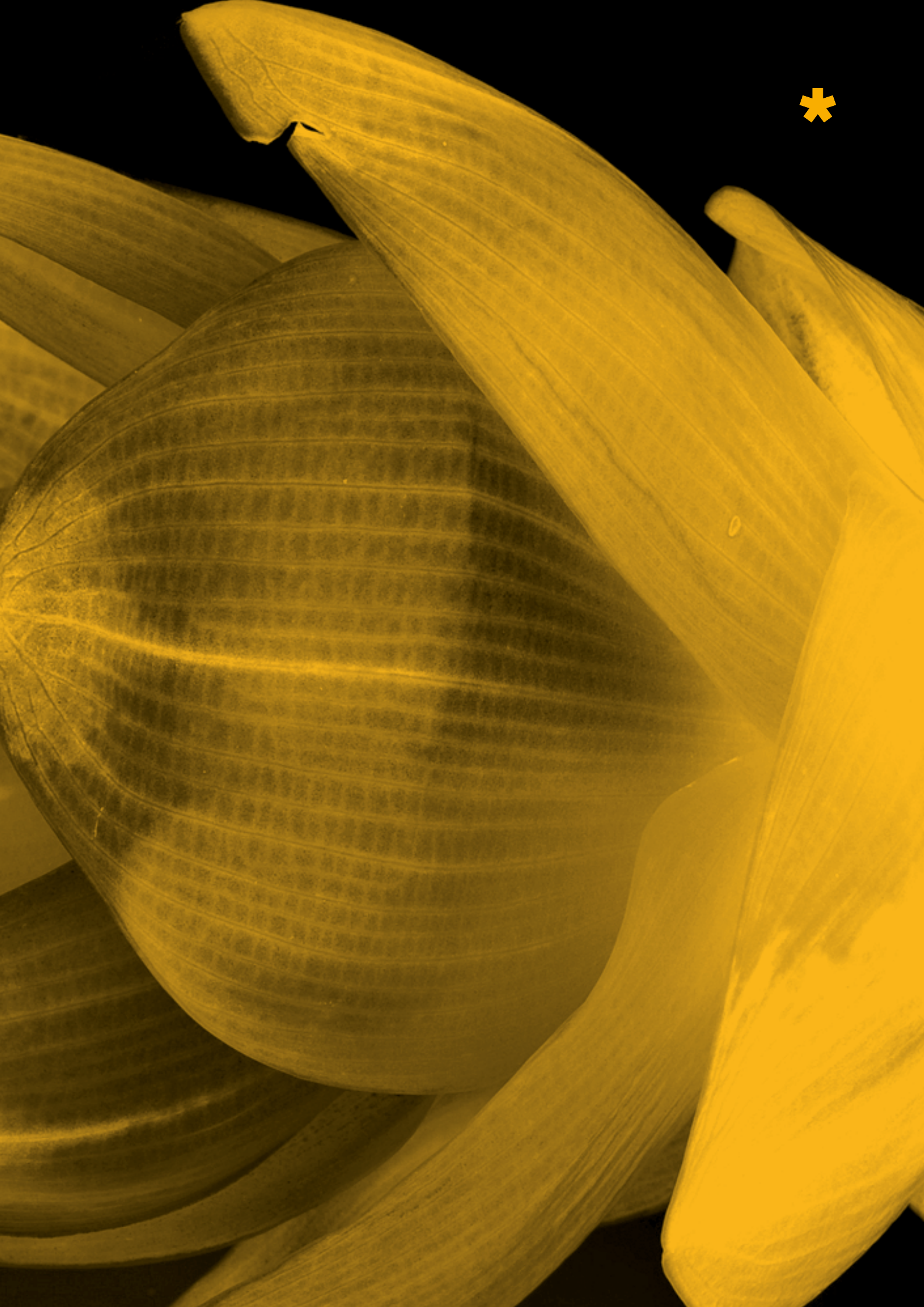
The answer is BIOSYSTEMS, Nature's model of diffused and creative intelligence, the functioning of natural molecules of biological interest, thus replicating what molecules or their infinitely larger and more complex assemblages do, for instance enzymes and proteins.

For a whole generation of organic, inorganic, biological and physical chemists, "mimicking" biosystems is a continuous project framework challenge.

Mimicking Nature, re-making it with the brain power of researchers by building processes and principles on the bench of a laboratory, is irresistible for INDENA: not a mere embellishment label, but a real scientific gem.

INDENA steps with rationality, attention and depth of views into a topic that today is a focal point of the future and at which the company has been working for years.

The entry is that of natural derivatives, of their insightful and sensible use within the nutraceutical field, in an imitation of Nature aimed at achieving advantages in terms of rationalization, simplification, tolerability, health and people's safety.



Background and reference market



In recent years the turmeric market has become deeply crowded and “noisy”.

The attention paid to the original ingredient producers compared to the brands that certify curcumin-based products is scarce and limited to a few very specific health-related sites.

There is general confusion about the terms used, the absorption, the race for the highest bioavailability and so on.

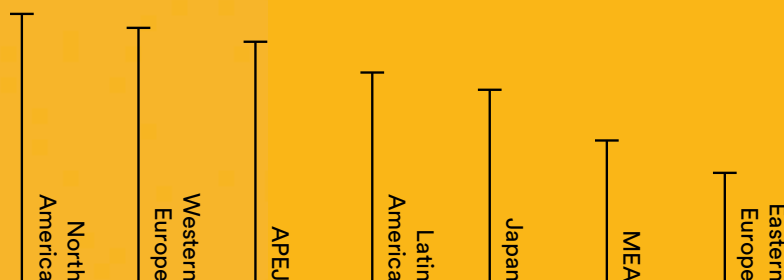
In essence, the sometimes too technical approach [and the related language] used by certain brands confuses consumers who sometimes, without expert guidance, cannot fully evaluate quality and functionality.

The growing demand for quality

There is a growing need to scientifically support consumers in making informed choices and avoiding products of uncertain origins. They are now more demanding of products backed up by a transparent composition, obtained from production chains and processes carried out in full accordance to best practices and consistent with traditional dietary uses.

Global Turmeric Market

By Region [2017]



Source: Future Market Insights, Turmeric Market Report, 2017.

Attention to the maintenance of our health

Consumers are adopting a healthier lifestyle. The overweight population is increasing in European countries, as the United States. And with increased age comes the increased risk of joint-related health conditions. This generates a further escalation in the demand for *Curcuma longa* as an important ingredient in their diet.

The increment of the markets

According to estimates by the Nutrition Business Journal [NBJ], **sales of turmeric in North America reached \$ 196 million in 2015 with an increase of 20% over the previous year, and are expected to reach \$ 433 million by 2020.**

Turmeric was the best-selling ingredient in herbal medicine in 2016.

The Western European turmeric market is estimated close to US \$ 800 million by 2017 and could increase to a CAGR of 5.8% by 2027.

It is expected that the market will be valued at more than US \$ 1.300 million by the end of 2027.



The problem

3.

Chronic inflammation is the *silent killer* of our health.

According to the World Health Organization, more than a third of the 57 million deaths each year in the world are provoked by **chronic diseases that are the main cause of death** [cardiovascular diseases, type-2 diabetes, hypertension, respiratory diseases and Alzheimer's].

90% of these diseases have an inflammatory origin.

Chronic inflammation is mainly due to the Western lifestyle, and understanding it has in fact become a crucial goal of modern clinical research.

For centuries, scientists have debated whether inflammation is good or bad for us.

Now they believe it is both: too little, and microbes fester and spread in the body, or wounds fail to heal; too much, and nearby healthy tissue can be degraded or destroyed.

The fire of inflammation must be tightly controlled: turned on at the right moment and, just as critically, turned off.

Lately, however, several lines of research have revealed that low-level inflammation can simmer quietly in the body, in the absence of overt trauma or infection, with profound implications for our health.

Using advanced technologies, scientists have discovered that heart attacks, diabetes and Alzheimer's disease may be linked to smoldering inflammation, and some researchers have even speculated about its role in psychiatric conditions.

As a result, understanding and controlling inflammation has become a central goal of modern clinical investigation.

The internal research arm of the USA National Institutes of Health recently designated inflammation a priority, mobilizing several hundred scientists and hundreds of millions of dollars to better define its role in health and disease.

The INDENA proposal



MERIVA®, THE LIFE GUARDIAN™

MERIVA® is the patented Curcumin Phytosome® by INDENA, based on the scientific biomimetic approach.

The application of the biomimetic principle NATURE AS MEASURE™ to its formulation places MERIVA® out of the fierce and conceptually reductive competition on the increase of bioavailability levels, because with MERIVA®, **INDENA has worked on the optimization of bioabsorption levels [NATURE AS MEASURE™] according to 3 basic parameters:**

EFFECTIVENESS, TOLERABILITY OVER TIME, SAFETY.

Its level of bioavailability, absorption modality and tolerability over time make MERIVA® compatible and appropriate to the permanent role of THE LIFE GUARDIAN™ over the levels of chronic inflammation, during the entire course of our life.

Thanks to its Phytosome® delivery system - which transports the 3 fundamental curcuminoids in a phospholipidic formulation - systematic supplementation with MERIVA® fosters the maintenance of healthy level of inflammation.

Effectiveness

MERIVA® contains all 3 curcuminoids [i.e. the active ingredients naturally present in turmeric] in the same proportions expected in Nature, and it is the formulation with the highest plasmatic levels of DMC [the most potent curcuminoid].

MERIVA® shows a unique profile of plasma curcuminoids.

The dose of curcuminoids per 1g of MERIVA® is 200mg, which is completely in line with the average Indian daily intake. This is the clinically validated dose and has proven effective in over 30 human trials.

Tolerability over time

Numerous studies conducted on humans, even within a long-term scenario, have validated the effectiveness of MERIVA®, proving that **it can be taken for extended periods of time, and making it appropriate for a long-term life-maintenance strategy.**

The average dose of curcumin in the Indian diet is 2.5mg/kg [over 160mg/die for an adult]. Turmeric is mainly consumed in an oily matrix that favors the absorption of curcumin.

MERIVA® [with curcumin transported together with phospholipids] is a sort of molecular translation of this dietary habit. This is obtained without resorting to pharmacological adjuvants or synthetic ingredients, but instead using simple interaction with a dietary ingredient [phosphatidylcholine] according to the unique Phytosome® delivery system.

MERIVA® is therefore the replication of a dietary habit consolidated over the centuries, because it mimics its quantity and composition with the added guarantee of rigorous production standards in accordance to absolute best practices.

Specific studies have also been conducted on safety in accordance with the most modern guidelines.



A lighthouse is situated on a rocky cliff on the right side of the image. The lighthouse has a dark, cylindrical tower with a lantern room on top, surrounded by a railing. The sky is a uniform, bright yellow-gold color. The ocean is dark, with white foam from waves crashing against the base of the cliff and the lighthouse. The overall mood is dramatic and serene.

Introducing
MERIVA[®]



The Life

Guardian™

BIOMIMETICS is the science that studies the best ideas in Nature and then imitates their design, plans and processes to solve human problems.

Summarizing the concept, one can speak of “innovation inspired by Nature”.

From the very notion of biomimetics in literature and its philosophical origins, we distilled the following concept:

Nature as

The strength of the primary concept of biomimetics is that **Nature is seen as the measure and the standard for judging appropriateness, sustainability and also the formal, strategic and ethical correctness of our technological product and process innovations.**

The central idea is that Nature, by necessity, has already solved many of the problems we are dealing with. Plants and microbes are consummate engineers. They have found what works, what is appropriate and what lasts over time and why.

This is the true news of biomimetics: after 3.8 billion years of research and development, the failures have turned into fossils and what surrounds us is the secret to survival.

So it is Nature, and only Nature, which can show us the way in a given situation.

This is why NATURE AS MEASURE™ is the biomimetic principle chosen by INDENA for the design of its active ingredients based on natural phytosomal extracts.





The basic steps of the biomimetic design approach are:

— 1

Identify / develop a brief for the needs to be answered.

— 2

Translate / *biologize* the question, i.e. express the project brief from a biological point of view.

— 3

Explore / study: how does Nature perform this function? How does Nature NOT perform this function?

— 4

Discover: look for examples in Nature that respond to the challenge.

Measure™

— 5

Synthesize: find models and repetitive processes within Nature that do achieve success.

— 6

Emulate / develop ideas and solutions based on natural models.

— 7

Evaluate how the identified solution is aligned with the project brief and with the principles of life, thus the principles of success in Nature.

Researchers who pursue biomimetic approaches have barely scratched the surface of biological inspiration. Biologists from all disciplines have an extraordinary knowledge that can lead incursions into a much richer diversity of natural systems. And this knowledge helps, encourages, orients and electrifies the experimental approaches.

Advantages



The uniqueness of MERIVA® formulated curcumin is its Phytosome® delivery system, based on the application of the biomimetic principle NATURE AS MEASURE™.

The Phytosome® delivery system within the field of food supplements was pioneered and developed by INDENA more than 20 years ago.

The INDENA Phytosome® is the only delivery system in the world entirely made of natural elements and for this reason is thoroughly food grade, as it manages to mimic the absorption of a fatty meal [fatty meals increase the absorption due to bile acids], such as curcumin / curcuminoids mixed with milk, a combination known as “golden milk”.
Therefore, the Phytosome® delivery system by INDENA is not only natural, but contains phospholipids that are naturally present in the cells of our body.

In the world of food supplements it is essential to make sure that there are no “non-food grade” excipients.

For all these reasons, MERIVA® Curcumin Phytosome® is not only BIOAVAILABLE and BIO-ABSORBABLE at an endogenous level, but EFFECTIVE, TOLERABLE OVER A LONG PERIOD OF TIME AND SAFE.

In almost 100 years of presence on the market, the commitment of INDENA has constantly focused on 2 main objectives: the development of extractive practices that guarantee the absolute highest quality standards of the extracts, and the finalization of processes able to reproduce the action mechanisms developed by Nature, to equip them with an appropriate delivery.

In recent years, INDENA has used its capital of profound scientific knowledge to further increase the safety of its ingredients, developing a strategy that can map even the genetic identity of the raw materials used for its botanical extracts. As no universal Genomic ID method is available, this knowledge has allowed INDENA to develop species-specific DNA identification analytical tools. As part of its quality system, INDENA is able to apply the appropriate technology to each case.

Find out more at <http://www.indena.com/quality/dna-barcoding/>



MERIVA® was independently endorsed by the prestigious Cleveland Clinic in the US as the curcumin formulation of choice in the turmeric market

Visit <https://health.clevelandclinic.org/2015/08/7-tips-for-taking-turmeric-infographic/>



MERIVA[®]
at a glance

Is based on a natural and foodgrade delivery system [Phytosome®] of a standardized turmeric extract containing the full bouquet of curcuminoids, not just curcumin.

Is supported by GLP preclinical safety studies.

Stands as the most pre-clinically and clinically documented curcumin bioavailable formulation.

Is now supported by different clinical studies validating its efficacy in the sports nutrition and muscular preservation categories.

Is documented with preclinical and clinical pharmacokinetic studies as an orally bioavailable and bioabsorbable product, with measurements related to the 3 curcuminoids of the natural mixture.

Is proven to have a long term high tolerability profile demonstrated in an 18 month clinical study with no side effects.

Has been documented with over 30 clinical studies in 10 different conditions involving 2000 subjects.

Is the curcumin formulation of choice for leading practitioners and their patients.

Was independently endorsed by the prestigious Cleveland Clinic in the US as the curcumin formulation of choice in the turmeric market.

Bibliography and online research material



Bibliography

- _ Allegri P., et al. Clin Ophthalmol, 2010. 4: p. 1201-6.
- _ Antiga A., et al. BioMed Research International, vol. 2015, Article ID 283634.
- _ Appendino G., et al. Panminerva Med, 2011. 53 [3 Suppl 1]: p. 43-9.
- _ Belcaro G., et al. Altern Med Rev, 2010. 15 [4]: p. 337-44.
- _ Belcaro G., et al. Eur Rev Med Pharmacol Sci, 2014. 18 [24]: p. 3959-63.
- _ Belcaro G., et al. Panminerva Med, 2010. 52 [2 Suppl 1]: p. 55-62.
- _ Belcaro G., et al. Phytother Res, 2014. 28 [3]: p. 444-50.
- _ Di Pierro F., et al. J Pain Res. 2013, 6, 201-205.
- _ Di Pierro F. and R. Settembre J Pain Res, 2013. 6: p. 497-503.
- _ Drobnic F., et al. J Int Soc Sports Nutr, 2014. 11: p. 31.
- _ Ferguson, Jessica JA, et al. Metabolism [2017].
- _ Franceschi F., et al. European Review for Medical and Pharmacological Sciences. 2016; 20: 762-766.
- _ Golombick T., et al. Journal of Cancer Therapy, 2015, 6 [7], 566-571.
- _ Kayabasi U., et al. Int J Ophthalm Clin Res 2014 1:002.
- _ Ledda A., et al. Panminerva Med, 2012. 54 [1 Suppl 4]: p. 17-22.
- _ Maccio A., et al. Nutrition, 2015. 31[1]: p. 239-43.
- _ Mazzolani F. Clin Ophthalmol, 2012. 6: p. 801-6.
- _ Mazzolani F. and S. Togni Clin Ophthalmol, 2013. 7: p. 939-45.
- _ Mazzolani F. and S. Togni, et al. Minerva Ophthalmol, 2016. 58: p 1-5.
- _ Pajardi G., et al. Evid Based Complement Alternat Med, 2014. 2014: p. 891310.
- _ Panahi Y., et al. J. Cardiovasc Pharmacol. 2016; 68: 223 -229.
- _ Panahi Y., et al. Drug Res [Stuttg]. 2017 Apr; 67 [4]: 244-251.
- _ Panhai Y., et al. J Functional Food 2014 [6] 615–622.
- _ Panahi Y., et al. Phytother Res, 2014. 28 [10]: p. 1461-7.



Online research material

- Riva A., et al. *European Review for Medical and Pharmacological Sciences* 2017; 21: 1684:1689.
- Sciberras J.N., et al. *J Int Soc Sports Nutr*, 2015. 12 [1]: p. 5.
- Serpe R., et al. 6th Cachexia Conference, Milan, Italy, December 8–10, 2011.
- Soldà C., et al. *International Journal of Pharmacology, Phytochemistry and Ethnomedicine*, Vol 2, 2017.
- Steigerwalt R., et al. *Panminerva Med*, 2012. 54 [1 Suppl 4]: p. 11-6.
- Szymanski M.C., et al. *J Appl Physiol* 2017. doi: 10.1152/jappphysiol.00515. 2017.
- Tenero L., et al. *Allergy Asthma Proc.* 2016; 37:e8-e13.
- Watson R.R., Preedy V.R., *Bioactive Foods as Dietary Interventions for Arthritis and Related Inflammatory Diseases*, Ch. n.5, Appendino, Togni, p. 66-81.
- Watson R.R., *Foods and Dietary Supplements in the Prevention and Treatment of Disease in Older Adults*, Elsevier Science, 2015, p. 16.
- <https://academic.oup.com/eurheartj/article/27/22/2640/2887469>
- <https://www.futuremarketinsights.com/reports/turmeric-market>
- <https://www.nature.com/articles/nature01322>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1087185/>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964958/>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5488800/>
- <http://onlinelibrary.wiley.com/doi/10.1111/j.1473-2165.2005.00194.x/full>
- <http://www.who.int/bulletin/volumes/81/9/PHC.pdf>
- <http://www.who.int/mediacentre/factsheets/fs311/en/>
- <http://www.who.int/mediacentre/factsheets/fs394/en/>
- http://www.who.int/medicines/areas/priority_medicines/BP6_11Alzheimer.pdf
- http://www.who.int/medicines/areas/priority_medicines/Ch6_12Osteo.pdf

**INDENA uses for MERIVA[®],
and will always use for its
active ingredients,
a natural nutraceutical talent
and biomimetic science,
to respond to the changing
needs of human beings,
to push the envelope
and support partners
and customers towards
new futures.**

INDENA
#scienceisournature





Call To Action / Contacts

Now imagine how the effectiveness of MERIVA® as THE LIFE GUARDIAN™ in a healthy life maintenance personal project should:

Enlarge your prospect target to non-pathologic situations.

Increase the average consumption per capita.

Widen the consumption window either in terms of consumerage [aging – longevity – prevention] or in occasions of consumption.

Strengthen your customers' brand advocacy and loyalty: INDENA will deploy a strong communication and divulgative program about MERIVA® THE LIFE GUARDIAN™ properties.



Contact Us

INDENA S.p.A.
Viale Ortles, 12 - 20139 - Milano [Italy]
communication@indena.com

indena.com



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 **indena**[®]
SCIENCE IS OUR NATURE

**Low-level
Chronic
Inflammation**

Low-level Chronic Inflammation

Chronic inflammation and turmeric

Chronic inflammation is associated with a constant increase of pro-inflammatory biochemicals in our body. Drugs can only contain but not cure this condition, because they do not remove the cause of the disease: silent inflammation.

Silent inflammation is defined as silent because it is not perceived by the individual, as opposed to acute inflammation that causes pain, but it can persist for years and provoke damages that can result in chronic diseases.

Inflammation is one of the primary mechanisms developed by nature to maintain our body's health and immune homeostasis [which is the stable balance and condition of the organism and its bodily functions] against the thousands of attacks we receive every day from the surrounding environment.

When this response is not properly regulated, the concentration of inflammatory markers rises and remains high, leading to a physiological status known as chronic inflammation.

Low-level Chronic Inflammation

Here are the main possible consequences of chronic inflammation, at the level of the various systems:

Brain and central nervous system: Alzheimer's disease, Depression. ¹

Cardio-circulatory system: Myocardial infarction, Atherosclerosis, Arteriosclerosis. ³

Organism in general: Diabetes, Metabolic Syndrome, Dismetabolism. ⁵

Sexual health: Impotence, Organic Dysfunctions. ⁷

Bone system: Osteoarthritis, Osteopenia, Osteoporosis. ²

Immune system: Cancer, Fibromyalgia, Chronic Fatigue Syndrome. ⁴

Skin: Wrinkles, Cellulitis. ⁶

Therefore, silent inflammation is one of our biggest challenges.

Thanks to recent progress in molecular biology, today we know more about the relationship between what we eat and the genetic expression of our inflammatory genes. This is also useful when choosing which supplements to add to our diet, in order to address specific conditions.

1. http://www.who.int/medicines/areas/priority_medicines/BP6_11Alzheimer.pdf
2. <http://www.who.int/bulletin/volumes/81/9/PHC.pdf>
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3488800/>
4. <https://www.nature.com/articles/nature01322>
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1087185/>
6. <https://onlinelibrary.wiley.com/doi/10.1111/j.1473-2165.2005.00194.x/full>
7. <https://academic.oup.com/eurheartj/article/27/22/2640/2887469>

Low-level Chronic Inflammation

Turmeric has a long history of dietary and also medicinal use in India to treat many conditions.

Modern studies on turmeric have validated most of its traditional uses and its potential to address the natural living conditions typical of Western peoples.

Dietary intake of curcumin in Asian countries can reach 200mg/day.

Today, curcuminoids are in fact one of the most studied herbal therapies in the world. ⁸

8. Ronald Ross Watson, *Foods and Dietary Supplements in the Prevention and Treatment of Disease in Older Adults*, Elsevier Science, 2015, p. 16.

As a result, curcumin has emerged as a main switch to address the response function to CHRONIC INFLAMMATION, with a both direct and genomic activity on relevant enzymes, transcription factors and cytokines.

The reputation of curcumin as a powerful anti-inflammatory substance is therefore increasing. It is actually believed to affect various stages of the inflammatory progression at the molecular level. In short, its action blocks the molecule known as NF-kB, which penetrates into the cell nuclei and triggers the genes related to inflammation. It is noted that NF-kb appears prominently in many chronic diseases.

That said, and without delving deeper into the complicated nature of inflammation, the most important thing to remember is that the bioactive substance of curcumin fights inflammation at the molecular level. ⁹

9. Ronald Ross Watson, Victor R. Preedy - *Bioactive Foods as Dietary Interventions for Arthritis and Related Inflammatory Diseases*, Ch. n.5, Appendino, Togni, p. 66-81.

**Low-level
Chronic
Inflammation**