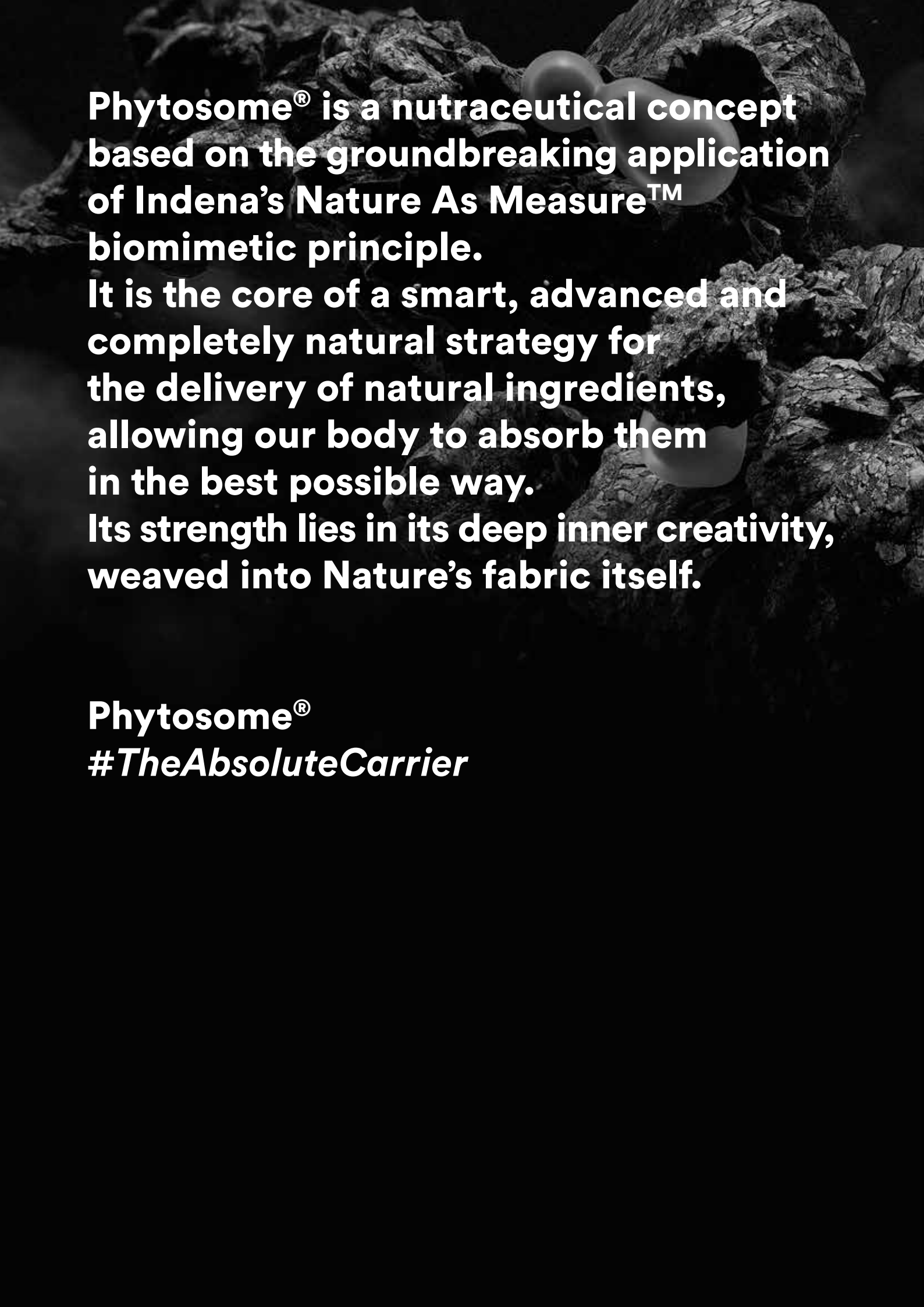


phytosome®

THE BIOMIMETIC DELIVERY SYSTEM



Phytosome® is a nutraceutical concept based on the groundbreaking application of Indena's Nature As Measure™ biomimetic principle.

It is the core of a smart, advanced and completely natural strategy for the delivery of natural ingredients, allowing our body to absorb them in the best possible way.

Its strength lies in its deep inner creativity, weaved into Nature's fabric itself.

Phytosome®
#TheAbsoluteCarrier

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Executive summary

Bioavailability is widely recognized as a central issue in the nutraceutical field. However, as many companies today tackle it with complex approaches and obscure communication strategies, consumers are often left confused and unable to evaluate products' quality.

With almost a century of history and scientific know-how on its side, Indena has long claimed that focusing on bioavailability alone is reductive to say the least.

The real goal should be to optimize bioabsorption levels, while upholding extracts' safety, effectiveness and tolerability. Indena has in fact reached this goal, by embracing the Nature As Measure™ biomimetic principle.

Nature As Measure™ perfectly reflects the concept of **innovation inspired by Nature** that stems from **biomimicry** – from the Greek *bios* = life and *mimesis* = imitate. Nature has already solved many of the problems that we face today: plants and microbes are expert engineers and have already discovered, out of necessity, what works, what fits, what lasts and why.

Nature, therefore, is the standard we should use to judge whether a product, process or technological innovation is suitable, sustainable and correct in terms of form, strategy and ethics.

It is on this premise that Indena has developed its Phytosome® formulations.

Introduced for food supplements, **Phytosome® is a biomimetic delivery system that optimizes the bioabsorption and pharmacokinetic profile of natural-origin compounds, using exclusively food-grade excipients – namely, lecithins.**

Phytosome®'s food-grade matrix maintains the original structure, complexity and chaos of natural substances, in line with the Chaos is the New Order principle.

This eliminates the need for chemical derivatives, pharmaceutical adjuvants or new chemical entities, effectively making Phytosome® safe and well tolerated over time.

Strict human studies, backed-up by pre-clinical trials, have proven Phytosome® formulations offer optimized solubility in gastrointestinal fluids, pharmacokinetic profiles and effectiveness, compared to non-formulated botanical extracts.

Indena compounds almost 100 years of expertise and experience with state-of-the art technological equipment and constant efforts towards quality. This has allowed Phytosome® formulations to be mass manufactured while still guaranteeing the natural component's matrix can be reproduced, controlled and verified batch after batch.

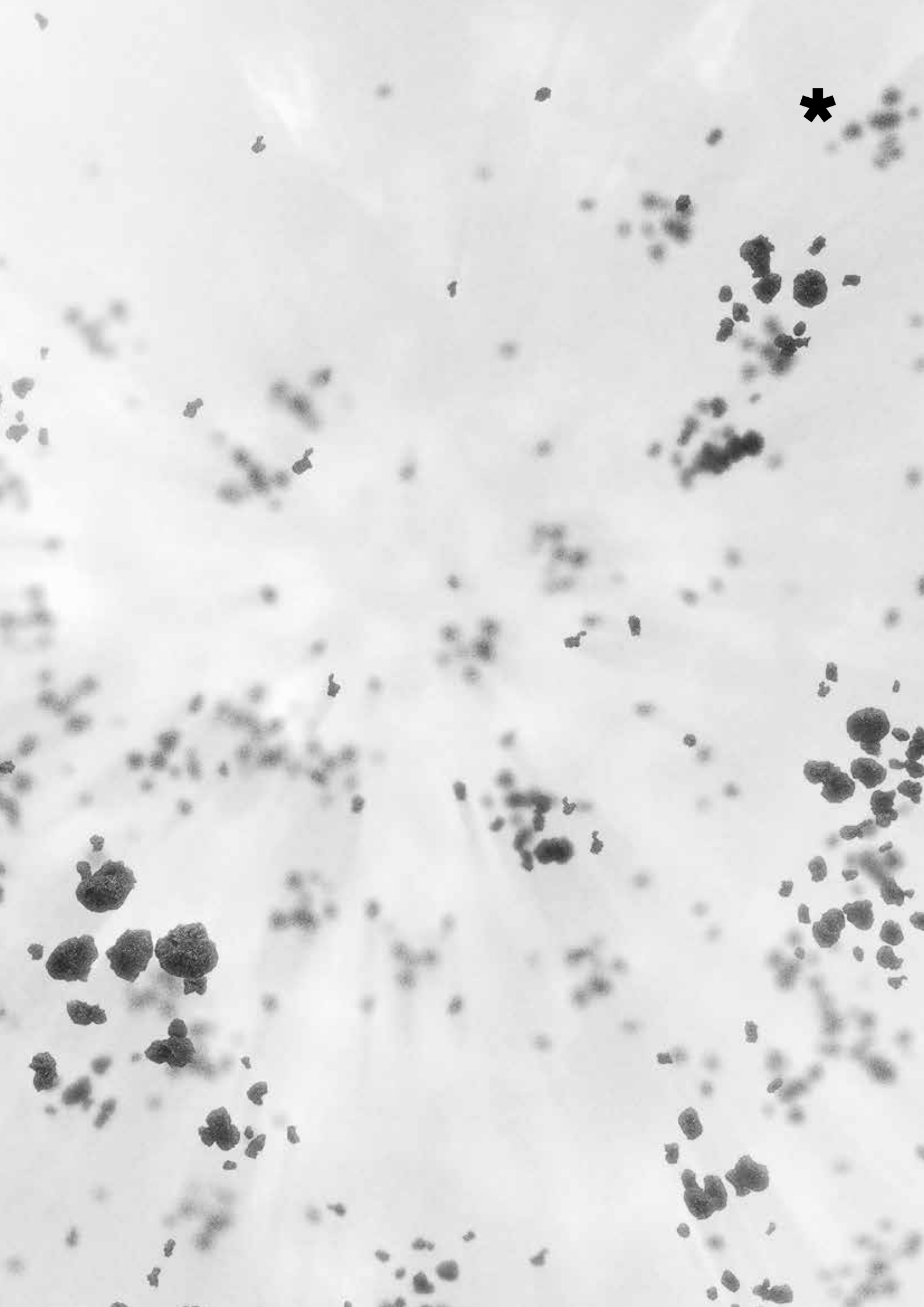
Indena's biomimetic approach

You might be surprised of how much and what powerful innovation stems from mimicry. The key, of course, is in mimicking the right thing.

Indena has long recognized the incredible potential of imitating biosystems – Nature's model for diffused and creative intelligence – in order to recreate every process that occurs in molecules or their larger and more complex assemblies, such as enzymes and proteins.

Mimicking Nature has proven a constant challenge for a whole generation of biologists and organic, inorganic and physical chemists. Indena sees it as more than that: it is its calling – not a shiny marketing claim, but the company's true scientific mission. With rationality, great attention and solid vision, for years Indena has tackled a topic that today has become a focal point for the future of nutraceuticals.

By championing the conscious use of natural derivatives, the company has upheld an approach to the imitation of Nature that improves rationalization, simplification, tolerability, health and safety for its consumers.



Background and reference market

According to Nutrition Business Journal 2017 report, **the global herbs & botanicals sector reached \$31.1 billion in 2016, with 6.3% growth, representing 25.6% of the global supplements industry. Strong growth is projected through 2020, with an estimated CAGR of 6.8%, reaching \$40.5 in annual sales.**

However, the exciting opportunities offered by this vibrant international market are hindered by rules and regulations that are heterogeneous and often lag behind consumer needs – forcing companies to adapt their R&D strategies to a complex legal context.

In this challenge, the quality of the herbs used to make standardized natural derivatives – such as extracts – is often critical.

In order to meet the requirements set forth for nutraceuticals, guidelines on good agricultural and collection practices (GACP) and good manufacturing practices (GMP) must be followed, allowing for the definition of standardized products that may be reproduced industrially and verified for safety and effectiveness through the necessary validation.

Indena, in particular, has always considered it a top priority to fine-tune high-grade standardized natural extracts. Indeed, going beyond all expectations, it was *standardization* that opened the door to the company's consistent scientific research on *bioavailability*.



The issue of bioavailability

Oral bioavailability can be defined as the percentage (or fraction) of a compound that reaches systemic circulation (in its active form) after ingestion (compared to the 100% bioavailability, by definition, of an identical dose administered intravenously).

While not hinged on the type of stringent legal requirements that dosages or health claims must comply with, it is a crucial aspect in designing new nutraceuticals.

The problem is oral bioavailability is very low in many botanical ingredients.

Most botanical nutraceuticals are based on well-purified extracts. Purification often allows scientists to better understand the chemistry of a product and manage it, but it also leads to a further substantial decrease in oral bioavailability. Indeed, **purification may eliminate the companion substances present in the original source, the ones contributing to its whole stability.**

Many phytoconstituents easily dissolve in water yet are not absorbed well due to their hydrophilicity which limits their ability to pass through enterocytes' lipid-rich external membrane in the small intestine.

On the other hand many phytoconstituents are characterized by very poor water solubility which limits their dissolution in the gastro-intestinal fluids, enhancing their self- aggregation and limiting their absorption.

To solve this issue, the nutraceutical sector has come to embrace the idea that products should be designed according to a rational strategy: one that gives paramount importance to the bioavailability of ingredients and disregards the exoticism that unfortunately is often the true, and only, motivation behind new formulations.

Therefore, over time, liposomes, micelles, nanoparticles, nanoemulsions, microspheres and various other complexes have been used to improve bioavailability. But while partially effective, none of these solutions can compare to the one pioneered by Indena.

The Indena strategy



As early as the mid-1980s, Indena confronted the issue of bioavailability focusing its research on Phytosome®s.

Phytosome®s are molecular formulations in which phospholipids act as vectors for natural active ingredients that are insoluble and tend to self-aggregate, such as polyphenols, terpenes or saponins. By recreating kinetic aspects lost during purification, Phytosome®s determine a significant increase in ingredients' bioavailability.

Indena was able to look ahead of its time, and follow a vision focused solely on natural extracts. It observed Nature, deciding to respect rather than alter it. Its approach was simple, yet extraordinary. And it led to a simple, yet extraordinary result: Phytosome®. Little importance was given to bioavailability in scientific research before the launch of Phytosome®: Indena is proud

to have started the conversation on the issue, although today many players in the market exploit the terms “bioavailable” or “bioavailable form” simplistically. Not only are empty marketing claims quite frequent, but **some competitors – in the name of bioavailability – resort to pharmaceutical strategies such as the use of chemical surfactants, instead of food-grade substances.** Their goal is to increase bioavailability as much as possible. Yet it is important to note that high bioavailability has never been the subject of rigorous studies.

Indena takes distance from this approach.

The company's goal is never to merely increase the absorption of its natural derivatives: Phytosome® solutions simply achieve the levels of bioabsorption that are appropriate for the active principle they contain.

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 biomimicry in literature and its philosophical origins, Indena distilled the concept of Nature As Measure™.

Nature as Measure™

The strength of biomimetics lies in seeing **Nature as the measure and the standard we should use to judge whether a product, process or technological innovation is suitable, sustainable and correct in terms of form, strategy and ethics.**

The central idea is that Nature has already solved many of the problems we face today: plants and microbes are expert engineers and have already discovered, out of necessity, what works, what fits, what lasts and why.

After 3.8 billion years of evolution and development, biomimetics is here to announce that fossils are the failures, and what surrounds us is the secret to survival.

Nature, and only Nature, can show us the most suitable solutions – in qualitative and quantitative terms – for any given context.

This is why Indena has chosen the Nature as Measure™ biomimetic principle to design its active ingredients based on natural extracts in Phytosome® form.



The basic steps in the company's biomimetic design approach are:

— 1

Identify the needs and develop a brief.

— 2

Translate the research question into biology's terms, i.e. express the project brief from a biological point of view.

— 3

Explore and study how Nature has solved the problem. How does it perform (or not perform) a function?

— 4

Discover examples in Nature that overcome the challenge.

— 5

Synthesize: find successful models and patterns in Nature.

— 6

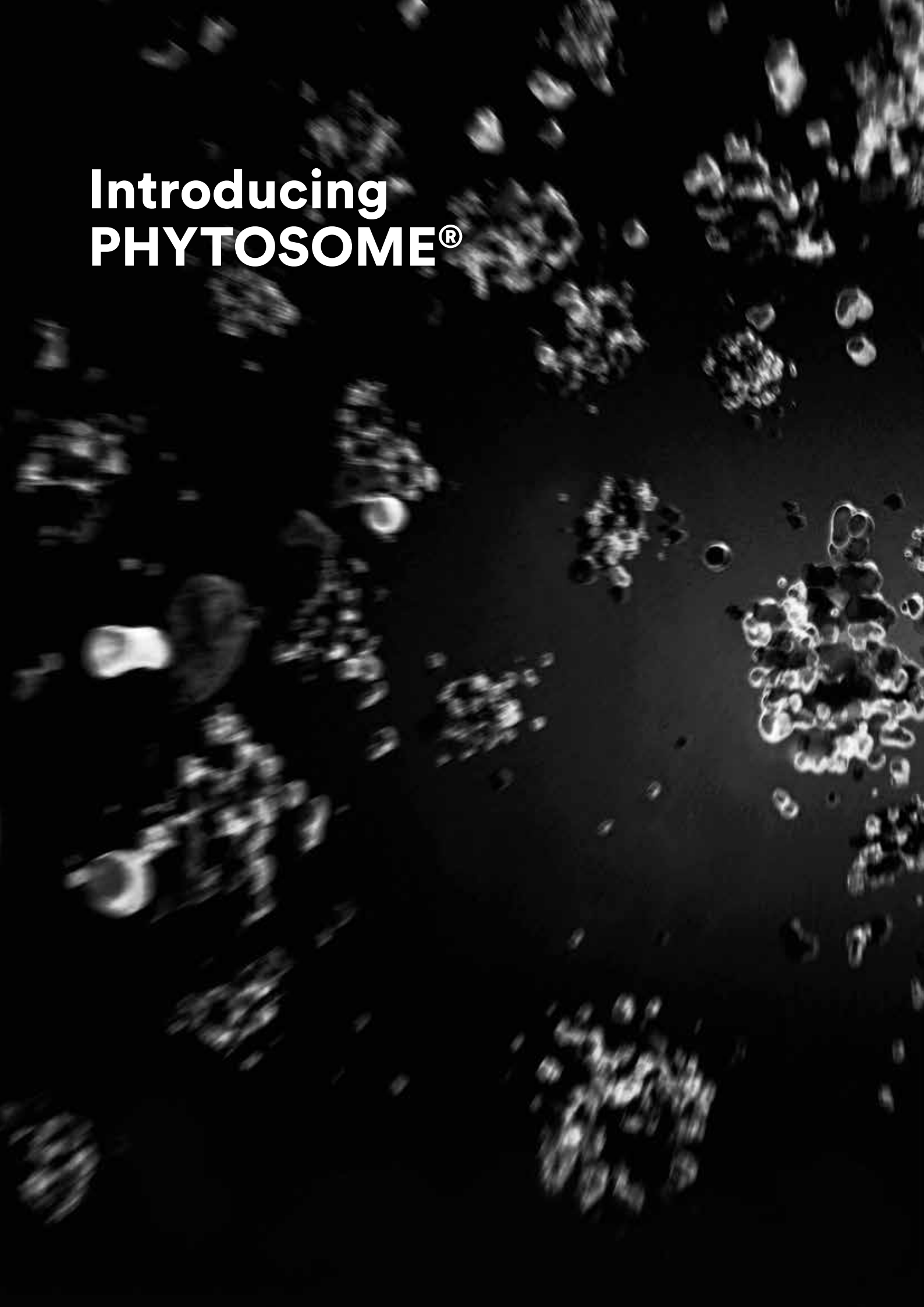
Emulate: develop ideas and solutions based on natural models.

— 7

Evaluate the alignment of the identified solution with the initial brief, as well as with the principles of life that grant success in Nature.

Today, researchers who embrace biomimetic approaches have barely scratched the surface of biological inspiration. Biologists in every field of specialization have extraordinary knowledge that can lead them to explore the much richer diversity of natural systems – helping, encouraging, orienting and electrifying experimental approaches.

Introducing PHYTOSOME®





The Absolute Carrier

The Phytosome® solution

With Phytosome®, Indena had the breakthrough intuition of blending a beneficial botanical ingredient with something that already exists in the human body: phospholipids.

With a super-hydrophilic “head” and super-hydrophobic “tails”, phospholipids like lecithins easily combine with molecules – improving their wetting, preventing them from self-aggregating and changing their physical state.

Phytosome® formulations are an emulsion in which lecithins break up, in a soft and fluid way, the interactions that lead to phytoconstituents’ self-aggregation.

The human body then recognizes phospholipids as its own and lets Phytosome® forms carry ingredients through membranes, optimizing bioabsorption.

Although there are a variety of phospholipids available on the market, Indena has chosen to work exclusively with lecithins: natural surfactants that – together with bile salts – take part in the physiological absorption process of lipophilic compounds in our body.

COMPLEX vs DELIVERY SYSTEM

Phytosome® is not a “complex” – although it was described as such until recently. Indeed, it is not a new chemical entity (NCE) and has no defined structure with strong covalent bonds.

Phytosome® is appropriately defined as delivery system, simply highlighting what it does best: carrying an active principle to its target, in the most natural possible way.

A NEW SCIENTIFIC PARADIGM: CHAOS IS THE NEW ORDER

Phytosome® is more effective than ordered structures because its internal chaos is able to carry more of the ingredient – while liposomes, for examples, can carry only as much as micelle size allows.

Phytosome® is not a mechanical blend but a physical process – in which even state-of-the art techniques like solid-state NMR have failed to evidence the presence of ordered structures like liposomes.

Phytosome® does not transform or alter: it creates movement, motion, mobility. It disaggregates and brings chaos – but leads to a superior, non-structural order.

Phytosome® is a disordered system that constantly seeks for balance, according to natural laws. Indeed, its scientific value lies exactly in its entropy.

During research and development, each Phytosome® formulation is specifically designed to optimize the bioabsorption of a specific botanical extract.

The final product's functional properties are fine-tuned by modulating and controlling every factor in the process. Phytosome®'s physical properties and technological features allow Indena to optimize the dissolution profiles and, consequently, the bioabsorption of natural ingredients; at the same time, they make the formulation process easier and allow Phytosome® to be used in a variety of dosage forms.

A black and white electron micrograph showing several spherical lipid vesicles of varying sizes. Some vesicles are intact and show a clear membrane, while others appear to be in the process of fusing or have released their contents. The background is dark and textured.

WHAT MAKES PHYTOSOME® UNIQUE

Phytosome® is made up exclusively of natural elements.

The food-grade quality of its formulations – fit for pharmaceutical, cosmetic, as well as nutritional uses – makes it a unique product on the market.

Phytosome® is based on Indena's revolutionary approach. It optimizes the solubility and bioabsorption of phytochemicals by reducing the self-aggregation of natural compounds.

Following the Chaos is the New Order philosophy, it embraces the original chaotic Nature and complexity of natural substances – and therefore has no need for chemical derivatives, pharmaceutical adjuvants or new chemical entities. Because it does not alter the structure of its ingredients in any way, Phytosome® is safe and well tolerated over time.

At Indena, innovation and evolution are constantly inspired by the imitation of our body's natural mechanisms, in line with the Nature As Measure™ biomimetic principle.

PHYTOSOME®: A STRONG CORPORATE IDENTITY ASSET

There will always be a strong bond between Indena and its key innovation, Phytosome®.

Indeed, if Phytosome® has become an international synonym for optimized bioavailability it is thanks to Indena's constant effort to foster its evolution, making it a rare example of innovation.

ABOUT INDENA

Indena compounds **almost 100 years of expertise and experience** with state-of-the art technological equipment and constant efforts towards quality. This has allowed Phytosome® formulations to be mass manufactured while still guaranteeing the natural component's matrix can be reproduced, controlled and verified batch after batch.



Phytosome® highlights

- * Food-grade dietary ingredients only
- * No synthetic ingredients or adjuvants
- * Optimized bioabsorption of natural phytochemicals
- * Tailor-made for selected natural compounds
- * Already applied at industrial scale
- * Free of nanoparticles
- * Suitable for formulation in all the most common dosage forms
- * IP and proprietary know how available
- * Supported by strict scientific tests
- * An effective delivery system, based on decades of experience, know-how and pioneering innovation by Indena

6.





Phytosome[®] at a glance

PROBLEM STATEMENT

Botanical nutraceuticals and natural compounds often feature poor water solubility and limited intestinal absorption, which hinder oral bioabsorption.

WORK ASSUMPTION

To achieve adequate bioabsorption, natural products must balance hydrophilia (so they can dissolve in gastrointestinal fluids) and lipophilia (to pass through lipidic biomembranes).

SOLUTION

Indena has developed Phytosome®, the 100% food-grade biomimetic delivery system that optimizes bioabsorption and the pharmacokinetic profile of natural botanical ingredients, by formulating them with a dietary ingredient (lecithin).

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Call To Action / Contacts

*Imagine how Phytosome®
– as THE ABSOLUTE CARRIER –
can make natural active
ingredients more effective
in any personal health regimen:*

Cater to your target market with
breakthrough innovation, improving
the perception of your products' value.

Open up new market opportunities
by increasing consumers' knowledge
and consciousness about the actual
effectiveness of botanicals, nutraceuticals
and natural compounds.

Strengthen your customers' brand
advocacy and loyalty, thanks to
the powerful marketing and popular
science communication program
Indena will deploy, about Phytosome®
as THE ABSOLUTE CARRIER of
your natural botanical ingredients.

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