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## A DEEPLY ROOTED CDMO

*by Stefano Togni*

The roots of Indena go back to 1921. This was the year in which Dr Carlo Boccaccio Inverni offered a series of extracts from medicinal plants to the nascent Italian pharmaceutical industry, until then dependent on foreign suppliers. Right from the start he was concerned about product quality and sought to counteract the adulterations implemented by less qualified suppliers.

This problem is still present in the pharmaceutical world, albeit in other forms, as demonstrated in the recent cases of the presence of genotoxic impurities and malicious violation of data integrity. It was not long before the company became a sector leader and since its inception the group has evolved incessantly, investing continuously in a spirit devoted to innovation, service and quality which has remained unchanged and intact. The Italian pharmaceutical system has evolved at a similar pace, and Italy is now the foremost API producer in Europe.

For years now, the main focus for Indena has been on custom development and manufacturing (CDMO) and this has become one of the most important factors in its success and evolution.

The production of taxanes on behalf of a multinational pharmaceutical company was a turning point for the company in the early 90s, as it entered the cytotoxic sector. Based precisely on this thirty-year experience in high containment, Indena has recently expanded its technological capability, with the opening of another kilolab for natural and synthetic high-potency products (OEL of 20 ng/m<sup>3</sup>).

To provide its partners with an increasingly flexible service, in 2019 the company completed the following installations: a PSD2 spray dryer capable of operating in the presence of organic solvents (this capitalizes on a twenty-year experience in this area and integrates a large-scale industrial spray dryer for the intermediate phases); a pilot plant for the preparation of active pharmaceutical ingredients, bringing together all the medium-scale extraction and synthetic technologies of the group; a multipurpose 100 to 20,000 litre fermentation plant capable of handling toxic compounds. These significant new technological investments are a tangible sign of the company's ability to continue to progress and offer partners a high level of service, at the same time enhancing the human capital of its operators in terms of dedication and know-how.

It is not only machinery however which creates value for our customers; this is also ensured by the operators supported in an integrated approach by colleagues in other company functions such as R&D, Industrial Operations, HSE and Business Development in line with clear company policy. It is in fact in a relationship of mutual trust that these customers entrust to Indena the development and

production of a new molecule or extract, an asset on which often the entire destiny of the client company depends.

Some 56% of all pharmaceutical and biotech companies are now estimated to resort to outsourcing for the synthesis of small molecules in the clinical phase, and about a third do so for their commercial molecules.

At the same time, we are seeing a return to qualified Western suppliers, moving against the trend recorded in previous years, in which Asian suppliers were the preferred choice. Repeated concerns about quality and serious deficiencies in safety have led to dramatic events as well as being a major and self-evident ethical issue; against any potential monetary savings, the risks are too high in terms of continuity for the development a new drug. Sustainability and the adequate management of environmental issues has always been given the maximum importance by Indena; for this reason the production sites of the group have long held ISO14001 certification for the management of their environmental impact and the OHSAS18001 certification for the health and safety of workers, the most valuable resource for any company.

The recent plant developments implemented by Indena, does not mean the company intends to distort its positioning: natural derivatives remain one of the strengths, but the adoption of new technologies (synthesis, fermentation, spray drying on an intermediate scale) enables the company to capitalize on decades of business know-how with complex molecules. As the centenary celebration of the foundation approaches, Indena continues to evolve while the mission remains unchanged: offering a safe haven to innovative companies for the production and clinical development phase of their active commercial ingredients.





Nutra

## PHYTOSOME®: CHAOS IS THE NEW ORDER

### **BOTANICAL EXTRACTS: PRECIOUS THOUGH OFTEN HARD TO ASSIMILATE**

Natural products have been used since ancient times and often form the basis of traditional medicines. Today the importance of their role in protecting and maintaining people's health is widely recognized: it is also through these products that nature can exert its beneficial effects on man. However, the potential of nature does not always manage to express itself fully. Substances which derive from edible plants and natural compounds are indeed often difficult to dissolve in water and hard to absorb by the intestine; this has a negative effect on the bioavailability of these substances.

This is not all however. Optimal bioabsorption requires natural products to strike a good balance between hydrophilicity (the ability to dissolve in gastrointestinal fluids) and lipophilicity (passing through the lipid membranes of cells).

By way of example, many phytocomponents such as glycosylated polyphenols have good water solubility but are still poorly absorbed [1] both because of their large size, which prevents passive transport, and because of their low aptitude to mix with oils or other fats. The result is a very limited ability of flavonoids to cross the outer membrane of the enterocytes of the small intestine which is rich in lipids.[2]

Moreover, natural compounds are natively available in complex forms and matrices which, although this accounts for the beneficial effects of these substances, also means they need to be optimized to improve their physiological absorption levels.

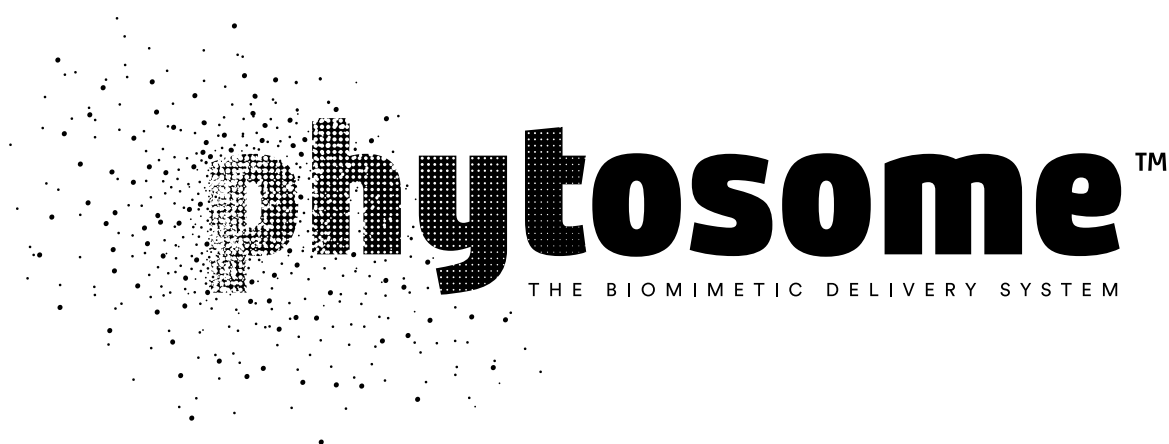
### **INDENA AND THE PHYTOSOME® REVOLUTION USING THE BIOMIMETIC APPROACH**

For many years now Indena has adopted a biomimetic approach to its research: from bios meaning life and mimesis meaning imitation [3],

the company has applied this approach to the study of a solution that would improve the bioabsorption of natural active ingredients while fully maintaining their profile and effectiveness. Phytosome® is the answer; this is the delivery system developed by the company to improve the bioavailability and the pharmacokinetic profile of active compounds of natural origin using 100% food grade ingredients (lecithin).

Lecithins are natural surfactants which, together with bile salts, participate in the physiological process of absorption of lipophilic compounds and constitute the lipid bilayer of cell membranes, making even water-soluble compounds easily absorbable, for example by the intestine. As an amphipathic molecule composed of a polar head and two neutral apolar tails, lecithin acts as an inhibitor of self-aggregation, leaving poorly soluble compounds in a dispersed state which is absorbed more rapidly.

Phytosome® provides therefore a natural way of obtaining a solid dispersion of compounds that are poorly bioavailable orally and that can promote the solubility of natural substances and their bioabsorption, reducing self-aggregation.



#### **A NEW SCIENTIFIC PARADIGM: CHAOS IS THE NEW ORDER**

The Phytosome® delivery system, known as Nature as Measure™, developed by Indena using the biomimetic approach, allows the original chaos of natural products to be maintained without using chemical derivatives, new chemical entities, pharmaceutical adjuvants or structural modifications, thereby ensuring the safety and tolerability of the active ingredients.

Tests carried out according to rigorous scientific criteria show that the botanical extracts formulated with Phytosome® present greater solubility in models that simulate gastrointestinal fluids, and higher pharmacokinetic and efficacy profiles compared to non-formulated extracts.

Indena's deep-seated knowledge and long experience in industrial processes and production, state-of-the-art instrumentation and equipment have enabled the company to produce Phytosome® formulations on a large scale, ensuring the reproducibility of the natural component matrix, with each and every batch controlled and guaranteed.

Some examples of botanical extracts formulated with Phytosome® technology are: Siliphos® (silymarin and silybin), Greenselect® (green tea polyphenols), Meriva® (curcumin), Casperome® (*Boswellia serrata*), Quercifit™ (quercetin) and Vazguard™ (polyphenols of bergamot).

Finally, the physical and technological characteristics of Phytosome® allow effective formulation processes, making the active ingredients available at different dosages and with various formulations for oral use such as tablets, capsules, softgels and granules.

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# DRUGS AND QUALITY SUPPLEMENTS: A POSSIBLE, EVEN EFFECTIVE COHABITATION

## **POLY THERAPY AND POLYPHARMACY: THE NEEDS OF TODAY'S WORLD**

Rising standards of care and the progress of medical science have led to improved health conditions in the world over recent centuries. A natural consequence of this phenomenon on most of the planet is that people are living longer: according to United Nations figures, the world's population aged 60 or over amounted to 962 million individuals in 2017, and the number of elderly people is destined to double by 2050 when it is expected to be around 2.1 billion.[1]

A further consequence of aging is the simultaneous occurrence of different pathologies which creates the need for polytherapy and polypharmacy (i.e. the use of different products for different treatments for the benefit of the same subject); this in turn raises the issue of monitoring and managing the phenomenon of drug interactions.[2-3]

Another significant development in recent decades has been the growth in complementary health maintenance approaches, based for example on foods and plants that have proven to be effective for people's well-being.[4] It has become fundamental in this scenario, to study and understand if and how the ingredients contained in foods and plants interact with the drugs normally used.

The major causes of risk to the health and well-being of elderly people are linked to cardiovascular, cerebrovascular and metabolic phenomena [5-6] and the most frequently prescribed drugs in these cases are anticoagulants and anti-aggregants.[7-8] There is also an increase in the spread of diabetes, which according to the World Health Organization has almost doubled since 1980 and now affects around 8.5% of the adult population.[9]

Control over the possible interactions between drugs and foods, including some food supplements, is therefore particularly important.

## **INDENA INGREDIENTS AND MEDICINES: WELL-BEING IS FIRST AND FOREMOST**

The study of possible interactions between botanical derivatives and medicinal drugs is one of the areas to which Indena dedicates resources and research, with the scientific approach typical of the company. To date it has been applied to Phytosome® quercetin and Phytosome® curcumin.

Quercetin is a flavonoid widely found in vegetables and fruit. The main natural sources of this compound are walnuts, apples, onions, tomatoes, broccoli, lettuce and green and black teas. [10] Researchers have, in recent years, begun to investigate the many important biological activities of quercetin, and interest in this flavonoid has grown considerably in the health and wellness sectors.

Quercetin, like many other natural compounds, displays certain disadvantages such as low solubility and poor oral absorption. The Indena product Quercefit™ is based on Phytosome® technology which optimizes the biological absorption of the flavonoid. As further proof of the excellent safety profile of Quercefit™, a pilot study was conducted to investigate any possible interaction of this natural product with pharmacological treatments.[11]

Preliminary results suggest that taking Quercefit™ may not alter the anti-aggregating activity of the most common antiplatelet agents (acetylsalicylic acid, ticlopidine or clopidogrel after 10 days of

administration); it does not have adverse effects in subjects treated with common anticoagulants such as warfarin or dabigatran (after 20 days of integration); and finally, it may not influence metabolic control in diabetic subjects treated with metformin.

Meriva® is the Phytosome® curcumin produced by Indena and used to help maintain good health and in particular osteoarticular and muscular efficiency. Any possible interaction between Meriva® and antiplatelet agents, anticoagulants or thyroid hormone replacement therapy was analysed.[12] Interaction with antiplatelet agents was evaluated by measuring the anti-aggregation activity with the bleeding time in subjects who had been taking acetylsalicylic acid, ticlopidine or clopidogrel for at least 2 years before and after 10 days of taking Meriva®. Interaction with anticoagulants was measured in subjects who used warfarin or dabigatran for previous episodes of venous thrombosis, and International Normalized Ratio (INR) levels were assessed before and after 10 days of Meriva® intake. In subjects with hypothyroidism who took LT4 replacement therapy, thyroid functions were checked before and after 15 days of Meriva® intake. Finally, in diabetic subjects treated with metformin, blood glucose and glycated haemoglobin levels were measured before and after 10 days of Meriva® intake.

The results of the study suggest that the Phytosome® curcumin produced by Indena may not interfere with the activity of the most common anti-aggregating agents and not modify the INR values in subjects in stable conditions who are taking warfarin or dabigatran. Similarly, in subjects taking Meriva® as a complementary treatment the dosage of LT4 and metformin may not be modified.

These findings, although preliminary, are good news for all subjects who need to adopt different and complementary treatment approaches, relying both on medicinal drugs and the treasure trove of nutraceuticals and in particular food supplements of quality.

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# PROBIOTICS AND BOTANICAL EXTRACTS: AN ALLIANCE FOR GUT HEALTH

## THE DIFFICULTIES OF MODERN LIFE FOR THE INTESTINE

Stress, our increasingly pressing commitments, the speed and intensity of our daily routine: these are aspects of the contemporary lifestyle that have repercussions on health and in particular on that of the intestine.

It is not surprising therefore that there is a constant increase in gastrointestinal dysfunctions, such as dyspepsia and irritable bowel syndrome. IBS affects about 10% of the population, especially women and with a higher rate of prevalence those between 20 and 50 years.<sup>[1]</sup>

Preventing or minimizing these disorders requires a healthy lifestyle, starting from a careful and personalized diet. These are commitments however that are often not easy to maintain, or difficult to pursue in a consistent manner. For such cases natural supplements such as probiotics and botanical extracts can be a valuable help.

## THE ROLE OF PROBIOTICS AND BOTANICAL EXTRACTS

Defined by FAO and WHO in 2001 <sup>[2]</sup> and more recently by the International Scientific Association for Probiotics and Prebiotics (ISAPP) <sup>[3]</sup>, probiotics represent those “living microorganisms that, when administered in adequate quantities, provide a benefit to the health of the organism that hosts them”.

Taking probiotics to maintain the balance of the intestinal microflora makes it possible to obtain a condition of well-being of the intestine both in the case of simple digestive disorders (dyspepsia) and in the presence of real diseases of varying severity, such as Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD).

Alongside probiotics, another important source of useful substances for the health and balance of the intestine is provided by botanical extracts which are used in functional foods and supplements.

From these botanical extracts, Indena has developed high quality ingredients with great potential for gastrointestinal and digestive well-being: Prodigest<sup>®</sup>, a unique and synergistic combination of artichoke and ginger extracts; and Casperome<sup>®</sup>, a formulation of *Boswellia serrata* produced with Phytosome<sup>®</sup> technology to ensure optimal bioavailability.

The safety and overall effectiveness of the botanical extract is ensured by Indena production processes and controls which also guarantee the quality of the phytochemical profile and rigorous standardization.

## A PRECIOUS ALLIANCE

Indena needed to ascertain whether there was biological compatibility between the botanical extracts contained in its products and the various types of probiotics, and therefore prove the absence of any negative effect on the vitality of the probiotics themselves.

The biological compatibility between probiotics and natural ingredients is in fact a prerequisite for their possible integrated and targeted association, or for the future development of a single bifunctional proposal (probiotic and botanical extract).

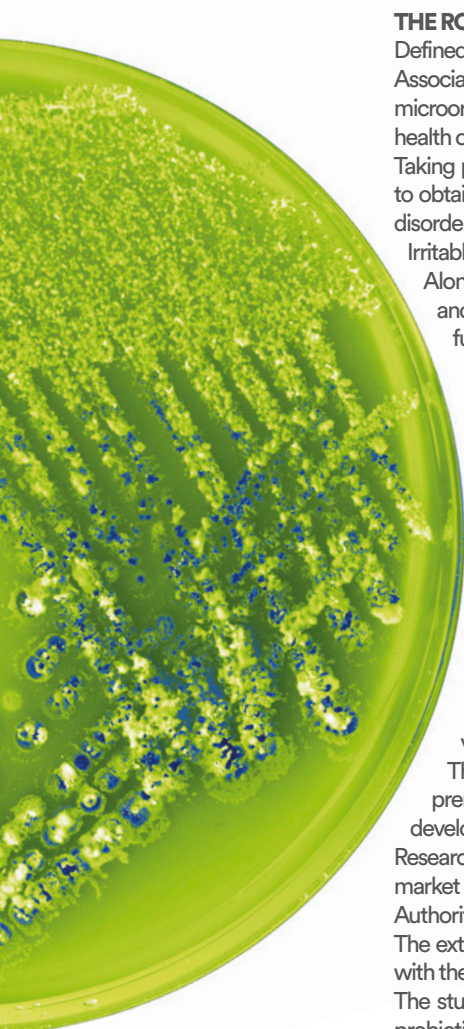
Research has recently been conducted on model probiotics, all found on the Italian market and chosen on the basis of indications provided by the Canadian Regulatory Authority (Health Canada) <sup>[4]</sup>, but also accepted by ISAPP.<sup>[3]</sup>

The extracts contained in Prodigest<sup>®</sup>, Casperome<sup>®</sup> and Meriva<sup>®</sup>, curcumin formulated with the Phytosome<sup>®</sup> delivery system were covered by the analysis.

The studies demonstrated that the microbiological stability and *in vitro* vitality of the probiotics considered were not adversely affected by the presence of the botanical ingredients, which could therefore be considered compatible with most species of probiotics commercially available for their concomitant use or even for the development of new bifunctional associations.

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# UBIQSOME®: COENZYME Q10 HAS NEVER BEEN SO READILY AVAILABLE

It is well known that Coenzyme Q10 (CoQ10) plays a fundamental role in the production and regulation of cell energy. In fact, through the cellular respiration process, it participates in the production of adenosine triphosphate (ATP), the compound used by cells to store the energy necessary for metabolic functions.

Coenzyme Q10 is recognized for its antioxidant properties and its ability to intervene in maintaining the well-being of the human organism at different levels: examples can be found in circulation, the immune system, metabolism, in the overall energy regulation available in humans, which is why it is particularly important for those who practice sport.

Coenzyme Q10 is present substantially in all cells of the human body and indeed the molecule's very name "ubiquinone" derives from this characteristic of ubiquity. It can also be taken in food as it is found in some vegetables and some meats, and especially in fatty fish.

The endogenous amount of Coenzyme Q10 may however decrease due to several possible causes, such as aging and changes in health conditions or after intense physical effort by people who do sport. In athletes the reduction of CoQ10 during the most intense workouts can cause metabolic stress and the formation of free radicals. In situations of ubiquinone deficiency it is possible to resort to CoQ10 integration, but the efficiency of this solution depends on the bioavailability of Coenzyme Q10, which is extremely variable and tends towards scarcity.

## UBIQSOME®, THE MOST INNOVATIVE FORMULATION OF COENZYME Q10 FOR OPTIMAL BIOAVAILABILITY

Ubiqsome® is the most recent product made by Indena with the Phytosome® formulation; it is an innovative formulation of Coenzyme Q10 produced industrially and standardized to contain a quantity of CoQ10 no less than 20%. With the Phytosome® delivery system, a formulation based on the use of 100% food grade ingredients (lecithin), Ubiqsome® enables optimization of CoQ10 levels in both plasma and muscles. So there is now a product available on the market which makes it possible to enhance the great potential of CoQ10 in the various situations where it is required.

## STUDIES CONFIRM THE EFFECTIVENESS OF UBIQSOME®, PARTICULARLY FOR SPORTSPEOPLE [1]

The bioavailability of Coenzyme Q10 formulated as Ubiqsome® is confirmed by the results of single and repeated dose pharmacokinetic studies conducted on healthy volunteers. The studies reveal, in the subjects examined and in comparison with an unformulated CoQ10 intake, a significant optimization of the physiological level of CoQ10 in the plasma both after a single dose of Ubiqsome® (150 mg) and after 2 weeks of treatment with two different daily dosages (150 and 300 mg).

Furthermore the tolerance profile of the different dosages was analysed, comparing the results of Ubiqsome® at a dose of 150 and those at a dose of 300 mg. The results were positive: no significant alteration of vital signs was observed in the comparison between the two treatments, either with a physical examination or with ECG.

Further scientific evidence has been gathered regarding the function and efficacy of Ubiqsome® for dietary supplementation in people who practice sports, through a randomized controlled trial in athletes between 45 and 60 years of age. Integration with Ubiqsome® for 30 days confirmed a significant increase in CoQ10 plasma levels and above all the presence of Coenzyme Q10 in the muscles, i.e. where it is needed.

Proof therefore that Ubiqsome® is a product with great potential for nutritional integration in athletes but also in any situation that requires an effective contribution of Coenzyme Q10 for the well-being and balance of the body.

Ubiqsome™

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[1] Indena data on file



# QUERCETIN: A NATURAL ALLY IN ALLERGY SEASONS

TM  
QUERCETIN

How asthma is dealt with and how to prevent attacks in those prone to it are issues that significantly impact on the health system. They also cause heavy suffering for people affected and call for careful handling on the part of general practitioners. Asthma management and prevention systems are well known but the problem is represented by the incidence of side effects associated with the various therapies used, and by the high costs for public health due to the chronic nature of the condition.

According to the GINA classification (Global Initiative for Asthma) [1] the standard management of asthma consists mainly in controlling the triggers, in monitoring and educating the subjects concerned, handling acute forms and in medicinal therapy. The main types of drugs used are bronchodilators (beta-2 agonists, anticholinergics), corticosteroids, leukotriene modifiers, mast cell stabilizers, methylxanthines and immunomodulators.[7,1] Adults who are basically healthy may also be affected causing them to take time off work as a result and visit the doctor with particular frequency.[1,2]

In this context, also taking environmental factors into account [1,2], such people may derive health benefits with the support of effective "quality" supplements.

Quercetin is a natural flavonoid occurring abundantly in green vegetables, fruit and nuts. Studies in humans have shown that Quercefit™, quercetin formulated with Indena's delivery system Phytosome®, has an excellent profile in terms of bioavailability, efficacy in sports activities and high tolerability. [3,4]

Two recent studies have shown that the administration of Quercefit™ has contributed to maintaining the well-being of healthy individuals, occasionally intolerant to environmental factors.

Early results show that Quercefit™ is potentially effective due to the persistence of a state of relative well-being in subjects who are healthy but intolerant towards certain environmental factors. The airways of these subjects were kept open and relaxed compared to the control group.[5] This provides an interesting opening for possible further studies that investigate the potential role of quercetin in this field.

In a second study on healthy volunteers who had previously taken Quercefit™ before being brought into contact with histamine, the occurrence of skin phenomena such as redness or itching proved to be limited.[6]

Such recent findings offer further confirmation of the effectiveness of Phytosome® technology in optimizing the activity of a natural compound; they also reveal the promising beneficial effects of Quercefit™ as a new and innovative ingredient to combat intolerances.

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## Personal Care

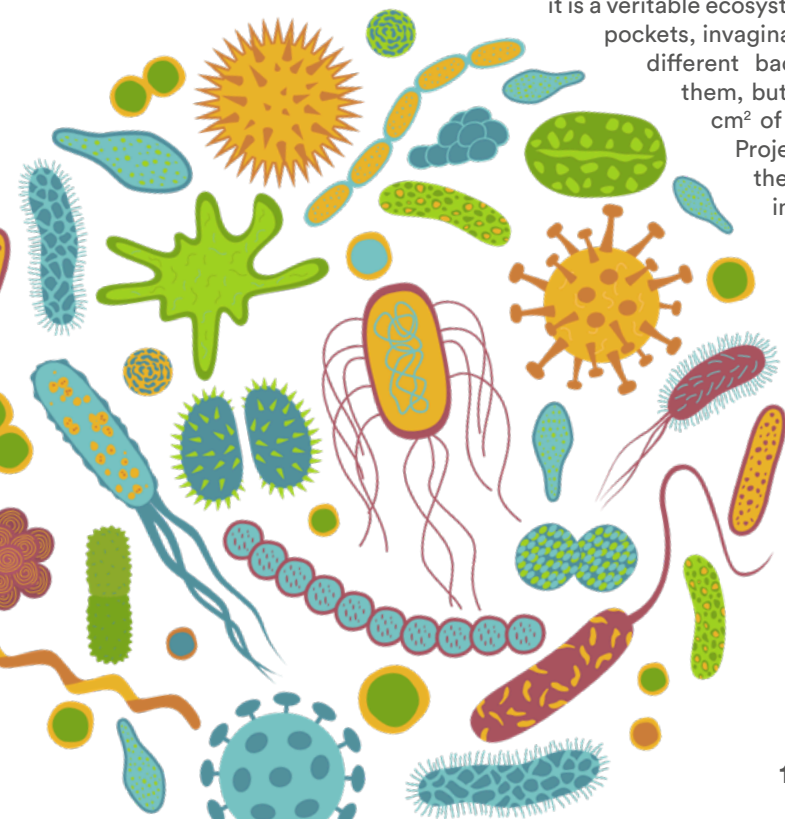
# THE HIDDEN LIFE OF THE SKIN

For some time now, alongside the research on intestinal microbiota, research on skin microbiota and its impact on skin health has been growing at the same rate. In the last 3 years alone, over 950 works have been published with the keywords "skin microbiota".

Compared to intestinal microbiota, the skin is more accessible, being exposed as it is directly to the external environment. Despite this, the correlation parameters between the enormously variable characteristics of skin flora and the functional state of the skin are not yet clearly defined.

In fact the skin is not only our interface with the external environment, it is a veritable ecosystem made up of different habitats (with pockets, invaginations and follicles suitable for hosting different bacterial populations). We cannot see them, but there are about  $10^7$  bacteria for each  $\text{cm}^2$  of skin. "Integrated Human Microbiome Project" [1] is a study which evaluated the cutaneous, nasal, oral, vaginal and intestinal microbiota of 250 volunteers grouping the bacterial populations in 4 phyla: *Firmicutes*, *Actinobacteria*, *Bacteroidetes*, *Proteobacteria*.

These resident bacteria are hidden but functionally very present on the skin; they are made up of relatively constant groups that renew themselves and re-establish their pre-existing ecological niches after a skin perturbation. Their function is to produce defence molecules



and natural antibiotics, such as bacteriocins. Transient bacteria are also present, which derive from the surrounding environment and persist on the skin for a few hours or days.

Skin flora begins to form at the moment of birth. Babies born by natural childbirth acquire bacterial communities similar to the maternal vaginal microbiota, while children born by caesarean section reveal microbiota more akin to that present on the skin of those who delivered the infant. Bacteria that live on the skin actually exert an influence on the skin surface and even below it. They in turn are strongly influenced by the physiology and genotype of their host, by the nature of the external environment, by lifestyle and by any underlying pathological conditions.

In the absence of defined correlations in a subject area still largely unexplored, a scientific approach to the study of the skin microbiota can be undertaken by the evaluation of the effect of certain active substances in the presence of cutaneous dysbiosis. An initial survey of this type involved a cohort of subjects with acneic skin that showed an overproliferation of *C. acnes*. Vitachelox™, a ternary mixture of standardized extracts based on natural polyphenols with different structures and whose synergy has been demonstrated in the protection of various cellular compartments, showed selective action against the strain causing dysbiosis, without however modifying the populations of the resident flora. The exact pathogenesis of acne is by no means completely understood, however the hyperproliferation of some strains of *C. acnes* is generally present on acneic skin. A placebo study conducted on 20 volunteers (half-face model) demonstrated the ability of Vitachelox™ to modulate resident flora, thereby protecting the skin from dysbiosis caused by *C. acnes* hyperproliferation. [2]

These results, although on a cohort of limited subjects, suggest that polyphenols of natural origin may have relevance in the selective reduction of cutaneous dysbiosis, at the same time guaranteeing protection of the resident flora with which we live in a state of symbiosis.

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Corporate

## INDUSTRY AND ACADEMIA GO HAND IN HAND

Scientific research means confrontation, collaboration and sharing. This is not always the approach that is observed however, whether in the academic world or on the part of companies.

Indena goes against this trend. Our company vocation is to promote our own high-profile research which focuses on the manufacture of quality botanical ingredients, and our policy has always been to share these studies and know-how with external scientific organizations - universities, research centres and specialist schools - through collaborations, master's degrees and seminars as well as providing high-level training for young people in the company.

The numbers confirm this. In 2019 Indena has worked with academies, research centres and international scientific consultants on over 30 projects. The company also publishes annually on average about twenty learned papers in international or Italian journals (average calculated over the two-year period 2017-2019); these articles on our findings are almost all co-written with authors from external scientific research centres who participate in the projects.

Indena R&D officers and scientific advisors represent the company at numerous congresses all over the world. Many lectures are delivered on specialization courses and guided tours of the Settala production site organised for groups of students or scientific collaborators.

The involvement of young people is seen as one of the most important aspects of sharing and collaboration with the world of research. Indena was one of the first companies in Italy to open its doors to university students offering them high-level internships thanks to collaboration with academic institutions.

Indena is in fact investing in higher education apprenticeship courses leading to a research doctorate; on the one hand, this offers a great opportunity for synergy between industry and academia (Indena enjoys a particularly fruitful collaboration with the Chemistry department of the State University of Milan) and on the other, young students can develop true professionalism when faced with the complexities and technologies of the business world.

*A "winning" collaboration, first and foremost, for the student, who has the opportunity to obtain a higher degree qualification while working within a company, receiving a salary and opening up a professional career path; coming face to face with the specificity, needs and complexity of the company, students are able to acquire skills that complement the parallel academic training they receive.*

*The educational institution is also a "winner" since the distance with the business world is shortened as it consolidates its role as a promoter of professional opportunities for its students, bringing with it a significant payback in terms of image.*

*Lastly the company itself is also a "winner", since with this special contractual arrangement and "tailored" contributions, specialist personnel from the university world can be trained internally.[1]*

When the scientific community can access the wealth of industrial knowledge and companies come face to face with the world of research as in the Indena model, the result is a win-win opportunity for all: for researchers who can acquire cutting-edge know-how, for companies to improve the quality of processes and products, for young people who can become part of a high-level professional environment. The main beneficiaries of all this collaboration however, will be the consumers who will have as a result innovative, effective, and high quality solutions to safeguard their health.

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[1] (OU-I 2018, Report Osservatorio Università-Imprese, Fondazione CRUI, 2018, pp. 37-38)

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## SOLAR POWER AT TOURS SHOWS INDENA'S COMMITMENT TO THE ENVIRONMENT

The French city of Tours in the Loire valley is the location for one of Indena's production facilities. And here at the site, with its customary concern for the environment, the company installed a large photovoltaic system in July 2018. This is a 2,100 m<sup>2</sup> installation, consisting of three 700 m<sup>2</sup> modules supplied by Ellybox, a company specialized in energy self-sufficiency. The power plant has an annual production capacity of 250 MWh, and supplies this solar electricity directly to the factory.

In addition to solar energy, Indena Tours has built its own wastewater treatment plant and employs new clean technologies for treating gas emitted into the atmosphere. These are all factors that contribute to making this factory complex a beacon of respect for the territory and its environmental setting. Indena Tours has been certified with the international standard of environmental management ISO 14001 since 2011.

A dedicated management committee has been created to effectively oversee all actions and processes concerning the sustainability of the factory. Short and medium-term objectives are defined for reducing energy and water consumption, atmospheric emissions and the production of waste, which already undergoes recycling and transformation.

The guiding principle of the Indena Group's environmental policy is "Science is our Nature". This principle has been well and truly applied at the Tours site where, as far as is possible, these initiatives are designed to conserve the resources bestowed by nature.

# COGNITIVE SUPPORT FROM THE COGNIPLANT PROJECT

Population aging is a growing phenomenon as all surveys concur. In Italy, the percentage of people over 65 has almost tripled in 100 years (from 6.1% to 17.7%) and is expected to reach around 34% of the total population in the next 50 years, almost doubling the current level.

Against this background, one issue public health services will need to address is cognitive decline as it is a widespread phenomenon amongst the elderly whether they are in good or poor health.

This is not all. A cognitive deficit can be associated with the physiological progression of aging, but may also result from conditions of stress. A state of mild cognitive impairment (MCI) is characterized by a substantial memory deficit where no other form of dementia has been diagnosed.

Recent scientific evidence shows how some products of plant origin can help to maintain the cognitive state at normal physiological levels or in line with those expected in old age. These findings suggest the effectiveness of strategies that include plant-based products in the diet of the elderly subject able to provide health-giving support during the physiological cognitive trend typical of aging.

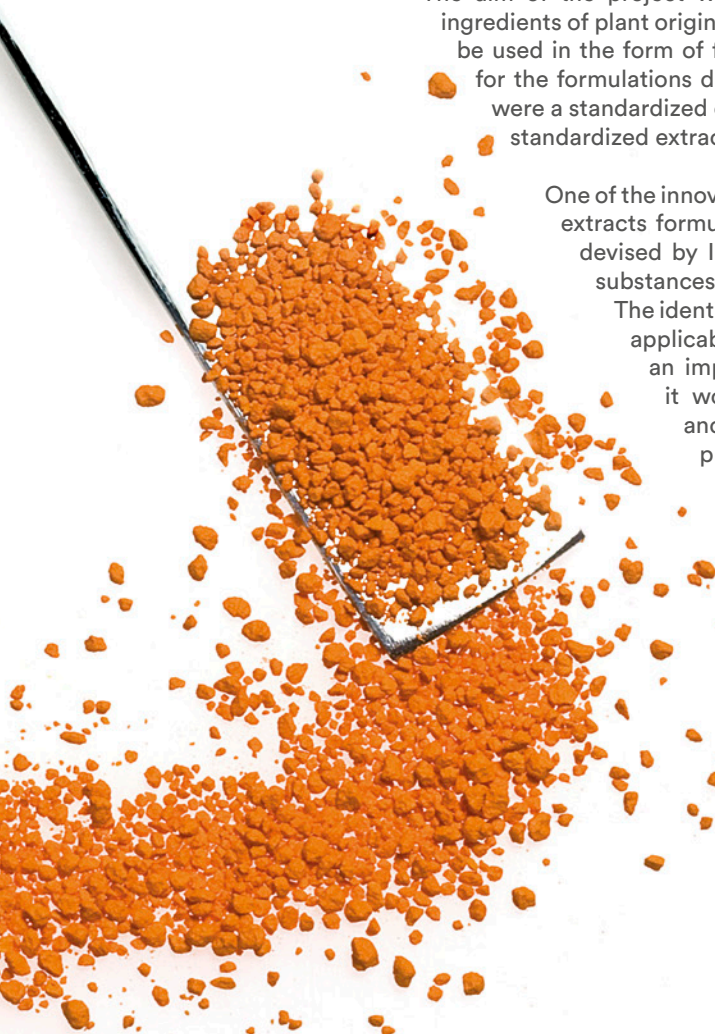
With the backing of the Lombardy Regional Government and the European Regional Development Fund (ERDF) The Cogniplant Project was promoted by a consortium including the Lombardy companies Indena, Axxam and GriarChemical, and by Milan University's Department of Pharmacological and Biomolecular Sciences (DISFeB).

The aim of the project was to develop new formulations based on ingredients of plant origin, which could aid cognition in the elderly and be used in the form of food supplements. The ingredients selected for the formulations during the development phase of the project were a standardized extract of *Centella asiatica* associated with a standardized extract of *Curcuma longa*.

One of the innovative aspects of the project is the use of plant extracts formulated with the delivery system Phytosome® devised by Indena, which is able to convey the natural substances by optimizing their absorption.

The identification of new effective biological products, applicable in the nutraceutical sector, would have an impact on the competitiveness of this sector; it would also benefit older people themselves and help to contain public expenditure in the provision of services for the elderly.

The project was completed in June 2019; both the *in vitro* tests conducted through a platform consisting of recombinant cell lines for molecular targets belonging to different classes, as well as the *in vivo* tests on healthy volunteers generated preclinical data which lend reasonable support to the use of this Indena formulation for cognitive well-being.



# ETHNOHERBS PROJECT: AN INTERNATIONAL COLLABORATION TO STUDY MEDICINAL PLANTS IN THE BALKAN PENINSULA

The EthnoHERBS project has been created to study the use of medicinal and aromatic plants of the Balkan Peninsula, with the aim of efficiently exploiting their potential for human health and well-being. This project will apply systematic ethnobotanical analysis and cutting-edge technologies and comes under the framework of Horizon 2020, the European program for research and innovation.

An international collaboration, the project involves leading experts from various areas of science and technology. Six academic groups and as many industrial partners, including Indena, from five member states and from one EU candidate country, will work together with an exchange program of young researchers and scholars, to share their know-how and make an important contribution to scientific research.

One of the objectives of the project is indeed to build an efficient and sustainable model of collaboration across different countries and different sectors to look into the most effective ways of conserving and using natural resources and to work on the development of innovative products.

The EthnoHERBS project on medicinal plants from the Balkan Peninsula will focus on the use of traditional knowledge, the study of plant biodiversity and the application of eco-compatible technologies for the efficient extraction and purification of bioactive ingredients; it will also consider the chemical characterization of these ingredients and will evaluate their positive effects on the skin.

Key points of the project are innovation and sustainability: the optimization of production processes and the use of the latest formulation technologies will lead to the development of innovative products whereas the biological cultivation of selected plants will ensure the conservation of biodiversity and the sustainability of the project.

The researcher exchange program will include training courses and seminars and envisages the sharing and mutual transfer of scientific knowledge, good practices and know-how. It will build on the experience of the academic partners in ethnobotany, phytochemistry and biology and that of industrial partners in the development of innovative end-products and in the marketing of plant-derived products.

The project is to begin in October 2019 and will last for four years.



# ÉCOLES POUR TOUS

## A SCHOOL FOR ALL IN MADAGASCAR

The École pour tous project was created in 2015 as part of the Sustainable Sourcing program (SuSo) undertaken by Indena in 2013 in partnership with the voluntary organisation RTM and the local supplier of *Centella asiatica*. The plant is herbaceous and contains valuable active ingredients for cosmetic, nutraceutical and pharmaceutical use. It is harvested in the Alaotra Mangoro region in Madagascar where the project took shape. It involved five primary schools in the first three years and five new schools from 2018. Eléonore Rahainoro of RTM Madagascar is strongly committed to her home territory; to get an opinion from the ground, we spoke to her about the most important aspects of this initiative.

**Is this the first time that RTM has worked with a private company to manage a project connected to a botanical chain? And if so, what were the main strengths and difficulties?**

*Yes this is the first time. Initially we needed a while to get to know each other and understand what the strategies were, but the real difficulties were caused more by external factors such as changes in the weather and conditions on the road; there were also delays to the program from the local branch of Direction Régionale de l'Education Nationale (DREN). How the activities were defined and how the public-private partnership between DREN, RTM and Indena was consolidated can be seen as high points of the project. Infrastructure improvements in the area, such as the sinking of wells, sanitary services and rebuilding work have brought benefits to the school system, as has professional training, methodology and French language courses for the teachers and the consequent increase in school attendance.*

**Four years into this project, what are the results for teachers, parents and students?**

*The teachers were provided with classroom equipment and teaching aids and they have been able to take courses in pedagogy and language. This has made them more motivated, despite their low salaries. The pupils were given classroom material thereby saving their parents money and encouraging them to send their children to school; the very low subsidy is mainly intended for sustenance, especially for the families of the gatherers who live hand-to-mouth. The children themselves were more eager to go to school with their new satchels and good quality notebooks. Pupil attention span has even increased, and there are fewer interruptions due to lack of material. The school dropout rate has also decreased, apart from cases of force majeure or sickness.*

	2015 - 2016	2016 - 2017	2017 - 2018
Taux de réussite au CEPE/CEPE Success rate (Primary School Leaving Certificate)	70 %	72 %	75 %
Taux de passage en classe supérieure Pass rate to higher classes	74 %	83 %	81 %
Taux d'assiduité School attendance	≥ 90 %	≥ 90 %	≥ 90 %

Summary of School Results in the First Three Years of the Project



**Which parts of the project do you think have best responded to the needs of the community?**

*Providing basic school items for pupils and teachers together with classroom material, since unfortunately such things are scarce and in poor condition in state primary schools. Teacher training courses have also been a great investment for the improvement of the education system as most teachers had never had any kind of basic pedagogical preparation. In addition, by supplying clean water to each school, it has been possible to reach the minimum hygiene standards required to combat diarrhoea.*

**Based on your experience, what are the main needs for the community in the Alaotra Mangoro region?**

*As regards education, teacher skills should be improved and the level of teaching increased; awareness among parents about the importance of schooling should be encouraged and "parenting classes" set up; new classrooms should be built to reduce excessive class sizes; teacher salaries could be paid by the state to avoid expenditure falling on families. Other work and additional sources of income could also be found for the families of Centella harvesters, who could be given pieces of land. More care should be given to children's nutrition, especially during periods of drought and medical exams carried out in schools.*

**Have there been any moments which have given you particularly pleasure?**

*When the kits were being handed out at the official launch of the project in October 2015, all the helpers were astonished by the gift of a Petit Larousse dictionary to every school teacher and the schools authority confessed they were unable to provide them. And again when school kits and satchels were being distributed the children showed how happy they were by jumping up and dancing. Since then, whenever they see the RTM van, they jump with joy and dance around to welcome the team, even when there's nothing to give them.*





## News

# ANCIENT TRADITION FUTURE POTENTIAL

Indena could not fail to be part of the leading event in the field of ingredients for personal care: the In-Cosmetics Global 2019 Show took place in Paris in April.

This was the perfect opportunity for the company to present its recent publication to a wider audience. "*Centella asiatica: entering a new era*" aims to highlight the new frontiers for this singular plant whose use in traditional medicine is well-established and widespread. The monograph explores properties and areas of application for this precious natural resource, familiar for centuries but now proving to have an even wider potential.

Indena also focused attention on its methods for the certain authentication of plants, the primary source of natural substances, and described how the company is continually committed to their sustainability, in particular with regard to handling the numerous supply chains around the world.



# VITAFOODS 2019: ENERGY AND WELL-BEING FOR ATHLETES

Vitafoods Europe, the most important event for the health food sector, was held from 7th to 9th May 2019 in Geneva.

Indena played an important role in the event by presenting Ubiqsome<sup>®</sup>, the brand new product based on Coenzyme Q10 that has recently been added to the family of ingredients formulated with Phytosome<sup>®</sup> technology; this is the food grade delivery system designed by Indena to ensure better bioavailability of natural substances of botanical derivation.

Ubiqsome<sup>®</sup> was in fact the subject of a presentation given at the Vitafoods event by Dr Franchek Drobnic, Head of Sports Research at the Barcelona Olympic Training Centre. He spoke about its ability to effectively support energy production in the cells of the body, verified through rigorous scientific studies conducted on a sample of athletes.



Indena's second presentation in Geneva dealt more broadly with the theme of botanical extracts for sports nutrition.

This theme could not be more pertinent, since people's lifestyle especially in Western countries often prevents them exercising with the amount of movement required to maintain good health. A 10% reduction by 2025 in insufficient physical activity among people is now one of the targets of The World Health Organization.

Botanical and natural derivatives deliver a number of benefits for those who do sports and Indena's experience in this sector is and long and well-proven. Meriva<sup>®</sup> (*Curcuma longa*) is effective for supple joints; Casperome<sup>®</sup> (*Boswellia serrata*) can aid the musculoskeletal system, Quercifit<sup>™</sup> (*Sophora japonica*) provides antioxidant activity; Prodigest<sup>®</sup> (*Cynara cardunculus* and *Zingiber officinale*) is useful for an athlete's digestive system whereas the more recent Ubiqsome<sup>®</sup> (Coenzyme Q10) is a veritable energy-bank for cells.



## RENATO IGUERA AT THE HELM OF ASSOERBE

Assoerbe is the Italian national trade association that represents companies operating in the field of medicinal and aromatic plants, perfumes, spices, plant extracts, essential oils and their derivatives. On December 13, 2018 Renato Iguera became the association's President, succeeding Irene Minardi, who remains on the Board as Vice-president alongside emeritus chair Carlo Sessa.



Dr Iguera, a Milan University graduate, boasts 30 years of experience working with botanical extracts in Indena, where he has proven his skills in supply chain management and procurement, quality control and quality assurance, GACP applied to cultivation and wildcrafting; he is also a Team Leader in the company's sustainability and social responsibility projects.

Following his election as the association's President, Renato

Iguera said he took "great pride in his appointment" and thanked the Board of Assoerbe for placing their trust in him. *"May I express my gratitude to Irene Minardi for her admirable work in representing the association judiciously,"* he said. *"I hope now to be able to draw on my own experience to pursue the work of the association with commitment and passion."*

## VAZGUARD™ AND CARDIOVASCULAR HEALTH.

According to the World Health Organization, cardiovascular diseases are the largest cause of mortality in the world, leading to in 31% of all deaths. Figures from the British Heart Foundation reveal that in the United Kingdom more than one person in four dies of cardiovascular disease.

It is more and more evident that food and lifestyle play a fundamental role in the prevention of these diseases and that people are increasingly orienting themselves towards maintaining cardiovascular health through their choices of food, drinks and supplements.



This theme was the focus of a seminar during Food Matters Live 2018 which was held in London on November 22nd and 23rd in which Elisabetta Frattini, Senior Research Scientist, Indena Formulation Development, gave a presentation.

Ms Frattini underlined the importance of the contribution that comes from the world of edible plants and in particular those of the Mediterranean area. She illustrated that through research and technology, there can be real innovation using ingredients derived even from plants with a long dietary tradition.

Extracts from Mediterranean plants traditionally used in nutrition can in fact be improved in terms of bioavailability, standardization or formulation; they can therefore be used for specific objectives such as for instance the management of blood glucose or cholesterol levels, or appetite control.

One example of an innovative approach aimed at respecting and enhancing the characteristics of a botanical derivative of long tradition is that of Vazguard™, the purified Bergamot polyphenolic fraction (BPF) formulated with the delivery system Phytosome®, which optimizes the bioavailability and absorption of bergamot polyphenols.

Bergamot (*Citrus bergamia*) is a traditional Mediterranean fruit which grows in certain areas of southern Italy where it has been cultivated for centuries. In order to guarantee the highest standards of quality and efficacy, only the extract of Bergamot BPF which comes from a limited and specific area of Calabria is used for the production of Vazguard™. In-depth analytical characterization carried out in the laboratories of Indena has shown this to have an absolutely unique and characteristic phytochemical profile reflecting that of natural bergamot juice.

The active components of bergamot (flavonoids) are recognized scientifically to be effective in maintaining cardiovascular health, but they have poor oral absorption. In order to improve and enhance the efficacy of bergamot, it is therefore necessary to identify a formulation that allows a higher level of absorption at a lower dosage. This is where the technological innovation that is Phytosome® comes into play with the creation of Vazguard™. Confirmation of the optimized bioavailability of the extract and its effectiveness in maintaining cardiovascular health have been demonstrated by several human studies.

The bergamot phytosome was also the focus of a presentation given by Paolo Morazzoni, Indena Scientific Advisor, at the 4th International Conference on Pharma and Food (ICPF) which took place in Shizuoka, Japan in November 2018. Dr Morazzoni reiterated the importance of the supply chain from which the extract used by Indena derives and the unending tests carried out by the company to guarantee its traceability, safety and quality. He also documented the effectiveness of the BPF flavonoids in supporting the management of the metabolic syndrome. The Japanese audience then learnt of the results of a very new study on the interaction between bergamot phytosome and intestinal microbiota. This study, promoted by Indena, addressed the issue for the first time and showed a possible link between positive microbiota modulation and cardiovascular health.<sup>[1]</sup>

Dr Morazzoni also presented the launch of a study conducted by the University of Pavia on the effects of Vazguard™ in overweight subjects.

#### References

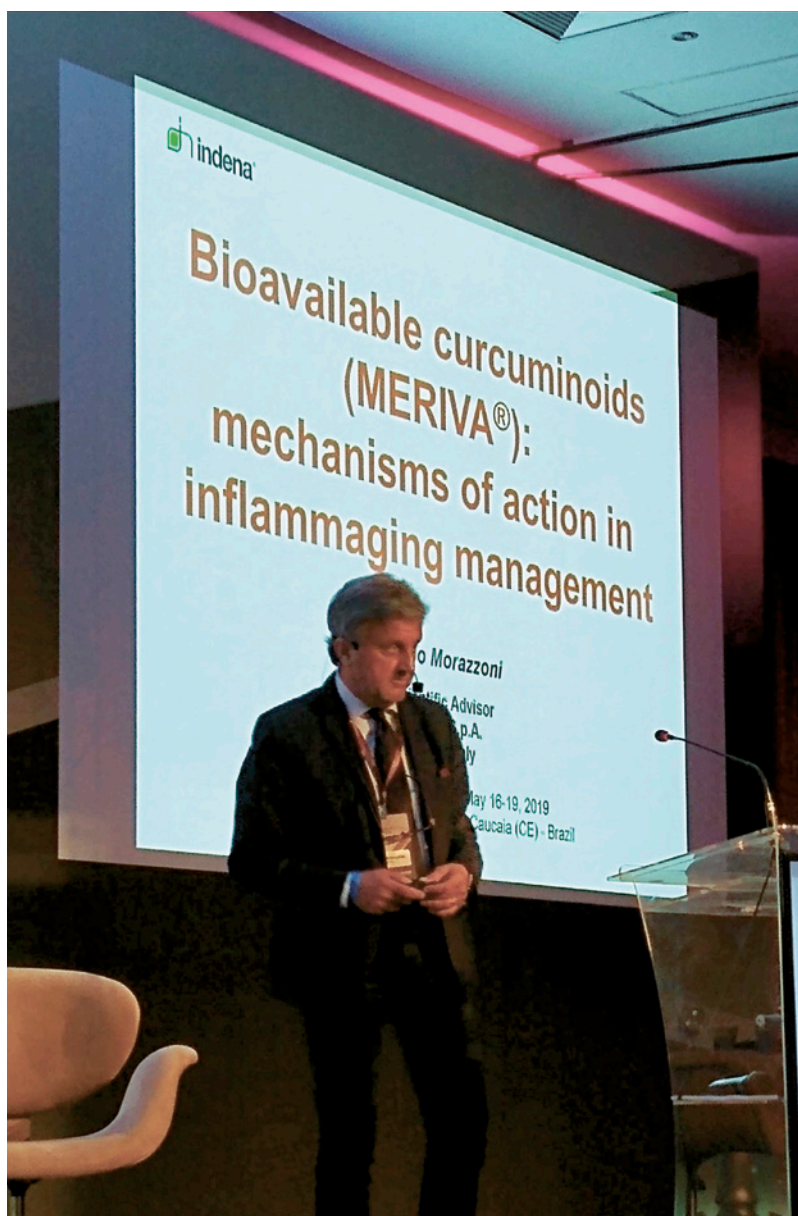
[1] Petrangolini G. et al.; Proceedings of the "10th PROBIOTICS, PREBIOTICS & NEW FOODS, NUTRACEUTICALS AND BOTANICALS for Nutrition & Human and Microbiota Health" Conference, Rome (IT), 8-10 September 2019

# FOCUS ON MERIVA® AT THE ACHÉ MASTER MEETING

There was a great reception for seminars conducted by Indena Scientific Advisor, Paolo Morazzoni, as part of the Vth Master Meeting, organized by the renowned Brazilian pharmaceutical company, Aché.

Dr Morazzoni illustrated the features and effectiveness of Meriva® to a significant number of Brazilian doctors in talks given in Buenos Aires in April and in Cumbuco in May 2019.

The main topics covered in the seminars were the secondary metabolites of plants, the history of curcumin, the action mechanism of curcuminoids, the Phytosome® delivery system, the most recent studies on Meriva® and a comparative example with *Harpagophytum procumbens*, commonly known as Devil's claw.



# MIRTOSELECT® AND EYE HEALTH IN BEIJING

The “*New Nutritional Business and Leading Summit 2019*” was held in Beijing at the beginning of June. Indena participated in this event and focussed attention on the role of bilberry in eye health.

Stephan Beszant, Customer Service Technical Coordinator at Indena, presented a paper entitled “*The Value of Uniqueness in Traditional Plants: The Role of Bilberry in Eye Care*” in which he highlighted the different situations that put the eye under stress and the benefits that can be derived from bilberry extract.



Out of all bilberry extracts available on the market, Mirtoselect® is recognized as a product leader and is backed up by numerous scientific studies. Compared with other extracts, the high quality and particular effectiveness of Mirtoselect® are due to the selection of raw materials, the rigour and accuracy of the preparation processes, as well as to its exclusive phytochemical profile.

# UPCOMING TRADE SHOWS

## Food Ingredients China

Shanghai, China  
17-19 March 2020  
*National Exhibition and  
Convention Center (NECCS)  
Stand 61S11*

## CPhI Japan

Tokyo, Japan  
16-18 March 2020  
*Tokyo Big Sight*

## SupplySide East

Secaucus, NJ, USA  
21-22 April 2020  
*Meadowlands Exposition Center*

## CPhI North America

Philadelphia, PA, USA  
5-7 May 2020  
*Pennsylvania Convention Center*

## Vitafoods

Geneva, Switzerland  
12-14 May 2020  
*Palexpo  
Stand E84*

## 60° Simposio AFI

Rimini, Italy  
June 2020  
*Palacongressi di Rimini*

## CPhI China

Shanghai, China  
22-24 June 2020  
*SNIEC Shanghai*

## Vitafoods Asia

Singapore  
23-24 September 2020  
*Sands Expo & Convention Centre  
at Marina Bay Sands*

## Health Ingredients Japan

Tokyo, Japan  
October/November 2020  
*Tokyo Big Sight*

## SupplySide West

Las Vegas, NV, USA  
October/November 2020  
*Mandalay Bay*

## CPhI Worldwide

Milan, Italy  
13-15 October 2020  
Fiera Milano  
Stand 18H30



[indena.com](http://indena.com)



#### HEADQUARTERS

Indena S.p.A. - Viale Ortles, 12 - 20139 Milano - Italia - tel. +39.02.574961

#### INTERNATIONAL BRANCHES

Indena Biotechnology Co. Ltd. - Unit 810, Plaza 336, No.336 Middle XiZang Road, Shanghai 200001 - China - tel.+86.21.2281.5900  
Indena Brasil Ltda - Rua Bandeira Paulista, 600 CEP 04532-001, São Paulo - Brazil - tel. +55.11.27.690.624  
Indena Japan Co. Ltd. - KDDI Bld. 21F 1-8-1, Otemachi, Chiyoda-Ku - Tokyo 100-0004 - Japan - tel. +81.3.3243.9924  
Indena USA Inc. - Two Union Square - 601 Union Street, Suite 330 - Seattle WA 98101 - USA - tel. +1.206.340.6140  
Indena S.A.S. - 23, rue de Madrid - 75008 Paris - France - tel. +33.1.45229128