

COMPANY PRESENTATION

Science is our Nature®

 **indena**®
INDUSTRIA
DERIVATI
NATURALI

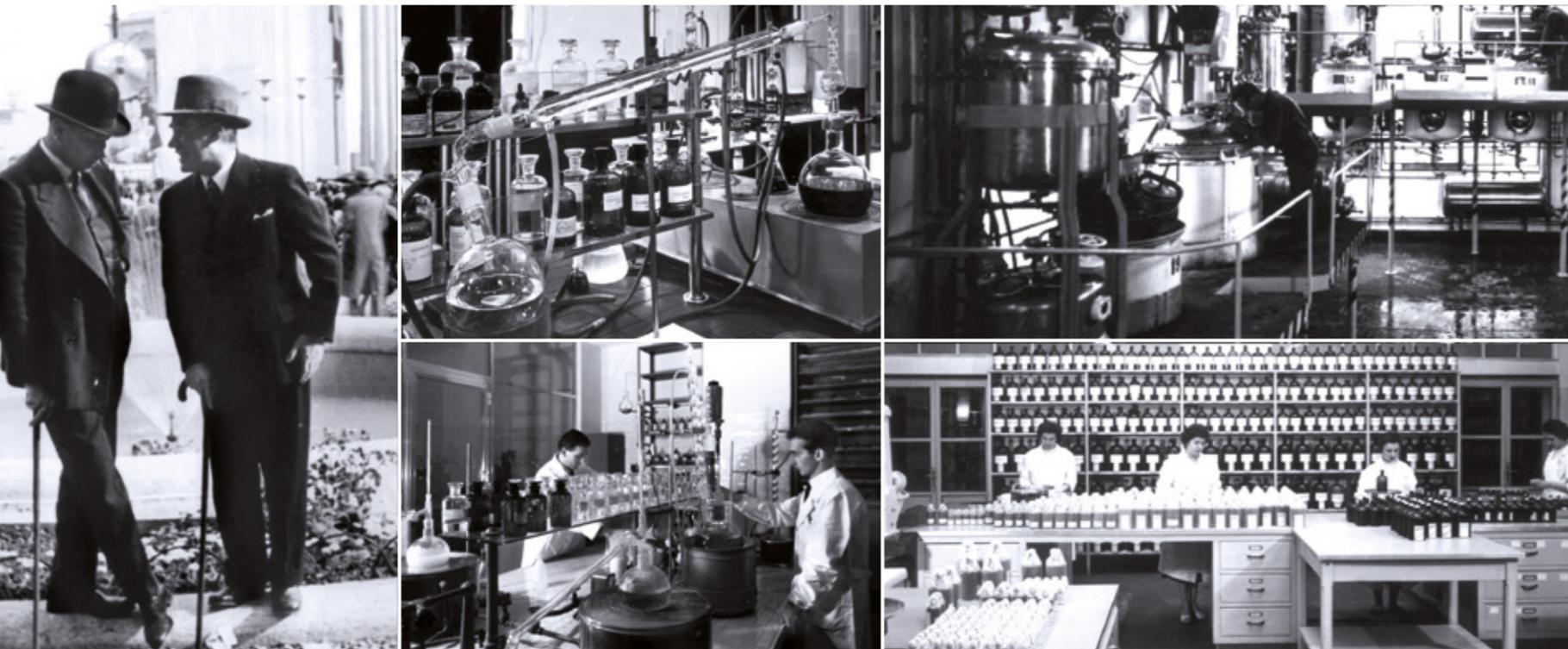


OUR MISSION

At Indena we believe that an in-depth knowledge in active ingredients derived from medicinal plants and the search for excellence at all times are crucial commitments to serving our customers in pharmaceuticals and health-foods.

Research and production technologies are the main focus of our mission and the way we create a “value difference” for our partners.

And we’ve got nearly a century of experience to prove it.



MILESTONES IN THE HISTORY OF INDENA

The origins of the company date back to 1921, when Carlo Boccaccio Inverni began producing extracts from medicinal plants for pharmacists and the emerging Italian pharmaceutical industry. When Biagio Alberto Della Beffa joined as partner and Managing Director, the firm became a joint-stock company, trading under the name of Dott. Inverni & Della Beffa S.p.A.

During the 1950s, Biagio Alberto's son Luigi Della Beffa added to the existing business a new pharmaceutical division (Inverni della Beffa S.p.A.) to manufacture and market finished dosage forms from botanical derivatives.

In 1969, a new site for the production of extracts and pure molecules, together with a pivotal research and development centre, was set up in Settala, near Milan.

In the early 1980s, the botanical derivatives business was reorganised as a new company, Indena S.p.A.

In the 1990s Indena, already present worldwide with a commercial and cultivation network, opened new production plants, notably in France and India, and additional commercial branches.

Throughout its long history, Indena has specialised in the identification, development and production of plant derived purified extracts and pharmaceutical active principles including flavonoids, glycosides, aminoacids, alkaloids and their semi-synthetic derivatives.



FACTS & FIGURES

800 employees

5 international branches

4 production sites worldwide

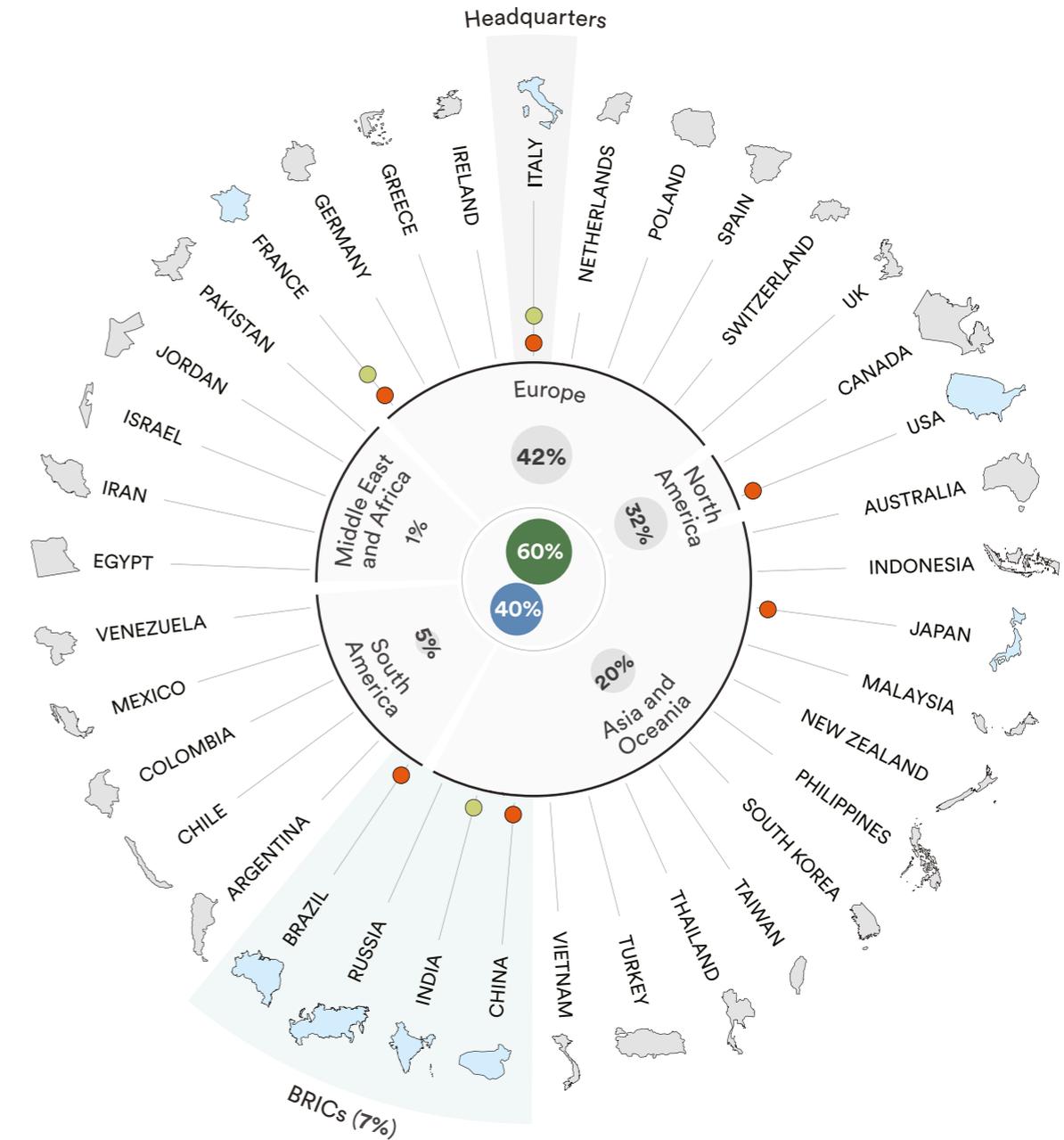
sales in more than **80** countries

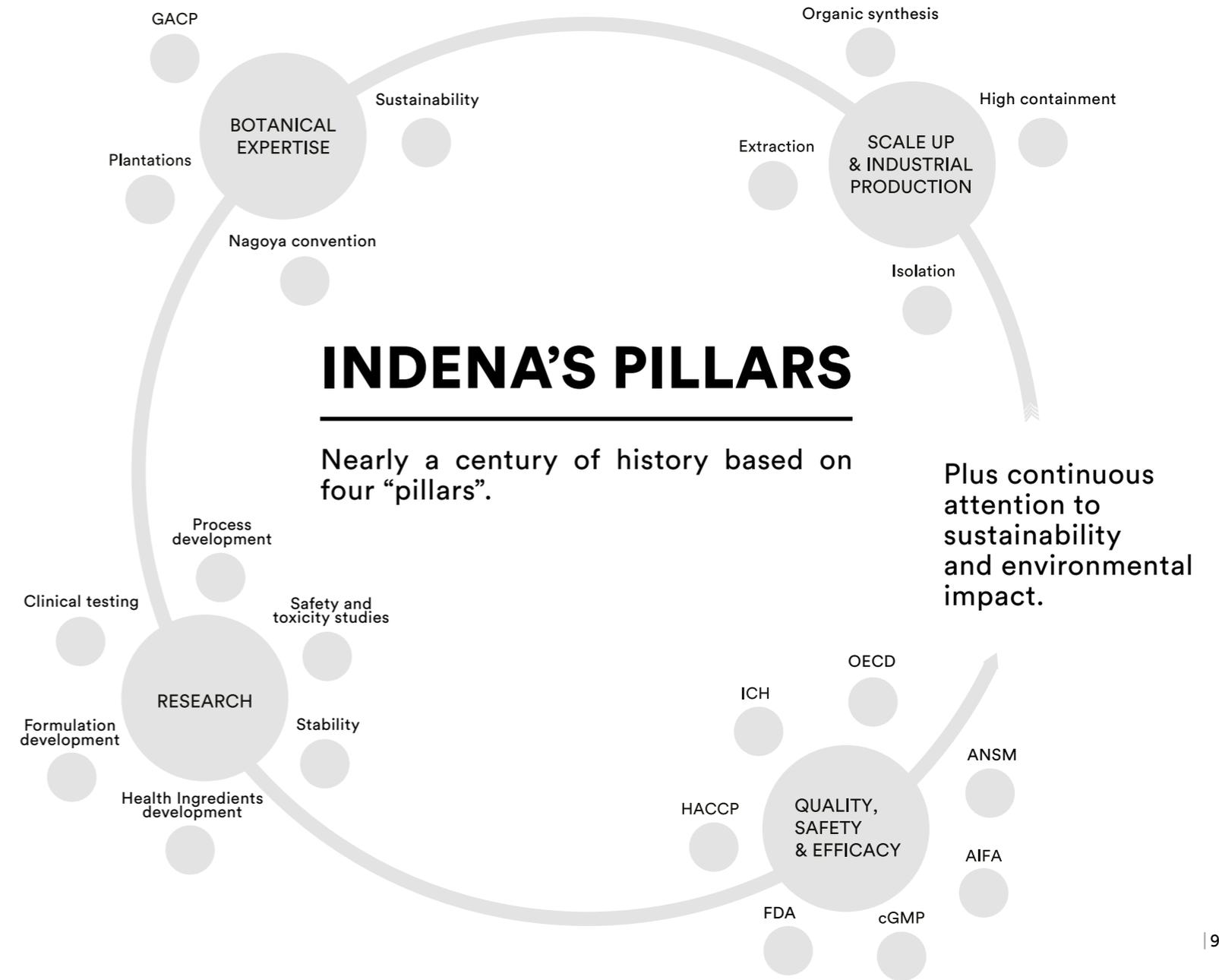
more than **100** primary patents

THE INDENA MARKET

BUSINESS SECTORS ● Pharmaceutical ● Health-food

ORGANISATION ● direct presence ● sales organisation ● production







A RESEARCH BASED COMPANY

At Indena, we have always been inspired by a rigorous scientific approach in our research.

In PROCESS RESEARCH, original advanced industrial production processes are designed and engineered for work on existing or new molecules, as well as for the development of new APIs and HPAPIs

In PRODUCT RESEARCH we focus on active ingredients for the health and nutrition market, supporting them with safety and efficacy data and applying innovative delivery technologies as needed.



BOTANICAL SOURCES

In addition to traditional gathering of wild plants, Indena has established a worldwide network of plantations to provide high quality vegetal raw material.

Internationally recognised botanical experts monitor more than 3,000 hectares of Good Agricultural and Collection Practices (GACP) compliant plantations, which today account for more than 60% of the vegetal raw material we use.

We pursue the highest botanical standards with maximum respect for the environment and biodiversity.

To achieve well-identified and consistently high-quality vegetal raw material, we use micropropagation and traditional plant breeding, but never GMO.



INDENA PRODUCTION

Advanced, highly flexible and environment-friendly state-of-the-art technology is used throughout the Indena manufacturing cycle.

Indena's facilities incorporate separate authorised areas for handling pharma and food grade natural derivatives, where the Quality System ensures compliance with cGMP and Hazard Analysis and Critical Control Points (HACCP) guidelines.

With more than 100 DMFs, Indena's pharmaceutical products meet US-FDA and EU requirements, and two production sites are accredited by Japanese authorities.

Health-food pre-mixed preparation.

Fermentation production capabilities.

Spray drying capabilities from organic solvents on different scales, developed in decades of operations.



MAIN PRODUCTION EQUIPMENTS AT OUR SITES

- Grinding apparatus (hammer- and knife-grinders) | plant material grinding
- Percolators (static and dynamic) | plant material extraction
- Reactors | reaction, crystallisation, concentration
- Concentrators (thin-film concentrators) | solvent evaporation
- Liquid-liquid extractors | selective extraction, purification process
- Columns for chromatography | concentration, purification, isolation
- Centrifuges, filter-press | solid-liquid separation
- Driers (tray driers, driers with stirring, microwave) | drying
- Spray dryers | Spray drying
- Mills and sieves | milling and sieving of powders
- Mixers | blending of powders, standardisation



PROCESS DESIGN FOR HIGH-CONTAINMENT SYNTHESIS

PROCESS DEVELOPMENT & SCALING-UP CAPABILITIES:

- Process design for High Potency Compounds synthesis
- Route optimisation (statistical Design Of Experiment) and scale-up
- Preparation of small scale material, from grams to kilograms
- cGMP manufacturing of APIs for clinical trials

ANALYTICAL & PRECLINICAL SUPPORT:

- Related substances and secondary metabolites identification
- Support to process development
- IPC and release analysis for GMP production
- Solid state characterization and polymorphism screening for IP protection
- Investigational and regulatory stability studies
- Collaboration with the most important international analytical organizations (EP and USP, AOAC) to promote analytical methods innovation

PRODUCTION SCALE CAPABILITIES:

- First purification of cytotoxic APIs
- Final purification and drying of cytotoxic APIs
- Semi-and-total-synthesis of HPAPIs
- Availability of industrial suites (equipped with 20 linear meter glove boxes)
- Availability of 2 kilolabs (LK1 and LK2) for clinical and smaller scale commercial supplies of HPAPIs with OEL 20 ng/m³
- Lab, pilot and industrial scale multipurpose fermentation plants
- Intermediate and large scale spray dryers, both working with class 2 organic solvents, also in the presence of excipients/co-polymers (for drug product intermediates)



INDENA QUALITY

1_ Quality of the raw material:

- identification of the plant through specific protocol and analyses, such as botanical checks, chromatographic profiles, or DNA analysis;
- purification of the botanical extract: if the plant contains toxic, allergenic or unwanted substances, it is important to remove these components and obtain an extract deemed purified;
- standardization combines different lots to ensure that the botanical extract always has the same composition of constituents.

2_ Control of the supply chain:

- suppliers are accredited on the basis of rigorous criteria of quality, sustainability and traceability;
- GAPC guidelines for good agricultural and collection practices are implemented in the supply chain;
- the need for high quality raw materials is reconciled with the principles of biodiversity and sustainability indicated by international conventions and standards such as the Convention on Biological Diversity (CBD);
- the entire supply chain is under continuous control from cultivation to the delivery of the raw material to the production sites.

3_ Quality of the manufacturing processes:

- technologically advanced and safe production plants for both raw materials and operators;
- process compliant with production standards and regulations such as Good Manufacturing Practices (GMP) and the Hazard Analysis Critical Control Points manual (HACCP);
- use of high-quality, precisely defined excipients to optimize the effectiveness of the active ingredient;
- meticulous inspection of the finished product.



SUSTAINABILITY & THE ENVIRONMENT

Nature has always been for Indena both a source of inspiration and an essential resource. We have always been conscious of how important it is to preserve and regenerate the natural balance of every living source and for this we strictly follow laws, guidelines, procedures and programs with the aim of guaranteeing the safety of employees, safeguarding environment and biodiversity. These aims lie at the heart of the projects undertaken within the Sustainable Sourcing Program and dedicated to the communities involved in the collection of the many species that Indena markets. On the other side, the ever increasing effort to reduce the environmental impact of production sites has led to significant results in its main facilities, all certified ISO 14001 and OHSAS 18001.



ACTIVE PHARMACEUTICAL INGREDIENTS

Isolated or semisynthetic pure products and extracts are produced in compliance with cGMP and supported by CTD-DMFs.

Among our main products:

PACLITAXEL

Taxus media Rehder - Root, leaf and twig - $\geq 97.0\%$ $\leq 102.0\%$ by HPLC - Anticancer

10-DAB III

Taxus baccata L. - Twig and leaf - $\geq 96.0\%$ by HPLC - Chemical intermediate

THIocolchicoside

Gloriosa superba L. - Seed - $\geq 98.0\%$ $\leq 102.0\%$ by potentiometry - Muscle relaxant

COLCHICINE

Gloriosa superba L. - Seed - $\geq 97.0\%$ $\leq 102.0\%$ by potentiometry - Antigout

DOCETAXEL

Taxus baccata L. - Twig and leaf - $\geq 97.0\%$ $\leq 102.0\%$ by HPLC - Anticancer

MYRTOCYAN®

Vaccinium myrtillus L. - Fresh frozen fruit - $\geq 32.4\%$ $\leq 39.6\%$ of anthocyanins, 1.0% anthocyanidins by HPLC - Capillarotropic

ESCIN

Aesculus hippocastanum L. - Seed - $\geq 97.0\%$ $\leq 103.0\%$ by potentiometry - Antioedema

GINKGO BILOBA

Ginkgo biloba L. - Leaf - $\geq 22.0\%$ $\leq 27.0\%$ of flavonoids, $\geq 2.6\%$ $\leq 3.2\%$ of bilobalide, $\geq 2.8\%$ $\leq 3.4\%$ of ginkgolides A,B,C, ≤ 5 ppm of ginkgolic acids by HPLC - Blood circulation improver



HEALTH - FOOD INGREDIENTS

Indena leverages its solid pharmaceutical background for the health-food field, developing biologically active ingredients for supplements, functional, medical and baby food products for more than 40 years. These include:

BEANBLOCK®

Phaseolus vulgaris L. - Common bean - $\geq 6.0\%$ as alpha amylase inhibitor by HPLC - 1,100 U/mg of alpha amylase inhibiting activity, $\geq 10,000 \leq 30,000$ HAU/g of hemagglutinating activity by spectroph./enzym. - Appetite regulator, Healthy blood sugar metabolism

GREENSELECT®

Camellia sinensis (L.) O. Kuntze - Young leaf - $\geq 60.0\%$ of total polyphenols, $\geq 40.0\%$ of (-)-epigallocatechin-3-O-gallate,

LEUCOSELECT®

Vitis vinifera L. - Seed - $\geq 95.0\% \leq 105.0\%$ of proanthocyanidins by GPC - $\geq 13.0\% \leq 19.0\%$ of catechin and epicatechin by HPLC - Antioxidant activity, Circulatory health

MIRTOSELECT®

Vaccinium myrtillus L. - Fresh frozen fruit - $\geq 36.0\%$ of anthocyanins by HPLC - $\geq 25.0\%$ of anthocyanins as anthocyanidins by spectrophotometry - Eye health, Circulatory health, Antioxidant activity

MITIDOL®

Zingiber officinale Roscoe - rhizome + *Acmella oleracea* L. - flowers - $\geq 2.4 \leq 3.9\%$ total gingerols and shogaols - $\geq 0.30 \leq 0.60\%$ spilanthol by HPLC - Natural ache relief

OPEXTAN®

Olea europaea L. - Fruit - $\geq 10.0\%$ of total polyphenols by spectrophotometry - $\geq 2.0\% \leq 3.5\%$ of verbascoside, $\geq 4.5\%$ of hydroxytyrosol and its derivatives by HPLC - Antioxidant activity, Healthy skin, Healthy cardiovascular function

PRODIGEST®

Cynara cardunculus L. + *Zingiber officinale* Roscoe - Artichoke extract - $\geq 28.0 \leq 34.0\%$ by HPLC Ginger extract - $\geq 6.0\% \leq 7.0\%$ by HPLC - Digestive health

Indena standardised extracts have full chemical characterisation backed by QUALITY, SAFETY AND EFFICACY TESTS.



phytosome[™]
THE BIOMIMETIC DELIVERY SYSTEM

HEALTH - FOOD INGREDIENTS

phytosome[™]
THE BIOMIMETIC DELIVERY SYSTEM

Indena has developed a proprietary technology to optimise the bioavailability of selected phytochemicals. Products include:

CASPEROME[®]

Boswellia serrata Roxb. ex Colebr. - Resin - ≥25.0% of boswellic acids by HPLC - For healthy inflammatory response

GINKGOSELECT[®]

Ginkgo biloba L. - Leaf - ≥7.0% of ginkgoflavonglucosides, ≥2.0% of ginkgoterpenes, ≥0.8% of bilobalide, ≥0.8% of ginkgolides, ≤5 ppm of total ginkgolic acids by HPLC - Cognition and circulation improver, Antioxidant activity, Vasokinetic

GREENSELECT[®]

Camellia sinensis (L.) O. Kuntze - Young leaf - ≥19.0% ≤25.0% of polyphenols expressed as (-)-epigallocatechin-3-O-gallate, ≥13.0% of (-)-epigallocatechin-3-O-gallate, ≤0.1% of caffeine by HPLC - Antioxidant activity, Weight loss agent

MERIVA[®]

Curcuma longa L. - Rhizome - ≥18.0% ≤22.0% of curcuminoids by HPLC - Joint health, For healthy inflammatory response

QUERCEFIT[™]

Sophora japonica L. - Flowers - ≥34.0% ≤42.0% of quercetin by HPLC - Sports nutrition, allergy seasons' discomforts control, antioxidant activity

SILIPHOS[®]

Silybum marianum (L.) Gaertn. - Fruit - ≥29.7% ≤36.3% of silybin by HPLC - Healthy liver

UBIQSOME[®]

CoQ10 Phytosome[®] - 18-22% of coenzyme Q10 by HPLC - Cellular energy

VAZGUARD[™]

Citrus bergamia Risso & Poit. - Fruit juice - ≥11.0% ≤19.0% of total flavanols by HPLC - Cardiovascular health



FLAVOURS

Botanical extracts with organoleptic properties

AMMONIUM GLYCYRRHIZATE

Glycyrrhiza glabra L. - Root | $\geq 98.0\%$ $\leq 102.0\%$ of monoammonium glycyrrhizate

ANISE

Illicium verum Hooker fil. - Fruit | $\geq 0.5\%$ of anethole by GC

CHAMOMILE

Matricaria recutita L. - Flowering head | $\geq 1.2\%$ of total apigenin by HPLC

GINSENG 1/2/10%

Panax ginseng C.A. Meyer - Root | 1.0, 2.0, 10% of total ginsenosides and malonyl-ginsenosides calculated on the dried substance by colorimetry

GRAPE SEED

Vitis vinifera L. - Seed | $\geq 95.0\%$ of proanthocyanidins by spectrophotometry, $\geq 5.0\%$ $\leq 15.0\%$ of catechin and epicatechin by HPLC

GUARANA

Paullinia cupana H.B. et K. - Seed | 12% of total alkaloids by HPLC

LEMON BALM

Melissa officinalis L. - Flowering head | $\geq 10\%$ of hydroxycinnamic derivatives calculated as rosmarinic acid

OPLODEX™

Quercus spp. Wood - *Camellia sinensis* (L.) O. Kuntze Leaf - *Vitis vinifera* L. Seed | Balanced and synergistic combination of polyphenolic botanical extracts

QUASSELECT®

Quassia amara L. Wood | $\geq 53.0\%$ $\leq 57.0\%$ as sum of quassin and neoquassin by HPLC



CDMO

CONTRACT DEVELOPMENT AND MANUFACTURING ORGANIZATION

CUSTOM SERVICES

With a century long experience and continuous technological expansion, Indena has focused on Contract Development and Manufacturing services for its partners, supporting product development from clinical trials to large scale commercial manufacturing.

Indena's R&D center is in Italy, while the production units are in Italy (Settala and Palestro), France and India and incorporate separate authorised areas for handling pharma and food grade natural derivatives, and the Quality System ensures compliance with cGMP and Hazard Analysis and Critical Control Points (HACCP) guidelines.

CYTOTOXICS AND HPAPIs

Indena HPAPIs contract manufacturing services include a full range of dedicated development and manufacturing solutions such as fermentation, extraction, isolation, purification, synthetic modifications and total synthesis for active pharmaceutical ingredients on a wide range of scales.

This facility incorporates appropriate room pressurization, airlocks, ventilation and isolators to properly handle highly potent solids and liquids down to 20 ng/m³ OEL (SafeBridge® Class 4). Settala site is regularly inspected by the main Regulatory Authorities.



DISSEMINATING KNOWLEDGE ON MEDICINAL PLANTS

Indena acts to foster interest in medicinal plants and natural products:

- By founding *Fitoterapia*, a Journal published since 1924 and today recognised as a premier source for research on medicinal plants (2012 Impact Factor: 2.231, currently distributed by Elsevier)
- By publishing monographs and books on medicinal plants
- By sponsoring Masters and specialist schools in phytotherapy
- By offering scholarship grants to young researchers



THE INDENA ORGANISATION

HEADQUARTERS

Indena S.p.A. | Milan | Italy

RESEARCH CENTRE

Indena S.p.A. | Settala (MI) | Italy

INTERNATIONAL BRANCHES

Indena Biotechnology (Shanghai) Co., Ltd. | China

Indena Brasil Ltda | São Paulo | Brazil

Indena Japan Co., Ltd. | Tokyo | Japan

Indena S.A.S. | Paris | France

Indena USA Inc. | Seattle | WA | USA

THE INDENA PRODUCTION SITES

Indena S.p.A. | Settala (MI) | Italy

Bernett S.r.l. | Palestro (PV) | Italy

Indena S.A.S. | Tours | France

Indena India Pvt. Ltd. | Bangalore | India



Indena S.p.A. | Settala (MI) | Italy



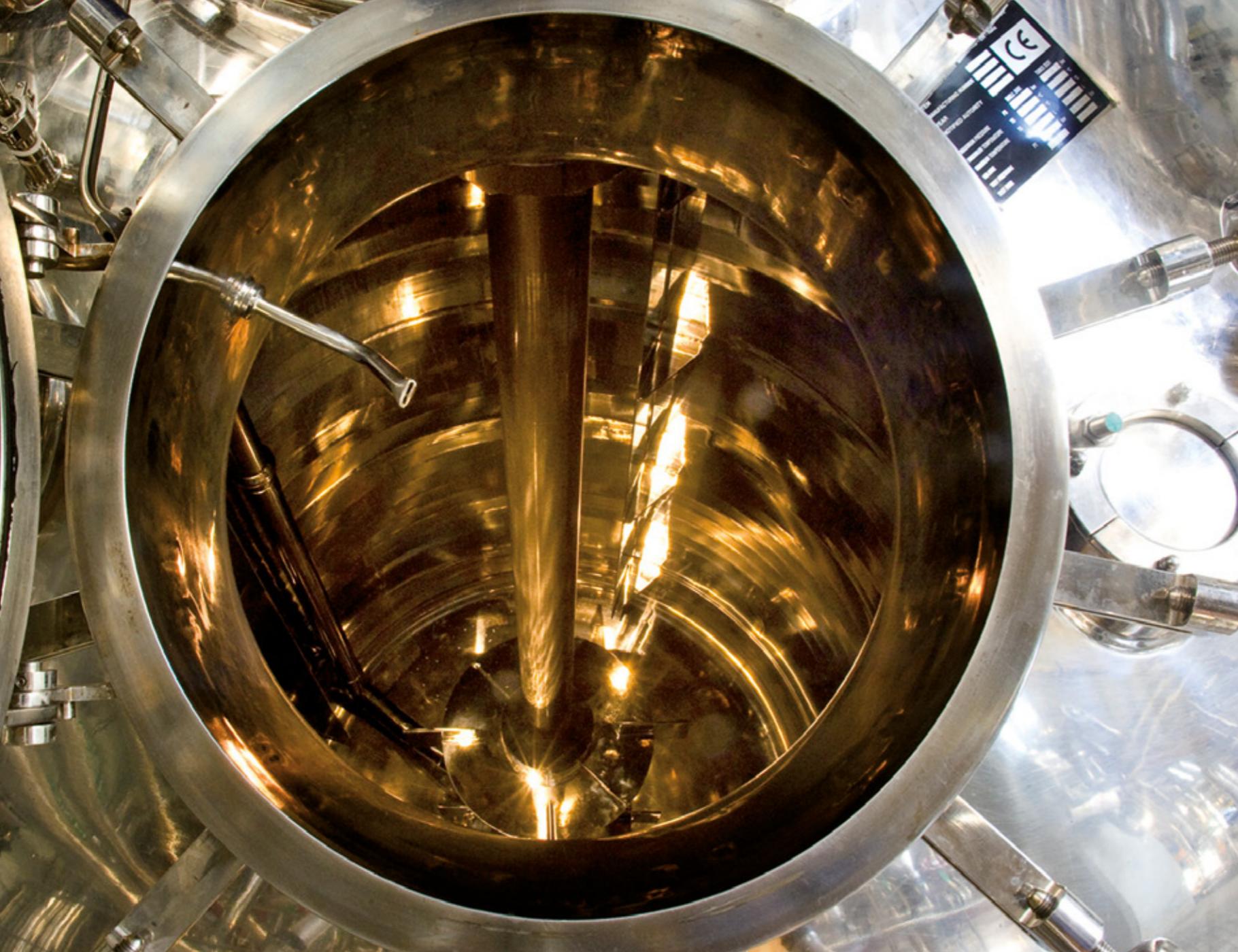
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