

indena



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SECONDARY IN NAME ONLY

Giovanni Appendino, Indena

In addition to macronutrients (proteins, fats and carbohydrates) and to the essential micronutrients (vitamins and mineral salts), edible plants contain a heterogeneous multitude of secondary metabolites of low molecular weight, better known as nutraceuticals or phytonutrients. A cup of coffee, for example, might contain as many as 10,000. However, their concentration varies within the same species and the same organ, and different varieties of the same species may have a very different profile of secondary metabolites, as can be seen by the different colours in varieties of fruit (red or white grapes etc.). The synthesis of secondary metabolites depends on external factors, which allow the plant to perceive and adapt changes in the environment. Moreover, secondary metabolites are often unstable in conservation and culinary manipulation, which can lead to massive losses, especially in the case of polyphenolic compounds when heated to high temperatures. One of the most studied cases concerns the concentration of catechins in a cup of green tea, with values which oscillate between 9 and 550 mg depending on the botanical variety used and on the temperature and infusion time.

Although they may be defined in a nutritional context as "non-essential micronutrients", since there are no known specific syndromes relating to their deficiency, their reduced intake has been connected to the increase in the onset of chronic-degenerative diseases, cancer being the first and

foremost. By way of example, the increase in the occurrence of prostate and breast tumours can be seen as corresponding to the passage from a diet rich in vegetal matter towards the "western diet". This pharmacological impoverishment can be ascribed to three factors:

1. the loss of food diversity: the greater part of the calorie intake in the modern diet derives from only four vegetal species (rice, wheat, soy and maize), in spite of the fact that over 3,000 plants are classified as edible and over 150 are cultivated systematically for use in food;
2. agricultural selection has favoured factors such as dimension, succulence and yield, without any consideration for secondary metabolites. Often these will have been superseded by pesticides employed in the protection of the plant itself;
3. the lower caloric (and therefore nutritional) requirement arising from modern sedentary life style. Average calorie intake has almost halved in the course of the last century, passing from 3,000 Kcal/die in 1900 to only 1,800 Kcal/die in 2000. Less movement leads to eating less, and consequently absorbing fewer phytonutrients, and to a substantial disconnection between dietary recommendations (for example 5 portions of fruit and vegetables a day) and the need to reduce the calorie intake associated with modern sedentary life style.

Hence the need to determine a healthcare role for phytonutrients and the necessity to extend their assimilation to functional foods and to food supplements. In the case of chemoprevention, even though the molecular mechanisms are as yet unknown, an interesting hypothesis would be to consider the dietetic consumption of vegetal micronutrients as a sort of metronomic chemotherapy, characterised by the constant presence of low doses of bland compounds nevertheless able to perform antiproliferative and antiangiogenic action. Acting both on a level of cellular proliferation and of angiogenesis, these compounds would be therefore able to inhibit the transformation of a multitude of microtumours, which we all develop almost "physiologically", in already identified tumours.

OPEXTAN® GOES ON LINE

Hot on the heels of the popular Soyselect® and Mirtoselect® pages, Indena has launched its latest website dedicated to yet another of its well-known brands. www.opextan.info is a virtual meeting place for Indena and its customers, in which the company is committed to providing clear and thorough information about its products. Visitors can find fascinating facts and figures about the olive plant and the unique characteristics of olive extracts; they can learn about the processes used to obtain and standardise them, see our communication campaigns and much more. Each section of the site is specially designed to meet the needs of both the industry and health professionals. Click on to Opextan!



www.opextan.info website homepage

FOOD THERAPY IN ONCOLOGY



Program for the meeting in Milan

PROMISING RESULTS AT CENTENARY CONGRESS

Pre-clinical data on the anti-tumoural activity of IDN 5404 were presented at the 100th Congress of the American Association for Cancer Research (AACR) held at Denver from 17th to 22nd April. The molecule, a thiocolchicine dimer selected by Indena for its cytotoxic activity on tumoural cells, was licensed in 2006 to Abraxis BioScience (USA), where innovative formulative technology has been used to improve the pharmacological formulability. Tests on various experimental models have shown how IDN 5404 is able to destroy the vascular system of tumoural formations, a mechanism which is focusing the attention of the scientific community. In virtue of its pharmacological characteristics, the molecule could play an important role in combination therapies with conventional anti-cancer drugs. Encouraged by these promising results, Abraxis will apply to the FDA within the year for authorisation to conduct clinical trials.

A congress on "Phytotherapy and food supplements for the oncology patient", was held last April at the IRCCS Foundation National Tumour Institute of Milan dedicated to the use of phytotherapy and food supplements in oncology. The potential efficacy of phytotherapeutic products and the concomitant need to understand their safety profile, the urgency to put in place regulatory standards for food supplements and herbal remedies, the importance of using products of unquestionable quality were just some of the topics of greatest interest discussed. In fact the issues surrounding quality control in vegetal drugs were explored in a lecture given by Indena's Botanical Laboratory chief, Renato Iguera. By supporting these two days of study and making an important contribution to such a topical and complex theme, Indena reaffirmed the company's interest in oncology, not only in the development of treatments which combat or prevent cancer, but in a wider scenario which sees the patient holistically as the focus of the quest for a better quality of life.

CARING FOR THE COMPANY ENVIRONMENT

In keeping with the philosophy which has always inspired Indena in its treatment of company employees and the world around us, this year Indena has set up its own Environmental Management Committee. This initiative is the means designed to strengthen the engagement of the Group and give structure to the environmental safeguards introduced. It is also part of the ISO 14001 certification application procedures for the single industrial sites. The Committee will take on responsibility for the definition of Group environmental policies and set objectives and programs for continuous improvement in this area. The company Chairman, CEO, General Manager and members of the Board will take part in the Committee as will the Settala and Tours plant managers and the officer in charge of the Prevention and Protection Service. We wish the committee well in its endeavour.

BIRTHDAY CELEBRATIONS FOR PROF. DANIELI



The group celebrating prof. Danieli

Some two hundred people from Italy, Spain and Germany came together on 24th April to mark the seventieth birthday of Bruno Danieli, Professor of Physical Methods in Organic Chemistry at the University of Milan and one of the greatest experts in the chemistry of natural products. During the symposium, held in his honour as "a birthday surprise" at the Italian Renaissance monastery of Abbiategrasso, near Milan, eminent scientists and researchers of international repute who have worked alongside the Professor debated the role of natural products in the twenty-first century. One of these, Gabriele Fontana, former Head of Medicinal Chemistry and now Indena Strategic Projects Manager, underlined the extraordinary importance of the Professor's

work to Indena. This collaboration has led to important discoveries and to the development of compounds of great interest, for example the transformation of 10-DAB into its 14 hydroxy-derivative, which led in turn to the synthesis of a new molecule today licensed to an American company. Gabriele went on to say that "The most important teaching which we owe to Bruno Danieli is that innovation is the application of scientific observation to everyday problems. Paradoxically, the best inventions are not the most elaborate or the most elegant, but are often the simplest of all". In recognition of his great contribution to the chemistry of natural products, Dario Bonacorsi, Chairman of Indena, presented Professor Danieli with a plaque on behalf of the entire company management.

LEUCOSELECT® BLASTS OFF INTO SPACE

It may still be too soon for astronauts to be able to tuck into a real earthly meal in an exclusive orbiting restaurant. However, Japanese astronaut Koichi Wakata, 45, has already been able to enjoy real apples carefully conserved inside the International Space Station (ISS).

The apples were wrapped in special tissues treated with a combination of Indena's grape seed extract Leucoselect® and other ingredients to keep them fresh and appetising.

The experiment, fruit of research carried out by Tohoku University in Japan together with a private Japanese company, allowed the astronaut for a brief moment to forget all about the usual freeze-dried foods used for nutrition in space.

The mechanism at the heart of maintaining the freshness of fruit is still the subject of research and does not seem related to anti-bacterial activity. However, buoyed by the results they have obtained, researchers claim they now plan to test the conservation qualities of these tissues on different fruits such as grapes and peaches.

This new application for Leucoselect®, one of Indena's best known and widely sold products, shows how research into botanical extracts provides continual stimulus and can even lead to the exploration of new worlds.



Koichi Wakata in the International Space Station

FURTHER TESTIMONY FOR MIRTOSELECT®

Numerous clinical studies provide ample proof of the effectiveness of the bilberry extract Mirtoselect® (*Vaccinium myrtillus* L.). Further confirmation has now been presented of its efficacy in patients affected by diabetic retinopathy. This disease is considered to be one of the principal causes of blindness, and its increasing occurrence is associated with the greater life expectancy of diabetic patients. According to results recently published in the *Korean Journal of Ophthalmology*, 49(10), 2008, 1629, the 88 patients involved in this multi-centre study were given Mirtoselect® (510 mg/die) for one year. This led to a significant improvement in visual contrast, preventing the loss of sharpness and the onset of macular edema. Treatment with Mirtoselect® contributed to the maintenance of good quality vision and to patient satisfaction. Further important clinical testimony of the role of Indena's standardised bilberry extract

in chemoprevention has recently been published: 25 patients suffering from colorectal cancer were given standardised bilberry extract at 36% in anthocyanins for a week prior to surgical removal of the tumour. The proliferation of tumoural tissue in the patients treated diminished by 7%. This pilot study confirms the potential chemopreventive activity of the bilberry extract as found *in vitro* (*J. Agric. Food Chem.* 57, 2009, 3094) and in animal models (*Int. J. Cancer* 119, 2006, 2213). Lastly, another very recent study on gene expression with DNA microarray technique (*Nutrition and Cancer* 60 [S1], 43) has shown that Mirtoselect® is able to attenuate the expression of pro-inflammatory genes and to re-establish the expression of anti-inflammatory genes in *in vitro* cellular models, suggesting a *rationale* for the anti-inflammatory properties found in anthocyanins in bilberry.

PAIN RELIEF FOR PETS ANIMALS

Turmeric is "the saffron of the Indies" and it is hard to imagine the colours and fragrances of India without this much used spice whose intense yellow colours and flavours the wonderfully rich masala sauce typical of Indian cuisine. Though turmeric is a remedy well known in Ayurveda medicine, only recently has western science recognised its therapeutic properties, attributable mainly to curcumin, a compound endowed with anti-inflammatory and anti-oxidant activity.

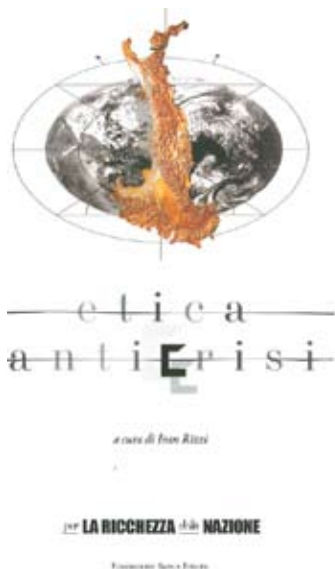
From the point of view of its absorption, however, curcumin exhibits low bioavailability and poor stability. Indena has managed to overcome these difficulties with its patented innovative complex of turmeric extract and phospholipids, which has shown an evident improvement in the absorption, and therefore efficacy of the active principle.

This compound, Curcuvet®, has been developed specifically for the treatment of inflammation in domestic animals (chiefly in dogs and horses), often affected by arthrosis / arthritis in advancing age. Curcuvet® has been tested clinically on these animals, employing



a modern nutrigenomic approach which has spotlighted its effectiveness in reducing the expression of the principal inflammatory mediators, as well as naturally reducing the painful swelling symptoms. Recommended as an active principle in supplements to be administered alongside traditional non-steroid anti-inflammatory drugs, the first remedies based on Curcuvet® will be available by the end of the year.

IDEAS FOR SUSTAINABLE DEVELOPMENT



The new book "Etica anticrisi"

With its project "For the wealth of the nation. Can Ethics help development?", the Banca Europa Foundation has brought to the centre of public attention the role of Ethics as an indispensable tool for development in our country.

The initiative has enabled intellectuals and business representatives, including Indena Chairman, Dario Bonacorsi, to exchange views on these issues, gathering together contributions from some of the most notable exponents in Italian culture, politics and business in a new book "Etica anticrisi" (Anti-crisis ethics), published in over 80,000 copies. In Bonacorsi's view, "only if there are precise terms of reference, shared and prescriptive universal values which regard firstly the person and, then immediately, society, businesses and the professions, can we achieve important, positive and consequently gratifying results, both for the individual and the company." According to Dario Bonacorsi in fact, only by reclaiming these values and dedicating the necessary resources to innovation will it be possible to match the needs of company employees with business objectives, sustainable development with respect for those caught up in the midst of it.

INDENA HONOURED BY THE AMERICAN BOTANICAL COUNCIL

Indena was presented with the American Botanical Council Varro E. Tyler Commercial Investment in Phytomedicinal Research Award during the 4th Annual American Botanical Celebration and Awards Ceremony which took place on March 5th, 2009 in Anaheim, California. The ceremony featured the presentation of the annual ABC Botanical Excellence Awards, honouring individuals and companies who have made a significant impact on the success and development of herbal medicines.

Indena which has always held research and development to be its priority, is very proud to receive this award from an important institution such as the American Botanical Council.

"It is indeed a great honour", said Greg Ris, Vice-president of Indena USA. "Indena has always had great esteem and respect for Dr Tyler, who was a real gentleman as well as an acknowledged expert in the field of phytotherapy, a great researcher and generous teacher".



Steven Foster, Christian Artaria, Mark Blumenthal, Greg Ris, Chris Tower at the Annual ABC celebration

CERTIFICATION FOR SEMI-SYNTHESIS PACLITAXEL

Indena is one of the world's major producers of Paclitaxel, a fundamental anticancer principle. In addition to natural Paclitaxel, the company has for some time also used a patented semi-synthesis process to manufacture Paclitaxel from 10-Deacetylbaaccatin obtained from *Taxus baccata* cultivated in the company's own plantations.

This process has recently been placed under the microscope of the European Directorate for the Quality of Medicines (EDQM) whose remit includes monitoring the quality of substances used in drugs for human and veterinary use.

Indena has therefore become the first producer to receive the Certificate of Suitability of the European Pharmacopoeia (CEP) for semi-synthetic Paclitaxel, which is recognised in all EU member states as well as by Australia, Canada and Switzerland.

This CEP together with the one Indena had already obtained for the production of natural Paclitaxel, means that Indena customers can save both time and resources which they would otherwise have to employ submitting process and quality control documentation to the EDQM.

INDENA MEETS UP WITH ASIAN PARTNERS

The picturesque resort of Bali was the setting for the third Asia Pacific Regional Meeting, held this year from 23rd to 25th March. Distributors and agents coming from various parts of Asia met with Indena professionals to analyse markets and exchange news. As on previous occasions, the objective of the meeting was to increase awareness of Indena products, examine their merits and potential on the various Asian markets.

Ezio Bombardelli and Giovanni Appendino explored the scientific aspects of both new and "historic" Indena brands whilst Stefano Togni presented some of the finished



products which have been created out of the fruitful collaboration with other companies. Besides providing a valuable progress report, this meeting was also an ideal opportunity

for socialisation and bonding, in which participants were able to share experiences, foster personal relations and gain a deeper understanding of the Indena philosophy.

HEALTH ISSUES TO CHEW OVER



Ever more functional foods, ever fewer capsules and tablets. Today's modern food supplements very often tend to make use of more familiar and appetising means of introducing active principles into the diet. Clearly there is growing popularity for functional foods, or foods which contain added nutrients and for which the producers can claim to be salutary as they target savvy health-conscious consumers.

Long associated with this new trend, Indena has set up an interesting project in partnership with Gum Base Co., one of the world's principal producers of compressed powder gums used in the confectionery, nutraceutical and pharmaceutical industries. Using next generation chewing gum technology, the beneficial effects of certain well-known Indena extracts (such as Opextan[®], Mirtoselect[®], Leucoselect[®] and Ginselect[®]) are released from the gum and absorbed by the organism.

In addition to the many ongoing projects with food companies, Indena also regards major producers in the confectionery sector as privileged partners in developing innovative systems of purveying its botanical extracts.

INDENA TOURS: BEST TRAINING SYSTEM IN THE REGION

At Indena quality is an extremely important matter. Consequently employees' continuous and effective training is considered a key effort to cope with ever higher quality standards required by an increasingly demanding market keeping an high level of expertise. Last May Indena Tours has been awarded by the MEDEF Touraine (Mouvement des Entreprises de France) for the excellence of its staff

training system, the best in the region. Commenting on the news, François Mairiel, Indena Tours Technical Director has said: *"We are much honored of this prize as it rewards one of the most felt topics for the whole company. At Tours we have in place high training standards complying with Indena's staff policies. That's why I consider this award as a great success of the Indena quality philosophy as a whole"*.

A WINNING COMBINATION TO FIGHT GLAUCOMA

According to the Glaucoma Research Foundation, one of the greatest risk factors in the onset of blindness is indeed glaucoma, and a 50% increase in its occurrence is expected by 2020. Whilst there are many risk factors which lead to the full-scale development of glaucoma, one of the most significant is raised intraocular pressure.

Mirtogenol[™], an innovative combination of two natural extracts based on Pycnogenol[®] - an extract of maritime pine bark (40mg) - and Mirtoselect[®] - a bilberry extract (80mg) - has been tested in a recent clinical study conducted on patients with above average intraocular pressure, even if asymptomatic. Administering this combination of the two natural extracts twice a day, a statistically

significant 95% reduction of intraocular pressure was observed in the patients treated. Mirtogenol[™] is the patented result of a fruitful collaboration between Indena and Horphag Research. Each of these two companies has focused uniquely on its own active principle to create a new formula for eye health. Mirtogenol[™] is indeed the first supplement which contributes effectively to the control of intraocular pressure whereas further clinical surveys on its prolonged use, even with lower doses, have recently confirmed the effectiveness of comparable compounds, even though these results are reached over a longer timescale. This new technology is made available on an exclusive basis only to customers around the world.

A RICH SOURCE OF INFORMATION



The educational session with prof. Della Loggia

Indena has always sought a dialogue with the organs of information endeavouring to meet their needs and respond to their enquiries. Indeed, it is not unusual to come across articles penned by Indena experts in specialist reviews and scientific journals. But there's more to Indena's commitment than that: to coincide with the latest edition of the international Cosmoprof Fair in Bologna, the company threw open the gates of the production plant in Settala and invited both Italian and foreign journalists to follow company products on their journey from the raw vegetal material right up to the standardised extract. In another initiative last June, Indena organised

an educational session intended for the non-specialised press entitled "Phytotherapy and woman's health".

Apart from the Indena speakers, the event was marked by the participation of prof. Della Loggia, Dean of the Pharmacy Faculty at the University of Trieste, who gave a brilliant talk on the myths and realities of natural remedies in women's health. Phytotherapy is a complex and ever topical science which underpins the business of Indena. Growing interest in it on the part of many journalists is a stimulus for the company to pursue its mission as an influential fount of information for all sections of the press.

INDENA EVENTS CALENDAR

- **CPhI 2009** - Madrid, Spain
13 - 15 October 2009
Feria de Madrid
Stand 3D40 - Hall 3.0
- **HI Japan 2009** - Tokyo, Japan
14 - 16 October 2009
Big Sight Exhibition Centre
Stand 2-243
- **Supply Side West 2009** - Las Vegas, USA
11 - 13 November 2009
The Venetian & Sands Expo
Stand 25027
- **In-Cosmetics 2010** - Paris, France
13 - 15 April 2010
Porte de Versailles
Stand N56 - Hall 7
- **CPhI Japan 2010** - Tokyo, Japan
21 - 23 April 2010
Big Sight Exhibition Centre
- **FCE Pharma** - Saõ Paulo, Brazil
25 - 27 May 2010
Transamerica Expo Center
- **CPhI China 2010** - Pudong-Shanghai, China
2 - 4 June 2010
SNIEC
- **Bulk@Europe 2010** - Venice, Italy
10 - 12 June 2010
Hotel Hilton Molino Stucky
- **CPhI Worldwide 2010** - Paris, France
5 - 7 October 2010
Paris Nord Villepinte
- **HI Europe 2010** - Madrid, Spain
16 - 18 November 2010
Feria de Madrid

APPENDINO TO EDIT FITOTERAPIA

Already a member of the Advisory Board of some of the principal scientific reviews dedicated to natural products, Professor Giovanni Appendino has been appointed Editor-in-chief of *Fitoterapia*, the historic publication on medicinal plants, founded in 1924 by Indena. *Fitoterapia* is now published by Indena jointly with Elsevier, and since January has appeared in a striking new format. The impact factor of this journal has grown steadily over the years and today *Fitoterapia* can claim to be one of the principal sources of scientific information in the sector. Many of the studies contained in *Fitoterapia* are submitted by researchers in emerging countries: the journal offers them a channel through which they can bring their expertise to the attention of the wider international scientific community.

Supported by a renowned international Editorial Board, *Fitoterapia* has always attracted contributions of value, and has become a fundamental reference point for the scientific community the world over.



The new Fitoterapia format



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, health foods and cosmetics.

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