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## PHYTOTHERAPY: A MODERN SCIENCE

Giovanni Appendino, R&D Director, Indena

The curative use of plants is lost in the depths of time and is linked to the discovery of health-giving properties of certain foodstuffs of vegetal origin by animals such as primates, distant relations of man from an evolutionary perspective. Phytotherapy does not have an official date of birth, although studies may be traced back to the experiments of the young German pharmacist Sertüner who obtained morphine from opium in 1804. The majority of plants however are not characterised, as in the case of opium or other "heroic" plants by the presence of a single active principle, but by a number of compounds. They are sometimes present in the plant in the form of precursors, and become active in our organism thanks to the acid environment of the stomach, bacterial flora in the intestine or those marvellous mechanisms present in the intestine and the liver, which enable us to maintain our chemical homeostasis. Starting from camomile (*Matricaria recutita* L.), a medicinal plant known to all, we discover how phytotherapy is a modern science. Camomile is bestowed with anti-inflammatory properties of a quality similar to those of NSAIDS. Only recently, however, have the molecular mechanisms been clarified and the active principles identified. Camomile contains flavonoids, polyacetylenic spiroethers, bisabolol, coumarins, polyphenols, and essential oil /oils. In reality the explanation of the anti-inflammatory

properties of camomile is complex: it contains, amongst other things, a bitterish compound, called matricina, with no biological activity itself, but which in the acid environment of the stomach transforms into a natural profen which mimics anti-inflammatory action on COX-2 (type 2 cyclooxygenase). With a potency comparable to nimesulide, matricina is in reality present in too meagre a quantity in a camomile infusion to ascribe to it uniquely the anti-inflammatory activity of the plant. This activity could be in fact amplified for example by the flavonoids, able to interfere with the transcription of the cyclooxygenase genes. Camomile taken in the form of a hot infusion stimulates the thermo-sensors in the mouth which have an indirect anti-inflammatory effect due to trigeminal stimulation. Even in the presence of a compound with well defined anti COX-2 biological activity, the picture is therefore much more complex thanks to the presence of other components in the plant and to the way in which they are taken.

The rational basis to continue to use medicinal plants in times of molecular medicine is to be found in what may be defined as synergy or the "entourage effect". Medicinal plants contain a cocktail of compounds which interact with each other creating an activity profile which transcends that of the single component. The biological action of very many plants cannot be traced simply to a "quintessence", and sometimes even what is thought to be a single active principle is constituted by a plethora of similar ones. An example is Aescin, found in horse-chestnut seeds and used topically for soothing bruises. It is in fact made up of a mix of over 50 saponins which may be very similar but are not equal.

It is clear therefore that the contrast between phytotherapy and pharmacology is not between the ancient and modern, but a distinction between the *technology of nature* and the *technology of man*. Natural remedies are the fruit of a timeless evolutionary process in which nature devised and perfected the chemical language of plants and which modern medicine continues to exploit.



### INDENA GRANTED ECOCERT VALIDATION

The most widely known international certification body Ecocert for the definition of eco-compatible standards in the production of natural cosmetics, has recently validated Indena for the ingredients Opextan™ and Zanthalene®. Validation from Ecocert fits perfectly into Indena's very own philosophy, and the company's special attention towards safeguarding the natural world in order to guarantee high quality products.

## A COLORFUL FUTURE FOR THE BILBERRY



*Vaccinium myrtillus*

Anthocyanins contained in the bilberry represent a great potential for health. Traditionally they have been used in the prevention of visual stress and for the protection of blood vessel lining, given that these molecules have a specific affinity for tissues of the vascular endothelium. Recent studies however have highlighted new fields of use: for example in the prevention of bowel cancer, or for the homeostatic control of body weight. Anthocyanosides in the bilberry proved in *in vivo* models able to inhibit mechanisms which form the basis of the tumour-forming process, while the cyanidin derivatives revealed a regulatory effect on the activity of adipocytes, preventing obesity related to the excessive consumption of fats. Recent results also suggest a contribution to

improvements in memory. In addition to that, bilberry extract (Mirtoselect®) has demonstrated significant protective activity on kidneys following damage provoked by potassium bromate (KBrO<sub>3</sub>). This is an environmental contaminant, which forms as a result of using ozone in water purification treatment; it has recently been discovered in bottles of mineral water both in Europe and the United States. Potassium bromate leads to the formation of free radicals, which cause the degeneration of cellular membranes, proteins, kidney cells, etc. Treatment with Mirtoselect® has in fact limited renal failure, promoting the normalisation of red blood cell and tissue parameters typically affected by potassium bromate intoxication.

## INDENA AND WOMENS' HEALTH: FROM RESEARCH TO MARKETPLACE

Indena has long devoted special attention to the health and well being of women. Soyselect®, the now well known soy extract standardised in isoflavones and saponins which increase its bioavailability is active on postmenopausal disorders and recent research has highlighted its potential tumour prevention properties.

Another safeguard for women's health, launched this year by Indena, is Emulgel®, a topical hormone-free preparation for the treatment of menopausal disorders. An original contribution to correct a local trophism imbalance and treat vaginal dryness, Emulgel® is available both in bulk and as a finished product.

Through its unceasing research and development, Indena makes effective use of its knowledge base and unrivalled expertise to create products based on natural ingredients, ready for distribution.

Emulgel® has been patented and is licensed to a number of pharmaceutical companies which market it under their proprietary brands. It was developed and tested in two clinical trials in collaboration with Dermogyn, a specialist Italian gynaecological product manufacturer.

First of a new line of products conceived for feminine hygiene, others will soon be alongside. Emulgel® follows on from the success of Sebacin®, a patented formulation created by Indena as an adjuvant in the treatment of acne.



### REGISTRATION IN SOUTH KOREA

Saw palmetto extract (*Serenoa repens*) produced by Indena has recently obtained registration for use in functionalised foodstuffs by the Korean Food and Drug Administration (KFDA). The extract was registered with the following market claim: "*Saw palmetto fruit extract can help maintain prostatic health*". Only food producers which use the Indena extract are authorised to display and advertise this claim.

This is in fact the second time an Indena extract has been registered for alimentary use in the country. The bilberry extract Mirtoselect® was registered by the Korea's leading company in the food sector, with the claim it could relieve tiredness in the eyes provoked by prolonged viewing of computer

수신자 (주)삼오제약 귀하 (우)135-080 서울 삼오빌딩  
(경유)  
피해 건강기능식품 기능성 원료 인허가 권리  
통)  
1. 민생서약-252510(2007.10.28)호의 권리발  
2. 위 미료와 관련하여 신청하신 "쏘팔메토  
농성분도 원료에 관한 유형(식약청)고시 제2007-518  
과, 통영과 같이 위정되었음을 알려드립니다.  
붙임 제2008-15호 기능성영양원질서(삼오제약). 끝

#### KFDA registration certificate

monitors. Mirtoselect® is the only bilberry extract with this type of registration in Korea. Products registered for use in functional foods require full clinical and toxicological documentation to support any claims regarding their activity.

There have already been two applications in the food sector: a chewable sweet and a soft drink containing Mirtoselect®, which can indeed live up to the claim.

## BERNETT CELEBRATES A DECADE WITH INDENA



*Bernett in Palestro, PV (Italy)*

Saturday 10<sup>th</sup> May. The date proved a perfect choice. A fresh spring morning in which the bright sunshine reflected in the calm waters of the rice fields and lit up the flight of the white and grey herons. But in this bucolic atmosphere of Palestro something else was shining too: this was the day when Bernett was celebrating its first ten years in the Indena group, and it did so by opening the gates of the plant to employees and their families.

In a perfectly organised programme, some 130 people filed through the different areas of the plant where they could observe a standard production cycle, from the drug storehouse to the production and packing departments, not forgetting the testing labs.

With the help of clear and thorough explanations provided by the "guides" from each department, visitors could see for themselves, and indeed marvel at what lies behind the apparently simple reality of a botanic extract production plant. All in all, Indena in miniature.

Visitors were offered light refreshments at the beginning of their tour and all received a souvenir gift for the occasion. In addition to the visit of employees and their families, Bernett was honoured to welcome representatives of the local authorities and a full turnout of the Palestro Fire Service.

There was widespread satisfaction among visitors and Bernett employees alike, the latter rightly proud of the results they have achieved in the ten years they have belonged to the Indena group.

## NEW APPOINTMENTS IN INDENA

Luca Giorgetti, a Bocconi University Economics graduate is the new Chief Executive of Indena. Dr Giorgetti has been with our Group for more than two decades. He was General Director of IdB Holding for fifteen years and has been a member of the Indena Board since 2000. At his side is the new General Manager, Daniele Giavini. With a background in

chemistry and previous experience with a German multinational, Dr Giavini joined Indena in December 1999, starting out as Area Sales Manager for North America and Germany, rising to Business Development Manager, and then Commercial Director. Dario Bonacorsi, for years at the helm of Indena, will continue to serve as Chairman.

## INDENA AND THE EXAMPLE OF CHICO MENDES

For some time Indena has adopted a multidisciplinary approach to optimise its Research and Development system and maximise the possibilities of obtaining a compound which can be produced on an industrial scale. Before any kind of phytochemical studies take place and researchers reach for their test-tubes, agronomic and botanical assessments are undertaken. Careful consideration should be given to certain important aspects when collecting samples from the widest variety of plants, originating from many different ecosystems. The natural environment in which the plant develops, in fact, could well be part of a precious biodiversity which it is important to preserve. It is also crucial to be concerned about striking a balance between intellectual propriety rights and a clear commitment to sustain the local community with part of the profits that could be generated from the industrialisation of new products.

It was to address such questions as scouting for materials that Indena participated in the 4<sup>th</sup> Nicaraguan Congress on Biotechnology which was held this year in Managua on 24<sup>th</sup> April. The meeting was organised by the Universidad Centroamericana with the support of a private company whose mission is to identify, cultivate and process biomass originating from Latin America whilst sustaining and employing the local communities.

The congress was reminded of the example of Chico Mendes and his "seringueiros", or rubber collectors, who tapped latex and gathered Brazil nuts without harming the environment and still living in the forest. Chico Mendes was assassinated for political reasons twenty years ago, but his message is very much alive: the economic benefits obtained from natural resources not only can, but must coexist alongside respect for and sustainability of the environment and the indigenous people.



## OUR FOOD BECOMES FUNCTIONAL

In line with new trends which point to ever greater attention dedicated to nutrition, the food industry is keeping pace: no longer only healthy food to satisfy our taste-buds, but a real “panacea” to integrate the micro-nutrients which are more and more lacking in our food. Already on our supermarket shelves we find milk products which help prevent ageing, bread and biscuits which protect the cardiovascular system and fruit juices enriched with antioxidants. These are just some of the foodstuffs and beverages made functional with various active ingredients.

These, alongside a number of other unexpected applications throw down an exciting new challenge for Indena. The company is exploring in various alimentary fields potential uses for its extracts, whose effectiveness has been clinically demonstrated. Dairy products, for example, could be an excellent medium for the incorporation of active extracts endowed with functional activity. Care must be taken however to assess formulatory



aspects. Regulatory issues will also be important given that food products require characteristics which are not necessarily interchangeable with those required for the active ingredients used in true nutritional integration.

The sector is new, wide-ranging and stimulating, and Indena intends to draw on its experience with natural products to create effective functionalized foodstuffs.

## INDENA SCIENTIFIC COMMUNICATION ACCLAIMED

The Mauro Prevedello Prize for the best scientific communication was awarded to Indena during the National Conference of the Italian Society of Cosmetic Chemists (SICC) held in December 2007.

The award was in recognition for the document “Ginkgo Biloba Dimeric Flavonoids Phytosome” and bore the following citation: *“The communication is rational, clear and concise; the target audience and message are readily perceived as are the product features. It contains clear and well-argued supporting evidence on differentiating and competitive factors and provides useful data for the laboratory and clever tips for marketing. Both its format and functional style are well suited to the needs of a laboratory.”*

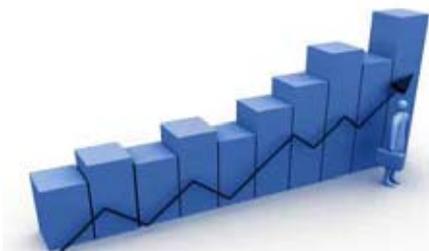
The prize honours the memory of the well-known cosmetologist and journalist Mauro Prevedello, an outstanding communicator whose life was dedicated to scientific communication.

Evidence yet again not only of the commitment of Indena to good science, but that the results of our labours are made known in a clear and thorough manner.



*The Prevedello award*

## INDENA IS TEACHING AND IT'S NOT JUST SCIENCE



The collaboration between Indena and the academic world to promote education and training in phytotherapy is well-established, but today there's something new.

Lectures given in Italian universities, in fact, will focus not merely on the science of phytotherapy, but also on its market, its very diverse segments and the different “lives” of the same product.

A product of natural origin has outlets in a number of sectors, sometimes with little in common: from pharmaceutical applications, mainly for pure molecules, to the food supplement market, from functional foods to the cosmetic world, from “oral cosmetics” to products for veterinary use.

We feel therefore that an overview of the tools available, knowledge of the main distributive channels in the phytotherapy market and a capacity to analyse are fundamental elements in the education of our future scientists.

And that's why we find the Indena Marketing Director, Christian Artaria, enlightening students on what market research is and what it does, what information it can give and just how this can be put to use.

## INDENA GREEN TEA BAGS FROST&SULLIVAN PRIZE



Indena has been given the 2008 European Green Tea Extracts Excellence in Research Award by the international consulting firm, Frost&Sullivan. This award is a recognition for companies which, in the various regional and global markets, have shown excellent performance and results in terms of leadership, research and development. Each year, the Frost&Sullivan prize for excellence in research is awarded to a company which has carried out innovative and pioneering research and which stands out for the provision of services and solutions which are fruit of this research. The prize was bestowed on Indena "for having been able to develop superior research capacity and innovative product solutions which meet the needs of the green tea market. Indena today can boast leadership in terms of safety, effectiveness and innovation and its standardised extracts have become the market benchmark."

Former winners of the Best Practice Award include: IMB, Ansaldo Energia, Nokia, BASF, DSM, Starpharma and AstraZeneca . The Award will be presented to Indena during the Frost&Sullivan Banquet to be held in London 11<sup>th</sup> November 2008.

## INDENA IN MADAGASCAR

Despite the change of ownership of the Fianarantsoa plant in Madagascar, Indena remains active and involved in the country to sustain the development of the manufacturing unit. The agreement for technical and commercial collaboration with the new owners is very important for Fianarantsoa, and they are committed to maintaining and sustaining the social policies espoused by Indena to aid the local population.

And thanks to the work of our colleagues Andrea Borsari and Vittorio D'Adago the local population continues to enjoy the traditional initiative "Another Place at the Table", the Christmas Party for the children of Fianarantsoa and their families with its special significance of giving and receiving presents. We are also delighted to see how the new Iakora Elementary School building is progressing. Brick upon brick, we see the fulfilment of this new facility which will be fundamental in the education of an ever growing number of children.



Madagascar in a child's picture

## INDENA TURNS TO THE PHARMACIES

Recalling the most ancient and noble tradition of the officinal art, when the apothecary concocted medicaments based on medicinal herbs, Indena is turning once again to pharmacies (though only in Italy for the moment), and inviting pharmacists, especially the younger ones, to look back to their origins. According to market research commissioned by Indena on a representative sample of Italian pharmacies, in fact, it emerged that the role of phytotherapy effectively "perceived" by pharmacists is much lower than it is in reality, as are the phyto-therapeutic products they acquire and recommend.

In fact, professional pharmacists are eager to receive greater scientific information on active ingredients of natural origin. In the light of this Indena has undertaken a series of communication initiatives aimed directly at pharmacies. Special documentation has been designed and produced together with Pharbenia (part of the Bayer group in Italy); Indena has also contributed editorial comment to an interesting dossier recently published in

the most important journal of the pharmacy sector. The competence and professionalism of the pharmacy channel, in fact, could prove crucial in conveying a message of quality, safety and effectiveness which are dear to Indena.



The new advert targeted to pharmacies shows a pharmacy sign and reads "Quality is always on call"

## INDENA IN A PIXEL



*The pixel painting*

Last year's international CPhI fair was held in Milan where Indena had the honour of inviting clients and partners to enjoy an unusual evening in an exclusive and exquisite setting: no less than the fifteenth-century cloisters of the Umanitaria, in the city centre. Guests were welcomed inside the magnificent Salone degli Affreschi, where they could admire renaissance art in all its glory. But this was not the only thing to capture people's attention during the gala dinner: one very special guest in fact was to give a performance of pixel painting before their very eyes. This was the German artist Christof Breidenich who in his unique style created



an enormous tableau inspired by the art of Indena. It depicted themes and topics dear to the company such as a sprig of yew, and the thistle flower. Starting out from a completely blank canvass, the artwork would gradually take on shape and colour in the course of the evening. And then the climax as this huge work was broken up into many smaller pieces which were framed, signed by the artist and presented to all the guests. Each individual "pixel" therefore became an original souvenir not only of a memorable evening, but also of a moment in which the values of Indena were shared and expressed in the universal language of art.

## ANOTHER YEAR WITH INDENA

The fascination with plants and also their flowers, seeds and roots, was the theme this year for a new, evocative desk calendar produced by Indena. Shown off in all their glory by the clever use of light, the marvels of nature accompany us through another year.



## BRAND NEW LOGO FOR SILIPHOS™



an  indena product

*Siliphos™ new logo*

One of Indena's most successful products, Siliphos™, has a distinctive new logo. Siliphos™ is a very extensively documented product from *Silybum marianum*: it results

## INDENA EVENTS CALENDAR

- **CPhI 2008** - Frankfurt, Germany  
30 September - 2 October 2008  
Messe Frankfurt  
Stand 30D12 - Hall 3.0
- **HI Japan 2008** - Tokyo, Japan  
15-17 October 2008  
Big Sight Exhibition Centre  
Stand 2-247 - East Hall 2
- **Supply Side West 2008** - Las Vegas, USA  
22-24 October 2008  
Sands Expo  
Stand 18017
- **HI Europe 2008** - Paris, France  
4-6 November 2008  
Paris Nord Villepinte  
Stand F049 - Hall 1
- **In-Cosmetics 2009** - Munich, Germany  
21-23 April 2009  
New Munich Trade Fair Centre  
Stand K200 - Hall A2
- **CPhI Japan 2009** - Tokyo, Japan  
21-23 April 2009  
Big Sight Exhibition Centre
- **Vitafoods International 2009** - Geneva, Switzerland  
5-7 May 2009  
Geneva Palexpo  
Stand 261 - Halls 1&2

from the complexation of silybin, one of the active compounds in silymarin, with soy phospholipids which increase its bioavailability. Safe and effective, it is an important tool in the prevention of liver disorders. The new logo is again a clear sign of assurance of the quality Indena provides.



*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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