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THE ROLE OF PLANTS IN HUMAN HEALTH

*Christian Artaria, Marketing Director, Indena
Giada Maramaldi, Scientific Product Communication, Indena*

Edible plants have always contributed hugely to improving human health.

Natural products have in fact been used since the earliest times, in various forms, both for the treatment of pathological conditions and for their beneficial effects on human health. The use of edible and medicinal plants in the Chinese, Indian, Egyptian, Greek and Latin civilisations is documented in numerous ancient works dating back thousands of years.

Recent findings reveal that an important role in the pathogenesis of the most common diseases is played by nutrition, when judged from an epidemiological standpoint.

As the prevalence of aging related diseases, for instance, is increasing not only in the Western countries, but emerging countries are also beginning to face disorders related to well-being, a growing attention to nutrition and its possible optimization is being dedicated to potential prevention.

Optimising human nutrition, which means integrating potential protective substances into a specific diet, is a concept arising from the converging information of basic biomedical science with epidemiological evidence, allowing the hypothesis of the optimization of human nutrition to prevent or reduce the onset of various diseases for populations or homogeneous groups of people.

In this sense, edible plants are not only defined as important foods for a healthy lifestyle, but are also object of phytochemical research aimed to identify the protective active ingredients. This has led to research and development of botanical extracts from the most interesting edible plants.

Polyphenols are one of the most representative examples of natural protective substances, and are present in almost all edible plants. Their consumption has been linked to a lower risk of chronic degenerative diseases, as their role is to counteract the "stress reaction", a sort



Olive fruits

of cell response to an attack, which seems to play a crucial role in most chronic pathologies. This harmful response is one of the typical targets of natural substances, usually found in botanical sources, which can modulate and control the production of oxidants.

A standardised approach to the dietary antioxidant treatment is therefore an open field where edible plants, in the form of standardised extracts, can contribute to optimise nutrition. Turning to pharmacognosy, botanical sources can provide us with not only extracts, but also with pure molecules. According to Newman et al (2003), 28% of the New Chemical Entities discovered in the last 20 years are natural products, or natural derivatives. Another 20% mimic natural products, indicating that the synthetic product has been created by researching into natural substances.

The potential of pharmacognosy is huge, considering that only a limited number of the molecules present in the botanical kingdom have been studied. Nature however, in millions of years of evolution, has already carried her own selection of molecules endowed with biological activity.

Research into edible and medicinal plants, long known in their traditional uses, is a vital means therefore of obtaining new standardised extracts or new active molecules able to improve human health.

97TH AACR MEETING: INDENA CONTINUES TO CONTRIBUTE TO ONCOLOGY

Indena's commitment to Oncological research was recently in the spotlight following the success obtained at the 97th American Association of Cancer Research meeting held in Washington in April 2006. Indena was present with the sponsorship of two oral and four poster presentations.

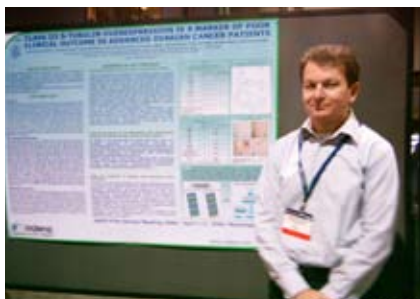
Dr. R. Giavazzi from the Mario Negri Institute in Bergamo, Italy, was invited by the AACR organisation to present an overview on the more advanced new taxanes originated by Indena IDN 5109 and IDN 5390. The talk entitled "The chemistry and biology of novel microtubule-stabilizing agents", was part of the educational session addressing new findings in the field of taxanes. The results examined by Dr. Giavazzi underlined the importance of Indena's research into finding innovative derivatives of taxol and taxotere, up to now the only taxanes marketed as anticancer agents.

The second Indena presentation was related to the innovative mechanism of tumour progression and chemoresistance involving the Class III of beta-tubulin and the hypoxia factor HIF-1-alfa. Dr. Ferlini from Rome's Università Cattolica del Sacro Cuore described new results showing the relationship between these two relevant factors which could open fresh perspectives in

understanding more about chemoresistance and how it is to be overcome.

Three of the four posters presented at this meeting considered new mechanisms involved in cell motility, the modulation of angiogenic factors and the clinical relevance of Class III beta-tubulin as a marker of poor prognosis in patients suffering from ovarian tumors. Finally, a poster was displayed describing the antitumor activity and the pharmacokinetics profile of IDN 5174, an innovative camptothecin originated by Indena.

The presence of Indena at one of the most important oncology meetings worldwide, is the fruit of successes obtained in different projects co-ordinated by the company and developed in conjunction with research centres of excellence in the field of oncology.



Dr. Cristiano Ferlini at the 97th AACR Meeting

INDENA AND NERVIANO MEDICAL SCIENCES JOIN FORCES IN R&D

Indena signed a co-development agreement with Nerviano Medical Sciences, the largest pharmaceutical R&D facility in Italy and one of the largest oncology-focused, integrated discovery and development companies in Europe. The aim is to handle the scale up and manufacturing of two new drug candidates, IDN 5404 and IDN 5243 which are currently in preclinical development. IDN 5404 is a highly potent API selected for its action against tumor resistance to cisplatin and topotecan. Based on the last research findings, it could represent an innovative and powerful therapy against several tumors, especially resistant to cisplatin and to topotecan. The second one, IDN 5243 is an original New Chemical Entity endowed with excellent muscle-relaxant action, to emerge from collaboration between Indena and major Italian Universities. Both molecules are approaching Phase I after having successfully undergone their preclinical studies. Indena and Nerviano Medical Sciences bring to this agreement their respective strengths. Indena discovered the two new molecules from botanical origin and has chartered the original semi-synthetic path. Nerviano, on the other hand, will draw on its specialization in highly potent compounds to scale up the process. The venture is coordinated by Gabriele Fontana, Indena's Chemistry R&D manager in Milan and is proof of the achievements that can be reached when two strong Italian companies work in unison.



Nerviano Medical Science Management and Oncology Business Unit Headquarter

INDENA AT THE 48TH ANNUAL MEETING OF THE ITALIAN CANCER SOCIETY

There is an emerging body of evidence that the extracts from edible plants play a role as chemopreventive agents in cancer over and above their chemotherapeutic activity. Indena, as a leading company in the production of natural extracts and drugs of botanical origin will organise a luncheon-seminar at the next Annual Meeting of the Italian Cancer Society to be held in Bari in October. The aim is to increase awareness of this approach to research in oncology, at this the most important meeting devoted to cancer research held in Italy. The seminar entitled "Edible plants against cancer: state of the art and future perspective" covers the most important topics

involved in the standardisation of botanicals, the development of natural occurring agents as chemopreventive drugs and the molecular mechanism of the action of plant derived molecules on angiogenesis. Based on Indena's experience, the talk on the standardisation of extracts will be given by the Scientific Director Paolo Morazzoni. The other two topics will be discussed by prominent researchers in this field, Prof. A. Gescher of Leicester University, UK and A. Albini from the National Tumour Institute of Genoa, Italy. The organisation of this event represents a further effort from Indena to support its growing presence in the field of Oncology Research.

INDENA BRANCHES OUT IN CHINA



Mr. Zhang Bin, Indena Biotechnology Shanghai Manager

New markets are emerging around the world, but nowhere more so than in China where Indena, after doing business in the country for more than 30 years, has just opened a brand new office in Shanghai.

The Manager is to be Mr. Zhang Bin, who previously headed Indena plantations in the Far East as part of the company's Indian arm. Indena already boasts long-standing operations

in China ranging from the harvesting of raw materials to scientific collaboration in traditional Chinese medicine; current market turnover is far from insignificant, but the potential for future growth is indeed exciting.

A foothold in China today is a must for a globalised company like Indena, all the more so when it can draw on three decades of successful cooperation.

AN INDENA BRIDGE BETWEEN EUROPE AND AFRICA



The group of Madagascan students

Last year Indena gave its wholehearted support to the twinning programme linking two high schools, one located in the Madagascan town of Tananarive and the other in the French city

of Tours. In place since 1996, the partnership aims to develop solidarity in education and help the "south of the world" gain an insight into developed countries. It is based on the regular provision of textbooks and learning

aids from France to Madagascar and on the study of a common subject that, every year, brings students of the two countries one step closer. In the school year 2005/06 the subject chosen was: "Aromatic and medicinal plants from Madagascar in the pharmaceutical and cosmetic industries; how they are sourced in Madagascar, how they are used in France".

Given the nature of the subject Indena willingly threw open the gates of its production sites in France and Madagascar to French and African students. In this way both groups had chance to find out much more about their subject and to discover Indena at the same time. The high point of the exchange came last May, when a group of students and teachers from the Madagascar high school visited France. A study and research gallery was set up, and the participation of Indena welcomed.

...AND A PERSONAL COMMITMENT

The personal commitment of Indena colleagues Andrea Borsari in Milan and Vittorio D'Adago in Madagascar, has forged a strong relationship between the company and the Indena Madagascar production plant in Fianarantsoa. Raising funds from among Indena employees of the Group they were able to provide a Christmas dinner for more than 1000 children with their parents in 2004 and 1300 in 2005. Thanks to the huge response of Indena people, the project was also able to provide desks and blackboards for the Ankijana School. The initiative called "Aggiungi un posto a tavola" took place last year for the second time and we are confident of the same generous response from our colleagues also in 2006.



"Aggiungi un posto a tavola" on Christmas Day

INDENA MEETS THE SCIENTISTS OF TOMORROW

A full day seminar was given by four Indena managers as part of the Post-Graduate Drug Chemistry course at Pavia University. Covering a whole gamut of issues, Gabriele Fontana opened the day by presenting the process of drug discovery and a historical perspective of pharmacognosy, the science behind medicinal plants. Beginning with Galen and Hippocrates, and then Paracelsus, Fontana traced the passage of herbal products and drugs of natural origin, highlighting molecules that have changed the world such as morphine, quinine and mevalonin. Ending with a more recent example of drug discovery from natural substances he illustrated the case of paclitaxel, derived from the yew tree, which is one of the most widely used anticancer molecules today.



Dr. G. Fontana, Research Manager

Following on, Andrea Giori examined the isolation of pure molecules and the complexities of botanical extraction and purification. The important issue of formulating a botanical active ingredient was extensively discussed

by Massimo Ronchi, as he described the crucial stages and critical concerns involved in creating a proper formulation of often complex extracts.

Finally, a broad overview of current regulation of botanical extracts was presented by Valerio Bombardelli. Bombardelli outlined the main regulatory issues for drugs and dietary supplements of botanical origin in the major markets of Europe, the US and Japan.

THE FUTURE OF HERBAL PRODUCTS IN EUROPE

In an endeavour to make a contribution to regulatory science, Indena offered to share its experience at the IBC conference on herbal medicines held in Vienna last June. The event brought together all the main players in the world of herbal products: the EU Health Authorities, interested associations and, of course, industrial manufacturers. The goal was to understand the scenario for herbal products over the next five years, whether as medicines or food derivatives, since the regulatory framework is still very uncertain and fragmented. The Herbal Medicinal Products Committee at EMEA is drawing up guidelines to facilitate the registration of traditional herbal medicines, though there is currently only one traditional product registered in Germany. At the same time there are initiatives at national level for more rational regulation of herbal products. The Belgian Health Service representative explained their regulatory model: the same plant or derivative could be considered as either medicine or food depending on dosages. A commission of experts should evaluate the proper dosage in relation to its expected use. In essence the scenario remains fluid, but it is very likely that member States with a strong interest in herbal medicines, will apply the new traditional herbal medicines directive. In countries where herbs are used mainly for food, national laws will apply. Indena's own position, as expressed in the presentation, is that each herbal derivative should be produced according to strict rules in order to obtain an "active" ingredient of constant and reproducible quality, irrespective of the final destination of the ingredient itself, be that in medicines or foodstuffs.

INDENA AT THE BILBERRY DAY



Vaccinium myrtillus

The first Italian Bilberry Day took place on June 8th, organized by the Faculty of Pharmacy at the University of Trieste under the patronage of the Italian Botanical Society, the Italian Society of Pharmacognosy and the Italian Society of Phytochemistry. The aim was to share state-of-the-art knowledge of the bilberry, from its botanical properties through to extraction methods and its role in medicine.

Indena researchers, recognized as the major experts on these subjects, gave three lectures before a gathering of scientists and young researchers. In an interdisciplinary seminar dedicated to the bilberry, over 150 delegates from various Italian Universities were illuminated on different aspects of the fruit, benefiting from both a practical and theoretical approach.

Dr Renato Iguera described the procurement problems for medicinal plants; Dr De Combarieu illustrated the different components of the bilberry, highlighting those more significant for quality evaluation, while Dr Cristoni focused on the bilberry's pharmacological properties, and particularly its content of anthocyanosides.

INDENA EMBRACES ACADEMIA

Indena has long been known for working closely alongside universities to foster and support education in phytotherapy. Not only do Indena specialists give lectures and take seminars at many University sites, the company has been proud to sponsor masters courses in Phytotherapy at the Universities of Trieste and Siena. This continues an educational process that has become part of the company's tradition, eagerly taken up by an ever-increasing number of post-graduate students.



Meanwhile on its home ground, Indena welcomed some 150 scholars to the Settala production site during the 2005/2006 academic year. University and high-school students from Italy and abroad were shown round the advanced laboratories and production units, to see for themselves the many facets of application of phytotherapy in industry.

INDENA IS LOOKING AHEAD



New glove boxes unit

Indena is constantly innovating and seeking new ways to make industrial production and processes ever more efficient. In order to cope with increasing customer demand, every year Indena is investing in cutting edge production equipment for its plants throughout the world. In its main Italian manufacturing site in Settala the company has recently launched a new production line for cytotoxic compounds and new solid/liquid separators are replacing older ones.

A new powder treatment department, which meets recent GMP regulation, is also under construction and is to be completed by 2008. Indena's second largest production site in the French city of Tours is to have a new purification line which will start operating from September 2006. Forward-looking Indena believes these efforts will allow the company to remain at the forefront of the industry and is investing resources today to ensure a secure future tomorrow.

THE BENEFITS OF SOY

Even among health professionals, confusion exists about proper nomenclature and the precise composition of the agents under investigation. Levels of isoflavones are frequently assumed to be constant within categories of soy food, and intakes are estimated rather than being directly analyzed, products with high variability in chemical composition are assumed to be the same in some study reviews.

In this conflicting arena Indena continues his educational commitment about standardization and is adding new consistency to his standardized product Soyselect®.

New results, based on studies of an experimental model designed to investigate consumption of soy-derived products as a natural alternative to hormone replacement therapy in post-menopausal breast cancer women, have been presented at the 6th International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Fruit of the now consolidated collaboration between Indena researchers and scientists from the Policlinico Gemelli Hospital in Rome, these results provide evidence that consumption of Soyselect® (a standardized soy extract containing isoflavones and saponins), does not stimulate the growth of breast cancer tumors in the experimental model used (xenograft MCF-7).

Daniela Gallo, a scientist with the Gynaecology Oncology Department in the world-famous Roman hospital, explained that "Soy-derived products may induce a moderate estrogenic effect on estrogen dependent cells, without increasing cellular proliferation and tumor growth".

The study also highlighted a decrease in the expression of other genes involved in tumor progression and angiogenesis, such as Thrombospondin 1 and Transforming Growth Factor β 2.

Though positive these experimental results have yet to be confirmed by a full clinical analysis.

The role of Soyselect® to alleviate menopause and post-menopause symptoms is well known as it has been extensively studied by Indena with pharmacokinetic, toxicological and clinical testing to ensure its safety and efficacy.

It's like a
double shot of soy.



Introducing patented Soyselect® soy isoflavones with two standardized actives

Soyselect® most recent advert

A SIGN OF QUALITY

Two new logos for our flagship products Mirtoselect® and Soyselect® have been filed this year. The new logos will make the products more distinctive and appealing to the consumer and are aimed to be a clear sign of assurance of the consistency and quality Indena provides.

mirtoselect[™]
an  indena product

soyselect[™]
an  indena product

To learn more, visit:



Mirtoselect.info



Soyselect.info

OPEXTAN™: FOR A BEAUTIFUL OLIVE COMPLEXION

The Olive Tree has been a symbol of the Mediterranean culture since antiquity. Both Pliny and Hippocrates prescribed medications from the olive to treat a number of disorders. Result of an Italo-Japanese collaboration, a novel olive fruit extract, OPEXTAN™ has been developed and quite extensively documented. From the selection of a specific variety of Italian olives with a unique polyphenolic profile, OPEXTAN™ is a patented olive fruit extract rich in polyphenols, the most characteristic and potent of which is verbascoside. Its free radical scavenging activity has been demonstrated in vitro, but also efficacy tests on human volunteers have shown the capacity of the extract to protect skin from UV induced damages, such as wrinkling, aging, etc. OPEXTAN™ is suitable both for topical and oral application, in order to guarantee protection both from the inside and the outside.

Presenting
the Mediterranean
skin diet.



Opextan™ most recent advert

INDENA'S EXHIBITIONS AGENDA

- **CPhI 2006** - Paris, France
October 3 - 5, 2006
Paris Nord Villepeinte, Stand 5J30 - Hall 5
- **HI Japan 2006** - Tokyo, Japan
October 4 - 6, 2006
Tokyo Big Sight Exhibition Center, Stand B - 239
- **Supply Side West 2006** - Las Vegas, USA
October 18 - 20, 2006
Sands Expo, Stand 4053
- **HI Europe 2006** - Frankfurt, Germany
November 14 - 16, 2006
Messe Frankfurt, Stand G31 - Hall 3.0
- **In Cosmetics 2007** - Paris, France
April 17 - 19, 2007
Porte de Versailles, Stand B46 - Hall 4
- **CPhI Japan 2007** - Tokyo, Japan
April 18 - 20, 2007
Tokyo Big Sight Exhibition Center
- **Vitafoods 2007** - Geneva, Switzerland
May 8 - 10, 2007
Palexpo Geneva, Stand 444
- **FCE Pharma 2007** - San Paolo, Brazil
May 15 - 17, 2007
Transamerica Expo Center, Stand 474
- **CPhI China 2007** - Shanghai, China
June 19 - 21, 2007
SNIEC - Shanghai New International Expo Centre
- **CPhI 2007** - Milan, Italy
October 2 - 4, 2007
Fieramilano Rho
- **HI Japan 2007** - Tokyo, Japan
November 20 - 22, 2007
Tokyo Big Sight Exhibition Center, Stand B - 239
- **Supply Side West 2007** - Las Vegas, USA
Sands Expo

 **indena**[®]
science is our nature

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.

HEADQUARTERS

Indena S.p.A., Viale Ortles, 12 - 20139 Milan - Italy tel. +39.02.574961 fax +39.02.57404620 www.indena.com

SALES BRANCHES

Indena France S.A.S., 23, rue de Madrid - 75008 Paris - France tel. +33.1.45229128 fax +33.1.45220291

Indena S.A., Gran Via de Carles III, 94, 10, 1º - 08028 Barcelona - Spain tel. +34.93.330.35.66/38.16 fax +34.93.411.02.46

Indena USA Inc., 811 First Avenue, Suite 218, Seattle, WA 98104 - USA tel. +1.206.340.6140 fax +1.206.340.0863

Indena Japan Co. Ltd., KDDI Bld. 21F 1-8-1, Otemachi, Chiyoda-Ku - Tokyo 100-0004 - Japan tel. +81.3.3243.9924 fax +81.3.3243.9925