

OLIVE FRUITS AS A SOURCE OF HEALTH

Indena innovative extract out of the Mediterranean tradition

Amsterdam, November 16th. On the occasion of Health Ingredients Europe 2004, a three day of exhibition, conferences and seminars which is going to be held in Amsterdam from 16th to 18th November., Indena will present its OLEASELECT™, a new standardised olive fruit extract.

HI Europe 2004 is an important opportunity for international ingredient experts for gathering to hear and see the latest applications and developments. More than 6.000 attendees will have the chance to come in touch with 450 exhibiting companies.

Indena OLEASELECT™ is a patented olive pulp extract from a selected Italian variety of olive, particularly rich in polyphenols.

Among the polyphenolic compounds, verbascoside and hydroxytyrosol are the most important ones and are reported to be responsible for many of the biochemical and biological effects of the extract.

Oleaselect™ contains not less than 1,5% hydroxytyrosol and 5% verbascoside: these two data are granted by Indena's quality and standardisation.

Moreover, an innovative patented extraction procedure allows to use water and ethanol as the only solvents.

The beneficial health properties of olive oil consumption have been correlated to a decreased incidence of cardiovascular diseases and of certain cancers in the Mediterranean area. The healthy properties of olive oil are not to be attributed only to its content of unsaturated fatty acid, but also to polyphenols: numerous studies, in fact, have shown that phenols in olive are potent inhibitors of LDL (Low Density Lipoproteins) oxidation, which is linked to the formation of atherosclerosis plaques. These ones contribute to the development of severe coronary heart disease.

Ever since ancient times, the olive tree is the symbol of the Mediterranean civilisation, which has been accompanied through the centuries by this traditional plant. It used to provide the Mediterranean populations with nutrients, light, heat and medicinal health remedies and soon created a very special relationship with people. Both Pliny and Hippocrates prescribed medications containing olive leaves and oil as cures for a wide number of disorders, ranging from inflammation of the gums to insomnia, nausea and boils. Many of these old remedies have passed into folk medicine and are still as relevant today as they were hundreds of years ago.

Indena, thanks to its depth of expertise and more than 80 years of experience in manufacturing pharmaceutical grade botanicals, sets the standards of excellence for active principles, destined for the pharmaceutical and dietary supplement markets. Moreover, Indena's long experience in botanical derivatives can be of assistance for developing reasonable regulations to ensure the quality and safety of botanical extracts.

To learn more please visit us at Stand D14 Hall 1A

For information about Indena:

<http://www.indena.com>

For information on the HI Europe:

<http://www.hi-events.com>

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PACLITAXEL RESISTANCE: AN ITALIAN WAY FORWARD

Indena presents two studies on IDN 5390 at the 16th EORTC-NCI-AACR

Geneva, 1st October 2004 – As part of the 16th International Meeting of EORTC-NCI-AACR, Indena presented a new line of research based on IDN 5390, a taxane derivative showing a good preclinical profile to counteract Paclitaxel resistance in cancer cells.

Organised by the European Organisation for Research and Treatment of Cancer (EORTC), in conjunction with the United States National Cancer Institute (NCI) and the American Association for Cancer Research (AACR), this international symposium bestows particular relevance on new molecular targets and drugs. The occasion provides an important meeting ground for over two thousand experts and researchers from all over the world to discuss the latest discoveries in cancer therapy. The four-day event opened in Geneva on September 28th.

Indena is actively engaged in pursuing new molecules for cancer treatment and presented two studies on IDN 5390, which are focused on overcoming Paclitaxel resistance with a more bioavailable taxane. Certain cancer cells in fact are not killed off by Paclitaxel, the antineoplastic drug extracted from yew tree. A taxane resistance mechanism was shown to be associated with an overexpression of class III beta

tubulin isoform in cancer cells. Tubulin is a protein normally present within cells, making possible processes such as cell division and the movement of materials within cells.

The first study, developed in co-operation with the Antineoplastic Pharmacology Laboratory of the University of the Sacred Heart in Rome, showed that IDN 5390 is active in cells expressing this resistance mechanism. Class III beta tubulin isoform underwent a significant reduction, both with IDN 5390 as a single treatment and in conjunction with Paclitaxel. In addition it would appear that the strong synergistic action of IDN 5390 and Paclitaxel, successfully targeting class I and class III beta tubulin, can open up a novel approach in overcoming Paclitaxel resistance.

A second study by Indena, conducted together with the Mario Negri Institute for Pharmacological Researches, sheds new light on the pharmacokinetic profile of IDN 5390. Backed up by in vitro and in vivo trials, IDN 5390 revealed good bioavailability by oral administration. The study also proved rapid metabolism and excretion, thus suggesting the drug has good tolerability.

Finally, in co-operation with the Roswell Park Cancer Institute, Indena presented a further paper focusing on new applications of Silybin, already known for its hepatoprotective activity, together with its phospholipid complex IdB 1016 (silipide). In vitro tests on human prostate tumour cells showed a significant reduction of PSA (prostate specific antigen) levels. When compared with Docetaxel, Silybin emerged as the more selective in reducing PSA levels, not only affecting human prostate tumour cell growth, but also directly reducing cellular PSA secretion, thus suggesting a potential use in the treatment of prostate cancer in men.

Indena, one of the principal worldwide producers of Paclitaxel, is in constant pursuit of new botanical derivatives of oncological interest. Participation in the Geneva Symposium is an example of the Italian company's commitment to cancer therapy.

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INDENA OPENS DEVELOPING PERSPECTIVES ON TAXANE DERIVATIVES RESEARCH

New Indena studies presented during the

228th American Chemical Society National Meeting & Exposition

Philadelphia, 22nd August 2004 – Indena, world leader industry in the research and production of active principles derived from plants, on the occasion of the 228th ACS Annual National Meeting & Exposition, presented its new lines of research based on innovative discoveries in the chemistry of taxanes, which are known to be important anticancer. The success of Paclitaxel and Docetaxel as anticancer agents stimulated the search of new analogues endowed with a more favourable pharmacological profile.

In cooperation with the Institute of Organic Chemistry and Fotoreactivity (ISOF, Istituto per la Sintesi Organica e Fotoreattività) of the CNR in Bologna and the "Alessandro Marchesini" Institute of Organic Chemistry of the University of Milan, Indena developed a semisynthetic protocol to solve the problem of supply of Ortataxel (14 β -hydroxydeacetylbaaccatin), a promising anticancer drug in clinical phase II. This new protocol uses 10-deacetylbaaccatin (or 10-DAB, molecule naturally abundant in *Taxus baccata* leaves, also known as yew tree) as a precursor. The enolization of intermediate 13-oxo-7-protected baaccatin, obtained in this semisynthetic protocol, not only granted the production of 14 β -hydroxyDAB (Ortataxel), starting from 10-DAB, but also allowed to introduce in position 14 plenty of different functionalities. Two lines of research were thereby developed, building a library of 14?-amino and 1,14-carbonate derivatives. This generated novel 14-functionalised taxoids. Since bioisosters are known in many cases to modulate the properties of a drug, both in terms of bioavailability and spectrum of activity, new promising anticancer agents were designed and developed in Indena laboratories.

Indena presented in Philadelphia the new class of 14-substituted derivatives and their early preclinical profiles. "Thanks to the enolate chemistry – says Indena's project coordinator Gabriele Fontana, who held the communication in Philadelphia – developed with ISOF and Alessandro Marchesini Institute, a wide range of 14-functionalised taxoids was generated and tested. They had their importance already supported by in vitro and in vivo data obtained in studies carried out at the Grace Cancer Drug Center at Roswell Park Memorial Institute. Indena will pursue the candidates selection for further development".

Once again, Indena's significant participation in this world oncology congress is testimony to its commitment to the pursuit of innovative cancer therapies, as a result of advanced Italian research.

Further informations and poster pdf version are available in [R&D section](#)

PRESIDENT OF THE INDENA SCIENTIFIC BOARD RECEIVES THE VARRO TYLER AWARD

Dr. Ezio Bombardelli awarded for research in botanicals during the American Society of Pharmacognosy 2004 International Congress

Phoenix, 2nd August – In occasion of the 2004 International Congress on Natural Product Research held by the American Society of Pharmacognosy in Phoenix, Arizona, Dr. Ezio Bombardelli, President of the Indena Scientific Board, has received the Varro Tyler Prize for Research on Botanical Dietary Supplements.

This award, bestowed on one of the world's foremost botanical experts, is testimony to the importance of classical botanical pharmacognosy.

Addressing the conference Dr. Bombardelli said he was honored to receive the award, which was recognition of his personal commitment and that of Indena to the science of botanicals. "*Pharmacognosy needs to be given special attention to ensure the quality, identity and purity of natural medicines*", declared the prizewinner.

For the first time in 5 years, the meeting was also sponsored by its European counterpart, the Society for Medicinal Research.

The American Society of Pharmacognosy was founded in 1959 as an outgrowth of the Plant Science Seminar which itself was established in 1923. The Society is international in scope and brings together men and women dedicated to the promotion, growth, and development not only of pharmacognosy but all aspects of those sciences related to and dealing in natural products. The Society currently has over 1,100 members, in the categories of active and associate membership. Approximately 40 percent of the active members of the Society reside outside of the U.S. and Canada and represent more than 60 countries throughout the world.

For more information about Indena:

www.indena.com

For information on the American Society of Pharmacognosy:

www.phcog.org

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Four Indena studies presented during the 95th American Association of Cancer Research Congress (AACR)

THE ITALIAN COMPANY INDENA PRESENTS A NEW LINE ON CANCER RESEARCH

Milan, 30 March 2004 – A new line of cancer research based on some of the active principles contained in broccoli was presented by the Italian company Indena during the 95th World Congress on Cancer Research in Orlando. Held from 27th to 31st March 2004, this Congress, organized by the American Association on Cancer Research (AACR), is one of the sector's most important gatherings and attracts an attendance of over 15,000 scientists including oncologists, epidemiologists and researchers from all over the world.

Exploration of these molecules, known as isothiocyanates, is parallel to Indena's oncological research into new taxanes, the topic of three other studies presented at Orlando. The Italian company, a world leader in research and the production of active principles and extracts derived from plants, aims to identify new and promising molecules of vegetable origin. These can then be developed by the pharmaceutical industry to produce innovative cancer treatment, which is less invasive as well as less subject to pharmacological resistance.

The new line of research which is particularly noteworthy, focuses on the specific active principles extracted from broccoli and other vegetables in the Brassica family. It has long been known that these vegetables possess properties important in preventing certain forms of cancer, lowering the risk of cataract, and reducing the effects of a stroke. Only recently however it has been discovered that certain molecules contained in broccoli, the isothiocyanates deriving from the enzymatic transformation of glucosinolates, directly inhibit cell growth, inducing the phenomena of programmed cell death (apoptosis). Moreover, exploiting the capacity of the isothiocyanates to stimulate cells in the production and activation of the detoxifying enzymes, studies have been made to explore the possibility that this mechanism is able to contrast the insurgence of pharmacological resistance, especially in the case of chemotherapy using cisplatin.

Indena's pre-clinical research has therefore shown that the use of glucosinolates/isothiocyanates could offer a considerable therapeutic advantage in overcoming resistance to radio and chemo therapy. This study was carried out in conjunction with the Bologna Research Institute for Industrial Crops and Rome's Catholic University of the Sacred Heart.

Again, during the AACR Congress, more detailed research findings were presented to illustrate IDN 5390, an innovative taxane derivative, previously selected by Indena in the chain of new taxanes. This drug's capacity was thus shown to induce an inhibition of motility in endothelial cells in non-cytotoxic concentrations. This property, combined with its oral bioavailability and high tolerance levels, allows daily treatment to be maintained over a long period. The study presented at Orlando was conducted together with the Roswell Park Cancer Institute in Buffalo (NY).

The other line of research in which Indena is involved and which was presented at the AACR, follows the route of ortataxel, an analogue of active paclitaxel taken orally and less subject to resistance. This derivative of 14-hydroxy-baccatin, at present in clinical phase II, is quite promising and it has stimulated a search for new analogues with better chemical-physical features and anti-tumour action. A series of synthetic molecules, object of this study, has shown interesting potential on breast tumors. This study was carried out in collaboration with the Roswell Park Cancer Institute in Buffalo (NY), the Institute of Organic Chemistry and Fotoreactivity (ISOF) of the CNR in Bologna and the A. Marchesini Institute of Organic Chemistry in Milan.

Finally, to illustrate Indena's interest in sponsoring translational research from the laboratory to the clinic, clinical results were presented with regard to patients with ovarian cancer. It has been shown that there is an increase in the beta tubulin isotype III (TUBB4) in tumors that resist paclitaxel therapy. Beta tubulin is the classical target of this class of compounds. Since TUBB4 expression is low in non-tumoral ovarian tissue, it could be an important target in developing new anti-tumoral agents that can overcome taxane resistance. This study was carried out at the Gemelli Hospital in Rome and the Catholic University of the Sacred Heart in Campobasso.

Indena, one of today's major manufacturers of paclitaxel, a cytotoxic molecule widely used in anti-tumor chemotherapy, is researching into new "oncological" molecules derived from plants. The company's significant participation in this world congress on cancer research is testimony to its commitment to the pursuit of innovative cancer therapies.

For more information about Indena:

www.indena.com

For information on Indena research presented at AACR:

www.indena.com/usrrd_log.asp

For information on the AACR Congress:

www.aacr.org/2004AM/2004AM.asp

New WHO guidelines on the cultivation of medicinal plants

INDENA MAKES PHYTOTHERAPY EVEN SAFER FOR BOTH PATIENTS AND THE ENVIRONMENT

Milan, 25 February 2004 – The recent initiative of the World Health Organisation in giving new guidelines for the cultivation, collection and harvesting of medicinal plants provides higher guarantees for patients and safeguards for the plant species at risk. The application of *Good Agricultural Practices* (GAP) is the means chosen by the Italian company Indena to ensure its supplies of botanical derivatives meet the required quality and safety standards.

The production of herbal remedies is today a business generating around 60 billion dollars. Faced with this growth, patients must be safeguarded and guaranteed products of proven efficiency and safety. At the same time, the environment must be protected, respecting its biodiversity and preventing the future extinction of certain medicinal herbs.

Indena is a pioneer in the debate on the quality of raw plant materials, favouring excellence in the criteria adopted for producing active principles, extracts and ingredients destined for the pharmaceutical and health food industries. Since 1994, for example, the company has made great strides towards the cultivation of *Echinacea angustifolia*, a typical American prairie plant, the harvesting of which has often been limited in the USA. The herbal remedy derived from this plant and known to Western medicine only at the end of the nineteenth century stimulates the immune system, preventing and combating colds and influenza as well as all bacterial or viral infections.

Indena set out to collect some seeds of the genus *Echinacea angustifolia* in various areas where the plant was growing spontaneously: the entire central-western belt of the United States east of the Rocky Mountains, from Texas to Montana. The seeds generated a first "bulk" of a plant population on which to start selection and improvement. The aim was to obtain plants with certain qualitative and productive characteristics which would be germ-resistant. This work has developed using various techniques, not least of which is micro-propagation: a very useful method of propagating, in a short timescale, a large

number of plants with the same characteristics of the selected mother plant. To meet their growing need for the roots of this plant, Indena has recently extended the cultivation of *E. angustifolia* to cover a surface of roughly 100 hectares, mostly in the USA and particularly in certain areas of Kansas and South Dakota where the plant grows spontaneously.

Indena guarantees the respect of precise methods for the cultivation, harvesting and identification of the botanical species. The company botanists accurately analyse the harvested herbs to guarantee their quality and reproducibility. In addition to ensuring the complete traceability of the production chain, Indena also selects the supplier and the areas of origin of the herbs: "steps" that are indispensable in maintaining product quality at a reliable and constant level.

Known the world over as a pillar of phytotherapy since 1921, Indena has always upheld the quality and efficacy of the raw materials used in crucial fields such as oncology and immunology. Other examples of originally spontaneous medicinal herbs are: Hypericum, for which Indena can provide total traceability from the field to the extract, Silybum marianum (L.) Gaertn, Yew Tree and Ginseng Panax.

For more information about Indena:

www.indena.com

For information on the WHO guidelines for good practice in the cultivation and harvesting of medicinal plants:

<http://www.who.int/medicines/library/trm/medicinalplants/agricultural.shtml>