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Milano, 30 Giugno - 1 Luglio

Due giornate intensive di incontri che, con la consolidata formula del confronto tra Università e industria, daranno l'opportunità di individuare come si sta evolvendo la ricerca scientifica in termini di prevenzione dell'invecchiamento e delle principali patologie legate ad alimentazione e stili di vita inadeguati ed alle mutate condizioni ambientali.

PIANTE E SALUTE

Paolo Morazzoni, Antonella Riva, Giovanna Petrangolini – Indena SpA, R&D

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HUMAN BEINGS AND PLANT KINGDOM: A DUAL RELATIONSHIP THROUGH THE CENTURIES

DRUG
- Toxicity
- Rapid Therapeutical effects

FOOD
- Palatability
- Energy source
- Deficiency syndromes

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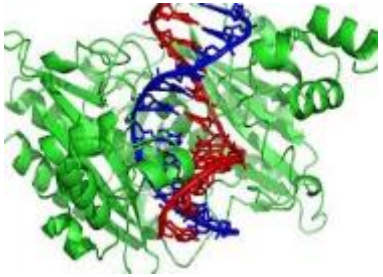
PRIMARY AND SECONDARY PLANT METABOLISM

PLANTS PRODUCE A HUGE AMOUNT OF

SUBSTANCES (METABOLITES) GENERALLY DIFFICULT TO

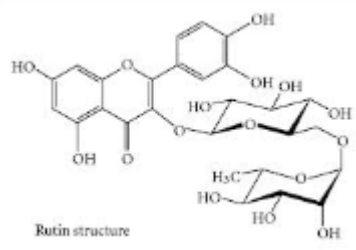
SYNTHETIZE DUE TO THEIR CHEMICAL COMPLEXITY.

THESE CAN BE CLASSIFIED AS



- PRIMARY METABOLITES

AND



- SECONDARY METABOLITES

PRIMARY *vs* SECONDARY PLANT METABOLISM

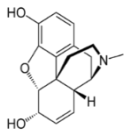
PRIMARY METABOLISM COMPRISES ALL METABOLIC PATHWAYS THAT ARE ESSENTIAL TO THE PLANT SURVIVAL.
PRIMARY METABOLITES ARE COMPOUNDS THAT ARE DIRECTLY INVOLVED IN THE GROWTH AND DEVELOPMENT OF A PLANT.

SECONDARY METABOLITES (PRODUCED THROUGH SPECIFIC METABOLIC PATHWAYS), ALTHOUGH IMPORTANT, ARE NOT ESSENTIAL TO THE BASIC FUNCTIONING OF THE PLANT
BUT PLAY AN IMPORTANT ROLE FOR DEFENCE PURPOSES.
SECONDARY METABOLITES ARE ALSO USED IN SIGNALING AND REGULATION OF PRIMARY METABOLIC PATHWAYS.

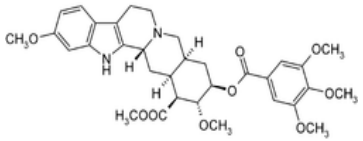
PLANTS AS HYSTORICAL SOURCE OF SECONDARY METABOLITES

Nitrogen-containing

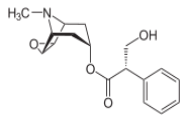
Alkaloids



Morphine

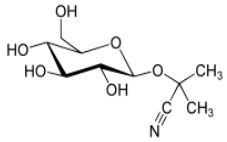


Reserpine



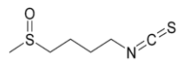
(-)-Scopolamine

Cyanogenic glycosides



Linamarin

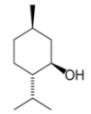
Glucosinolates



Sulphoraphane

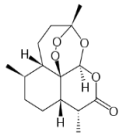
Terpenoids and steroids

Monoterpenes



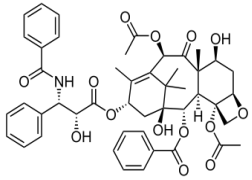
Menthol

Sesquiterpenes



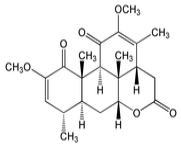
Artemisinin

Diterpenes



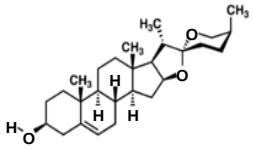
Paclitaxel

Triterpenes



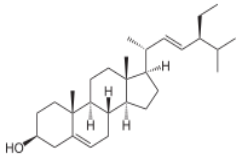
Quassin

Saponins



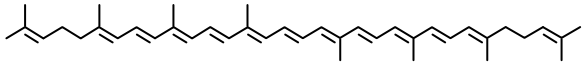
Diosgenin

Steroids



Stigmasterol

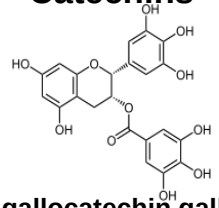
Tetraterpenes



Lycopene

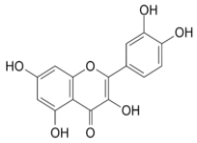
Phenolics, phenylpropanoids and polyketides

Catechins



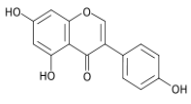
Epigallocatechin gallate

Flavones



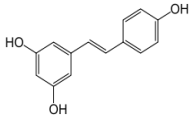
Quercetin

Isoflavones



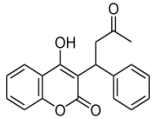
Genistein

Stilbenes



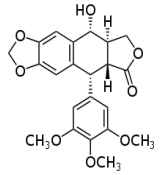
Resveratrol

Coumarins



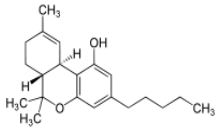
Warfarin

Lignans



Podophyllotoxin

Polychetides



Tetrahydrocannabinol

Phytotherapy

Therapeutical practice based on administration of "medicines" containing pharmacological active products constituted by compounds of vegetal origin usually called phytotherapic medicines or herbal medicinal products (HMPs)

The therapeutical action of HMPs depends on the nature and quantity of its pharmacological active constituents*.

****Here are excluded monomolecular principles of vegetal origin obtained by purification or other procedures.***

HMP definition

According to the Directive 2001/83/EC

HMP

Any medicinal product exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations

Target (by function)

To restore, correct, modify physiological functions by exerting a pharmacological, immunological or metabolic action; to make a medical diagnosis

Target (by presentation)

To treat or prevent diseases

A.R. Bilia
Journal of Ethnopharmacology 138, 487, 2014

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PHARMACEUTICAL MILESTONES FROM PLANT SECONDARY METABOLITES

Plant	Agent	Activity	Year of isolation
Papaver somniferum L.	Morphine	Narcotic analgesic	1806
	Noscapine	Antitussive	1817
	Codeine	Antitussive, narcotic analgesic	1832
	Papaverine	Smooth muscle relaxant	1848
Strychnos nux-vomica L.	Strychnine	CNS stimulant	1817
Cephaelis ipecacuanha (Brot.) Tussac	Emetine	Amebicide	1817
Cinchona ledgeriana Bern. Moens ex Trimen	Quinine	Antimalarial	1819
	Quinidine	Antiarrhytmic	1833
Coffea arabica L.	Caffeine	CNS stimulant	1819
Colchicum autumnale L.	Colchicine	Antinflammatory (gout)	1820
Filipendula ulmaria (L.) Maxim.	Salicin	Analgesic	1829
Atropa belladonna L.	Atropina	Anticholinergic, mydriatic	1831
Theobroma cacao L.	Theobromine	Smooth muscle relaxant	1842
Erythroxylum coca Lam.	Cocaine	Topical anesthetic	1860
Physostigma venenosum Bal.	Physostigmine	Cholinergic	1864
Pilocarpus jaborandi Holmes	Pilocarpine	Antiglaucoma, miotic	1875
Datura metel L.	Scopolamine	Anticholinergic	1881
Hyoscyamus niger L.	Hyoscyamine	Anticholinergic	1881
Ephedra sinica Stapf	L-Ephedrine	Sympathomimetic	1897
Digitalis purpurea L.	Digoxin	Cardiotonic	1930
Rauvolfia serpentina L.	Ajmaline	Antiarrhytmic	1931
	Reserpine	Antihypertensive	1952
	Rescinnamine	Antihypertensive	1954
Chondrodendron tomentosum Ruiz et Pavon	Tubocurarine	Skeletal muscle relaxant	1935
Catharantus roseus (L.) G. Don	Vinblastine	Antitumor	1952
	Vincristine	Antitumor	1958
Ammi visnaga (L.) Lam.	Visnadine	Coronary vasodilator	1961
Silybum marianum (L.) Gaertn.	Silybin	Antitoxic, liver protectant	1968
Coleus forskohlii Brig.	Forskolin	Adenylate cyclase stimulator	1977
Taxus baccata L.	Paclitaxel	Antitumor	1991
Camptotheca acuminata L.	Camptothecin	Antitumor	1993

MORE RECENT PHARMACEUTICALS OF BOTANICAL ORIGIN

Generic name (trade name)	Lead compound	Disease area
2008 Methylnaltrexone (Relistor ®)	Morphine	Opioid-induced constipation
2009 Vinflunine (Javlor®)	Vinorelbine (vinblastine)	Oncology
2009 Nalfurafine (Remitch®)	Morphine	Pruritus
2010 Cabazitaxel (Jevtana®)	Paclitaxel	Oncology
2010 Zucapsaicin (Zuacta®)	Capsaicin	Pain
2012 Ingenol mebutate (Picato®)	Ingenol mebutate	Actinic keratosis
2012 Omacetaxine mepesuccinate (Synribo®)	Omacetaxine mepesuccinate	Oncology
2012 Arterolane /piperaquine (Synriam™)	Artemisinin	Antiparasitic
2013 Ado-trastuzumab emtansine (Kadcyla®)	Maytansine	Oncology

M.S. Butler et al Nat. Prod. Rep. 31, 1672, 2014

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PLANTS AS SOURCES OF PHYTONUTRIENTS

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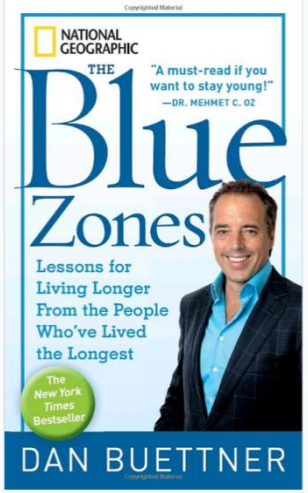
EPIDEMIOLOGY: AN INTRIGUING AND POPULAR SCIENTIFIC APPROACH



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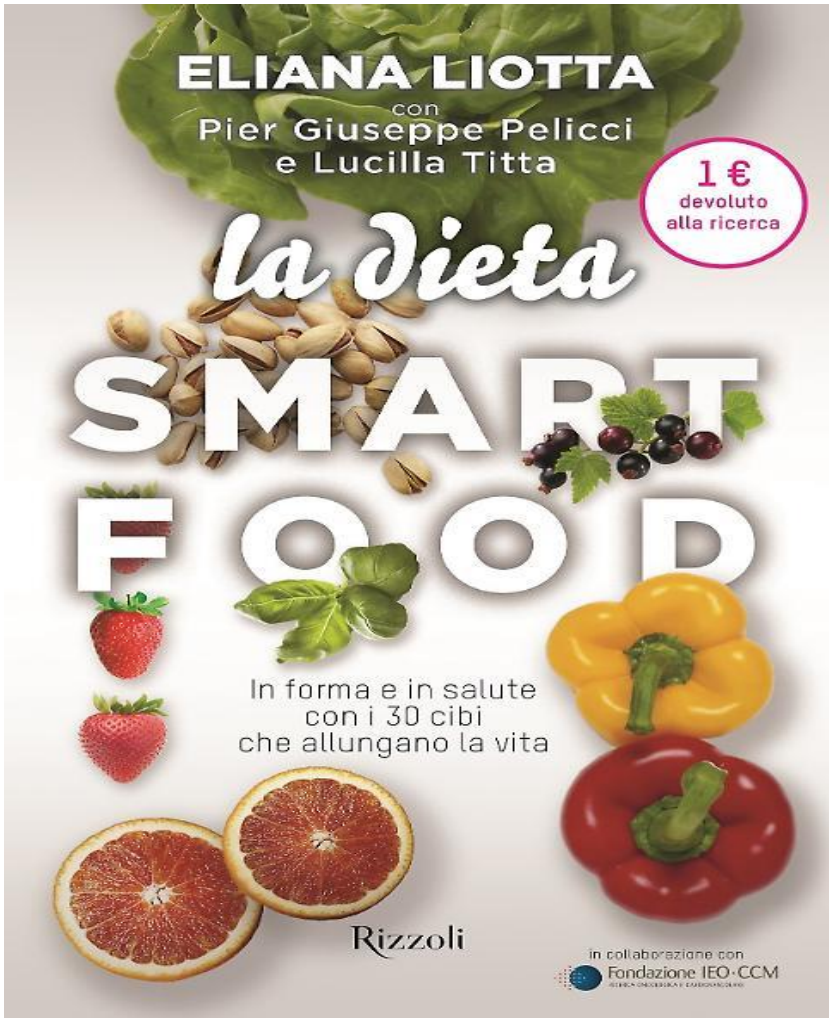
EPIDEMIOLOGY PLUS EVIDENCE BASED MEDICINE: A RELEVANT TOOL FOR OPTIMIZING NUTRITION

Il potere di cipolle e arance
quei cibi che "migliorano" i geni



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THE PROCESS OF

OPTIMIZING NUTRITION

BESIDES INDICATING CORRECT DIETARY HABITS

CAN BE ENVISAGED ALSO AS A

CONSTANT SUPPLY OF SELECTED PHYTONUTRIENTS

(MOSTLY FROM EDIBLE PLANTS)

CHARACTERIZED BY **WELL ESTABLISHED BIOLOGICAL PROPERTIES**

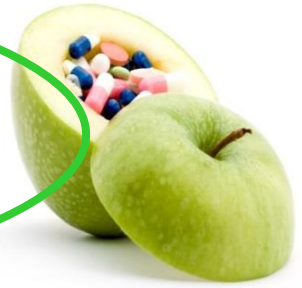
DIETARY SUPPLEMENTS

FUNCTIONALIZED FOOD

HIGH QUALITY INGREDIENTS

FULFILLING OF HEALTH CLAIM CRITERIA

COMPATIBILITY WITH FOOD PREPARATION PROCESSE



HEART DISEASES AND CANCER EVOLVED AS THE TWO MAIN KILLERS IN THE LAST CENTURY

CAUSE OF DEATH	N° OF DEATH /100.000 (UPDATED 2010)
Heart diseases	192.9
Cancer	185.9
Noninfectious airways diseases	44.6
Cerebrovascular diseases	41.8
Accidents	38.2
Alzheimer's disease	27.0
Diabetes	22.3
Nephropathies	16.3
Pneumonia or influenza	16.2
Suicide	12.2

N Engl J Med 366, 2333, 2012

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DIETARY PHYTONUTRIENTS AND RISK REDUCTION

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EU Register of claims applied and authorised: Situation in June 2015 in EU register of claims

- 256 claims authorised from the 2282 claims suggested/ applied for

- 13.1. function/generic claims: 229 authorised, 1875 not authorised
- 13.5. claims based on new knowledge: 2 authorised, 94 not authorised
- 14.1a. risk reduction claims: 14 authorised, 20 not authorised
- 14.1b. children's development claims: 11 authorised, 39 not authorised

→ About one in ten suggested claims has been approved

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Risk – reduction claims (14.1) approved by EFSA and European commission on botanicals

Art.14(1)(a)	Barley beta-glucans	Barley beta-glucans has been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease	Information shall be given to the consumer that the beneficial effect is obtained with daily intake of 3 g of barley beta-glucan. The claim can be used for foods which provide at least 1 g of barley beta-glucan per quantified portion.		Q-2011-00799	Commission Regulation (EU) 1048/2012 of 08/11/2012	Authorised	N/A
Art.14(1)(a)	Barley beta-glucans	Barley beta-glucans has been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.	Information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 3 g of barley beta-glucan. The claim can be used for foods which provide at least 1 g of barley beta-glucan per quantified portion.		Q-2011-00798	Commission Regulation (EU) 1048/2012 of 08/11/2012	Authorised	N/A
Art.14(1)(a)	Oat beta-glucan	Oat beta-glucan has been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease	Information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 3 g of oat beta-glucan. The claim can be used for foods which provide at least 1g of oat beta glucan per quantified portion.		Q-2008-681	Commission Regulation (EU) 1160/2011 of 14/11/2011	Authorised	N/A

Risk – reduction claims (14.1) approved by EFSA and European commission on botanicals

Art.14(1)(a)	Plant stanol esters	Plant stanol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.	Information to the consumer that the beneficial effect is obtained with a daily intake of 1,5-3 g plant stanols. Reference to the magnitude of the effect may only be made for foods within the following categories: yellow fat spreads, dairy products, mayonnaise and salad dressings. When referring to the magnitude of the effect, the range "7 % to 10 %" for foods that provide a daily intake of 1,5-2,4 g plant stanols or the range "10 %-12,5 %" for foods that provide a daily intake of 2,5-3 g plant stanols and the duration to obtain the effect "in 2 to 3 weeks" must be communicated to the consumer.		Q-2008-118, Q-2009-00530 & Q-2009-00718, Q-2011-00851, Q-2011-01241	Commission Regulation (EC) 983/2009 of 21/10/2009, Amended by Commission Regulation (EC) 376/2010 of 03/05/2010, Amended by Commission Regulation (EU) No 686/2014 of 20/06/2014	Authorised	N/A

Risk – reduction claims (14.1) approved by EFSA and European commission on botanicals

Art.14(1)(a)	Plant sterols/Plant stanol esters	Plant sterols and plant stanol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.	Information to the consumer that the beneficial effect is obtained with a daily intake of 1,5-3 g plant sterols/stanols. Reference to the magnitude of the effect may only be made for foods within the following categories: yellow fat spreads, dairy products, mayonnaise and salad dressings. When referring to the magnitude of the effect, the range "7 % to 10 %" for foods that provide a daily intake of 1,5-2,4 g plant sterols/stanols or the range "10 % to 12,5 %" for foods that provide a daily intake of 2,5-3 g plant sterols/stanols and the duration to obtain the effect "in 2 to 3 weeks" must be communicated to the consumer.		Q-2008-779, Q-2009-00530 & Q-2009-00718, Q-2011-01241	Commission Regulation (EU) 384/2010 of 05/05/2010, Amended by Commission Regulation (EU) No 686/2014 of 20/06/2014	Authorised	N/A
Art.14(1)(a)	Plant sterols: Sterols extracted from plants, free or esterified with food grade fatty acids.	Plant sterols have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.	Information to the consumer that the beneficial effect is obtained with a daily intake of 1,5-3 g plant sterols. Reference to the magnitude of the effect may only be made for foods within the following categories: yellow fat spreads, dairy products, mayonnaise and salad dressings. When referring to the magnitude of the effect, the range "7 % to 10 %" for foods that provide a daily intake of 1,5-2,4 g plant sterols or the range "10 % to 12,5 %" for foods that provide a daily intake of 2,5-3 g plant sterols and the duration to obtain the effect "in 2 to 3 weeks" must be communicated to the consumer.		Q-2008-085, Q-2009-530 and Q-2009-718, Q-2011-01241	Commission Regulation (EC) 983/2009 of 21/10/2009, Amended by Commission Regulation (EC) 376/2010 of 03/05/2010, Amended by Commission Regulation (EU) No 686/2014 of 20/06/2014	Authorised	N/A

ROLE OF DIET AND EDIBLE PLANTS

The role of diet, even at *epigenetic level*, in contributing to modulate chronic-degenerative pathologies has been established in a number of epidemiological studies.

In this contest, the role of secondary (and even primary) metabolites contained in edible plants seems to be pivotal in human homeostasis and in the modulation of the risk of pathological conditions including **cardiovascular diseases** and **cancer**.

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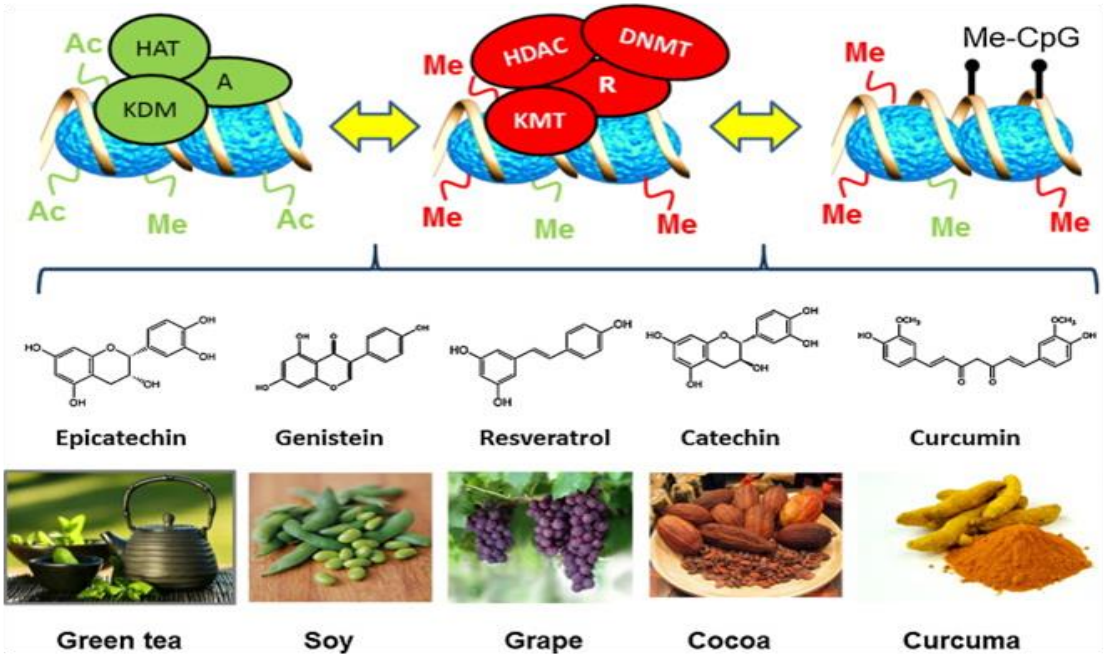
EPIGENETIC REGULATIONS AND ROLE OF DIETARY PHYTONUTRIENTS

Epigenetic regulations consist of potentially reversible changes in DNA methylation, histone modifications, alteration in microRNA (miRNA) expression, without any change in DNA sequence.

S. Reuter *et al*., Genes Nutr. 6,93 (2011)



Wim Vanden Berghe
Pharmacological Research
65 (2012) 565– 576

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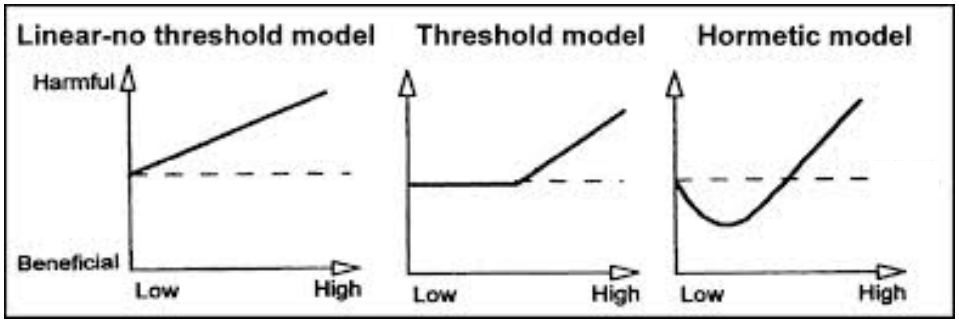
PHYTONUTRIENTS and HORMESIS

Hormesis describes a process in which exposure to a low dose of an agent that is toxic at higher doses induces a beneficial effect on the cell or organism



While xenohormetic (interspecies hormesis) compounds are harmful to insects and microorganisms, the subtoxic levels at which humans ingest them appear to result in moderate cellular stress responses. This, in turn, might activate stress-response adaptation pathways, leading to increased expression of genes that encode cytoprotective proteins such as antioxidant enzymes, chaperones, growth factors, phase 2 detoxification enzymes and mitochondrial proteins

Javier A. Menendez Cell Cycle 12:4, 555–578; February 15, 2013

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DIET AS MODULATOR OF MAIN **"INTERMEDIATE RISK FACTORS"** IN CVDs

The effects of unhealthy diet and physical inactivity may show up in individuals as raised blood pressure, raised blood glucose, raised blood lipids, and overweight and obesity. These "intermediate risks factors" can be measured in primary care facilities and indicate an increased risk of developing a heart attack, stroke, heart failure and other complications.

Cessation of tobacco use, reduction of salt in the diet, consuming fruits and vegetables, regular physical activity and avoiding harmful use of alcohol have been shown to reduce the risk of cardiovascular disease. The cardiovascular risk can also be reduced by preventing or treating hypertension, diabetes and raised blood lipids.

WHO Fact sheet N° 317, March 2013

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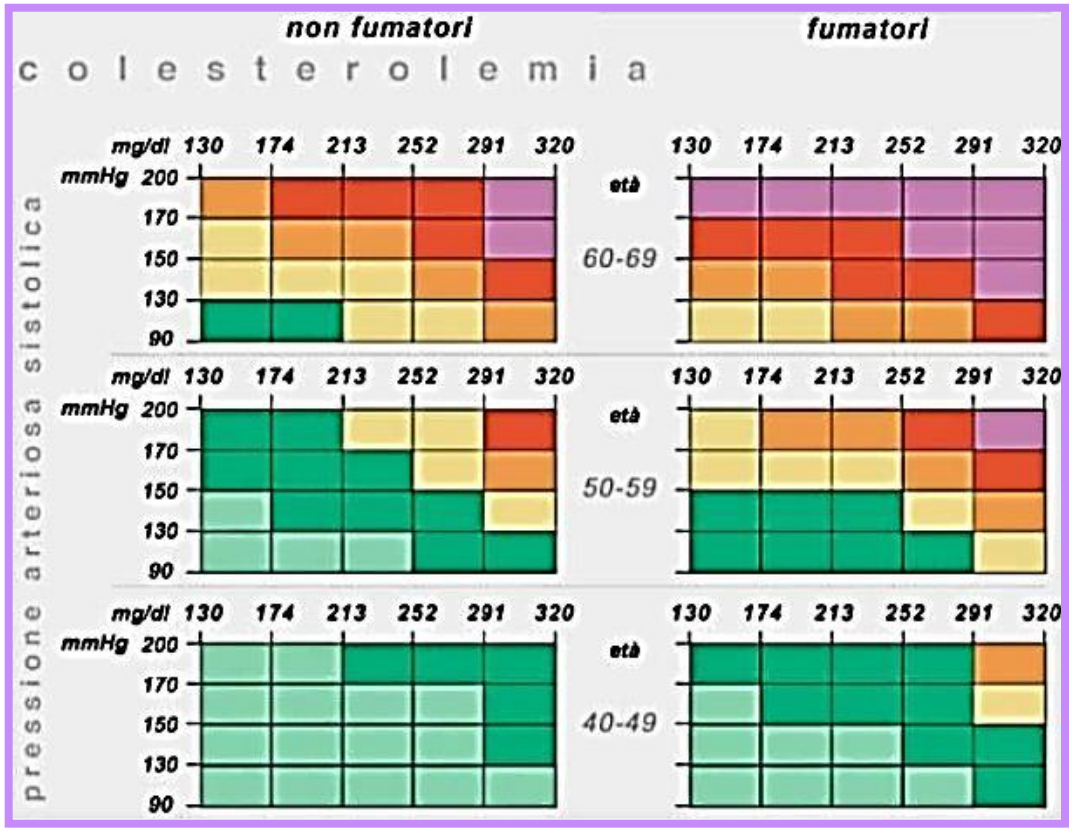
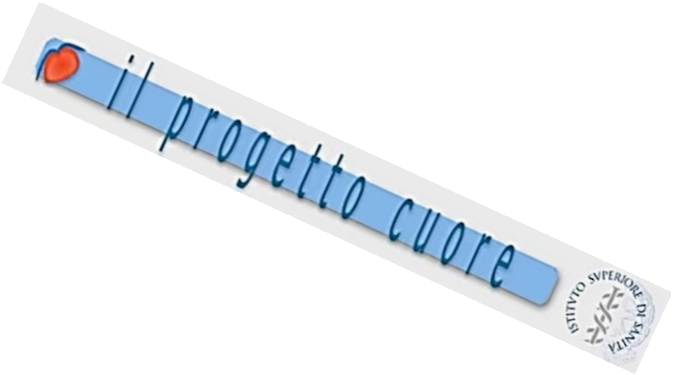
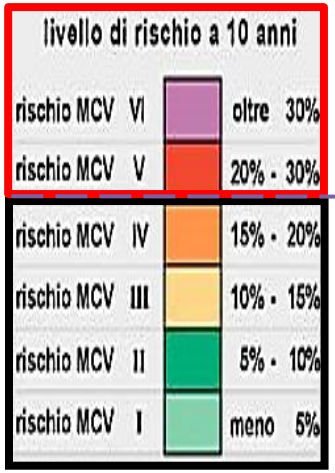
A MODERATE GLOBAL RISK OF CVDs IS WIDESPREAD IN POPULATION

60% of male and 25% of female Italian population between 35 and 75 years have **a moderate risk** of cardiovascular disease (Progetto Moli-Sani)!







High Global Risk (>20%)
Statins are reimbursed

Moderate Global Risk (<20%)
Dietary intervention

indena®

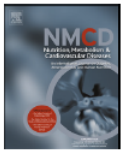
A MODERATE GLOBAL RISK OF CVDs WILL INCREASE DUE TO THE CRISIS

Nutr Metab Cardiovasc Dis 2014 Aug;24(8): 853-60

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd



Decline of the Mediterranean diet at a time of economic crisis. Results from the Moli-sani study

M. Bonaccio [a,*,1], A. Di Castelnuovo [a,1], A. Bonanni [b,1], S. Costanzo [a,1], F. De Lucia [c,1], M. Persichillo [a,1], F. Zito [d,1], M.B. Donati [a,1], G. de Gaetano [a,1], L. Iacoviello [a,1]

[a] Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Via dell'Elettronica, 86077 Pozzilli (Isernia), Italy
[b] Epicomed Research Srl, 86100 Campobasso, Italy
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[d] Transfusion Unit, Ospedale di Isernia, Isernia, Italy

Received 18 October 2013; received in revised form 13 February 2014; accepted 15 February 2014
Available online ■ ■ ■

KEYWORDS
Mediterranean Diet;
Economic crisis;
socioeconomic status;
Obesity;
Cerebrovascular risk

Abstract *Background and aims:* Adherence to Mediterranean diet (MD) is reportedly declining in the last decades. We aimed to investigate the adherence to MD over the period 2005–2010 and exploring the possible role of the global economic crisis in accounting for the changing in the dietary habits in Italy.

Methods and results: Cross-sectional analysis in a population-based cohort study which randomly recruited 21,001 southern Italian citizens enrolled within the Moli-sani study. Food intake was determined by the Italian EPIC food frequency questionnaire. Adherence to MD was appraised by the Italian Mediterranean Index (IMI). A wealth score was derived to evaluate the economic position and used together with other socioeconomic indicators. Highest prevalence of adherence to MD was observed during the years 2005–2006 (31.3%) while the prevalence dramatically fell down in the years 2007–2010 (18.3%; $P < 0.0001$). The decrease was stronger in the elderly, less affluent groups, and among those living in urban areas. Accordingly, we observed that in 2007–2010 socioeconomic indicators were strongly associated with higher adherence to MD, whereas no association was detected in the years before the economic crisis began; both wealth score and education were major determinants of high adherence to MD with 31% (95%CI: 18–46%) higher adherence to this pattern within the wealthier group compared to the less affluent category.

Conclusion: Adherence to MD has considerably decreased over the last few years. In 2007–2010 socioeconomic indicators have become major determinants of adherence to MD, a fact likely linked to the economic downturn.

indena®

TWO RECENT EXAMPLES OF INDENA PRODUCTS STRATEGICALLY TARGETED TO CVDs RISK REDUCTION:

- **BEANBLOCK®** (from *Phaseulus vulgaris* L.)

- **ENOVITA ®** (from *Vitis vinifera* L.)

indena®

BEANBLOCK®

Phaseolus vulgaris L.

indena®

BEANBLOCK®: composition

Control of diet and exercise are cornerstones of the management of excess weight. In this framework dietary supplements provided with the capacity to modulate appetite and glyco-metabolic parameters and can be of help in integrating this approach.

BEANBLOCK® is the Extract from *Phaseolus vulgaris* seed standardized in 2 group of proteins supporting a double mechanism of action (Patent: WO2007071334)

α-Amylase inhibitor

(HPLC - % w/w) ≥ 6% ≤ 14%

(Inhibiting activity - U/mg) ≥ 1000 ≤ 1600

Phytohemoagglutinins

(Haemagglutinating activity - HAU/g) ≥ 8000 ≤ 30000

indena®

BEANBLOCK®: preclinical development

Relevant conclusions in Wistar and Zucker rats

Acute administration significantly reduces spontaneous food intake (unlimited access) and the effect is suppressed by the co-administration of a colecystokinin (CCK)-antagonist.

Acute administration significantly reduces glycemia in controlled and standardized conditions of food consumption. The effect is independent from the effect on food consumption.

Acute administration drastically and selectively reduces the consumption of palatable foods.

Repeated administrations confirm the effects on spontaneous food intake and consequently on glycemia.

Repeated administrations are associated with a significant effect on body weight which is still present in the post-treatment period.

British Journal of Nutrition 104 (05), 624-628, 2010
British Journal of Nutrition 106 (05), 762-768, 2011
Fitoterapia 85, 14-19, 2013
Frontiers in Pharmacology 7 :109. doi:10.3389/fphar. 2016.00109

indena®

BEANBLOCK® – SAFETY

- ✓Acute oral toxicity in rats: >2000 mg/kg
- ✓AMES test: negative
- ✓NOAEL (13 weeks) in rats: 1500 mg/kg/day
- ✓ADI in humans (70 kgs BW): 1050 mg/day

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EFSA allowed risk – reduction claims

5. Blood glucose and insulin concentrations

5.1. Claims on the reduction of post-prandial blood glucose responses

Claims on the reduction of post-prandial blood glucose responses refer to the ability of a food/constituent to reduce the blood glucose rise after consumption of a food or meal rich in digestible carbohydrates (i.e. in comparison to a reference food or meal). This ability may be considered a beneficial physiological effect (e.g. for subjects with impaired glucose tolerance) as long as insulin responses are not disproportionally increased.

The scientific evidence for the substantiation of health claims on the reduction of post-prandial blood glucose responses can be obtained from human intervention studies showing a decrease in blood glucose concentrations at different time points after consumption of the test food during an comparison to the reference food.

EFSA Journal 2012; 10 (3):2604

indena®

BEANBLOCK® in Humans

British Journal of Nutrition, page 1 of 7

2013; 109 (10): 1789-1795

Phaseolus vulgaris extract affects glycometabolic and appetite control in healthy human subjects

Angela Spadafranca[1]*, Samuele Rinelli[1], Antonella Riva[2], Paolo Morazzoni[2], Paolo Magni[3], Simona Bertoli[1] and Alberto Battezzati[1]

[1]*Department of Food, Environmental and Nutritional Sciences (DeFENS), International Center for the Assessment of Nutritional Status (ICANS), Università degli Studi di Milano, Via Celoria 2, 20133 Milan, Italy*
[2]*Indena S.p.A., Viale Ortles 12, I-20139 Milan, Italy*
[3]*Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Via Balzaretti 9, 20133 Milan, Italy*

(Submitted 16 March 2012 – Final revision received 19 July 2012 – Accepted 20 July 2012)

Abstract

Extracts of *Phaseolus vulgaris* (beans) are known to reduce glycaemia and food intake in rodents and humans. The present study evaluated the effects of a new, standardised and purified *P. vulgaris* extract (PVE), when employed as a supplement in a mixed balanced meal (60% carbohydrates, 25% lipids and 15% protein), on glycometabolic and appetite control. To this end, a randomised, double-blind, placebo-controlled study was performed in twelve volunteers. Plasma glucose, insulin, C-peptide, ghrelin and satiety sensation ratings were assessed at baseline and during 3 h after meal consumption associated with PVE (100 mg) or placebo. Compared with placebo, PVE consumption resulted in lower increments in glucose (+15·4 (SEM 5·4) *v.* 26·1 (SEM 7·3)%, $P=0·04$ at 30 min), insulin (+981 (SEM 115) *v.* 1325 (SEM 240)%, $P=0·04$ between 45 and 120 min) and C-peptide (+350 (SEM 27) *v.* 439 (SEM 30)%, $P=0·04$ between 30 and 90 min). In the first 2 h, plasma ghrelin decreased similarly in both groups but did not rebound as in placebo thereafter ($P=0·04$). Correspondingly, satiety sensation in the third hour was significantly reduced in the placebo but not in the PVE condition. PVE induced a lower desire to eat than placebo ($P=0·02$) over the 3 h. In conclusion, PVE supplementation reduced postprandial glucose, insulin and C-peptide excursions, suppressed ghrelin secretion and affected satiety sensations, inducing a lower desire to eat. These results support that further studies are needed to prove the concept of employing PVE as a supplement in mixed balanced meals in obese, glucose-intolerant and diabetic subjects.

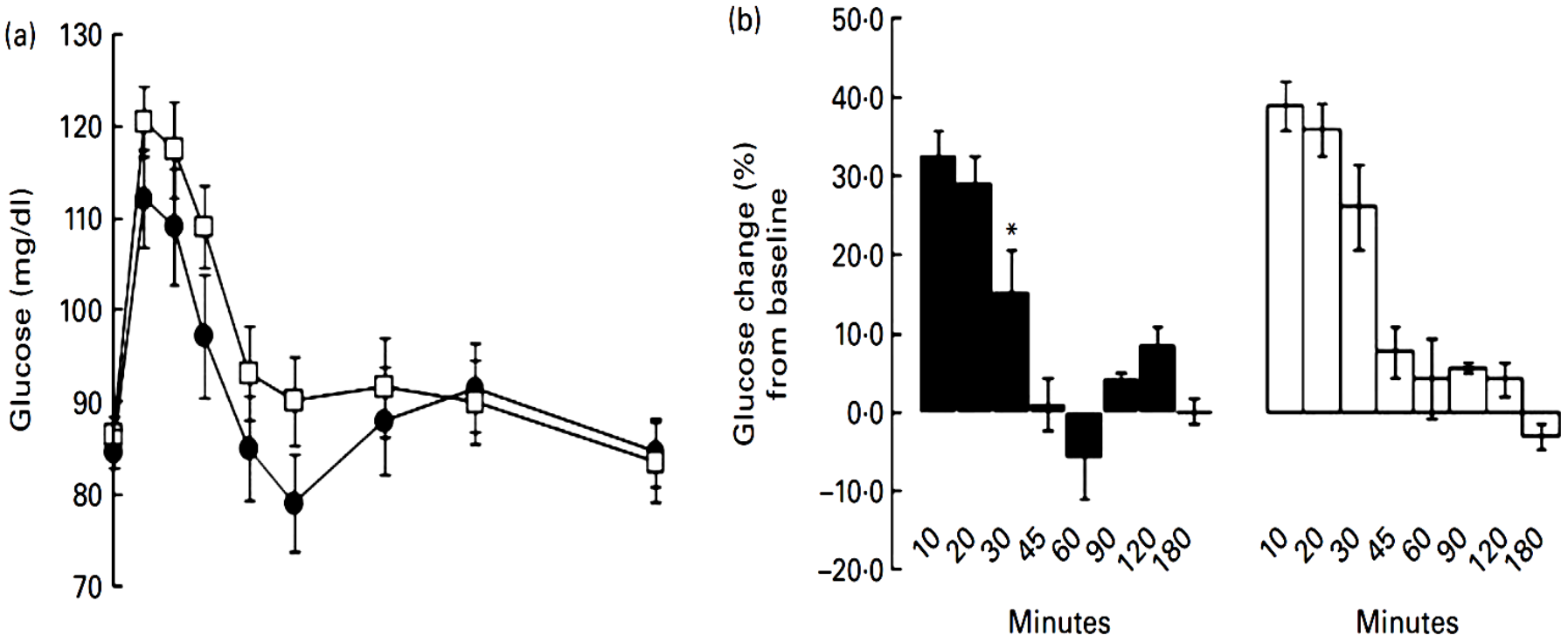
Key words: *Phaseolus vulgaris*: Supplements: Mixed meals: Glucose metabolism: Satiety

British Journal of Nutrition

indena®

BEANBLOCK® employed as supplement in a Mediterranean meal positively affected glucose metabolism

Fasting and postprandial glucose



Compared with placebo □, Beanblock® ● resulted in lower increments in glucose (+15.4% vs 26.1%, P=0,04 at 30 min)

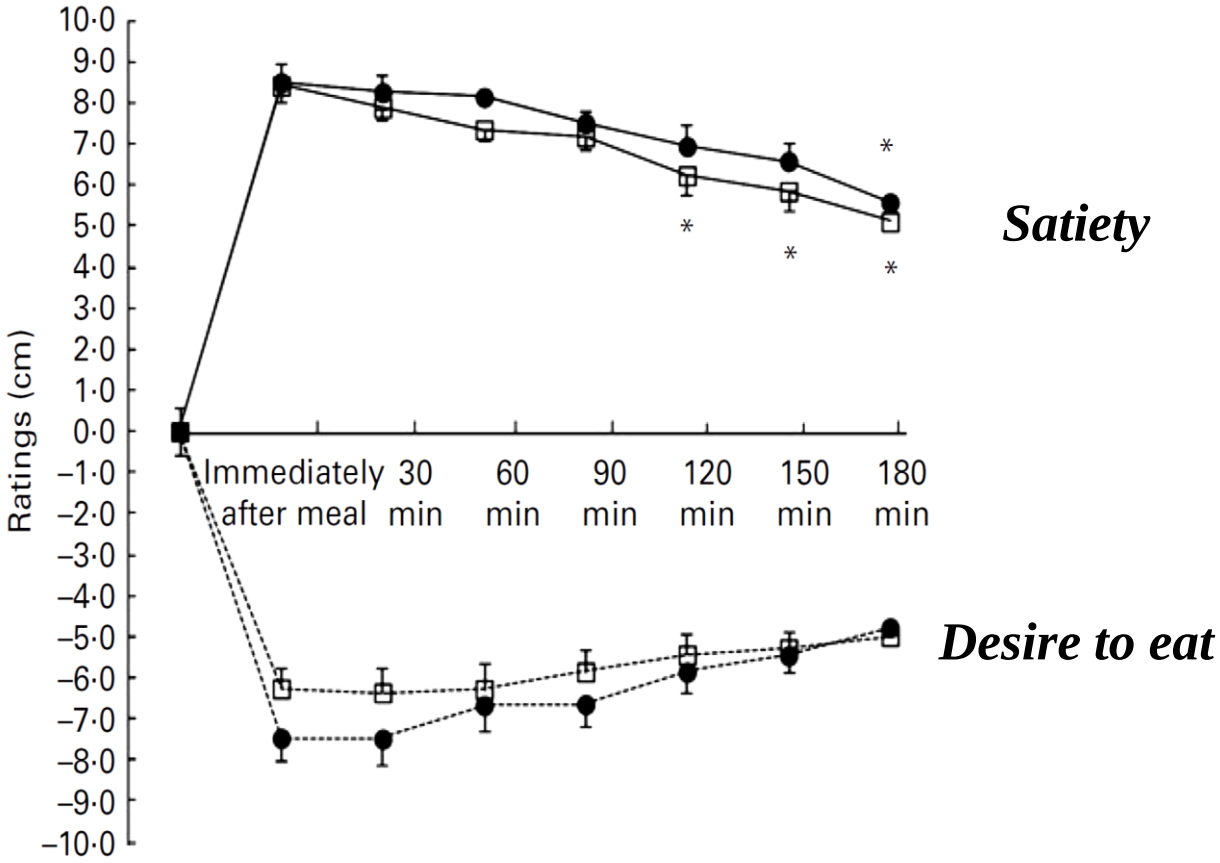
indena®

BEANBLOCK® employed as supplement in a Mediterranean meal positively affected appetite control

Fasting and postprandial satiety sensations

□ Placebo

● Beanblock®

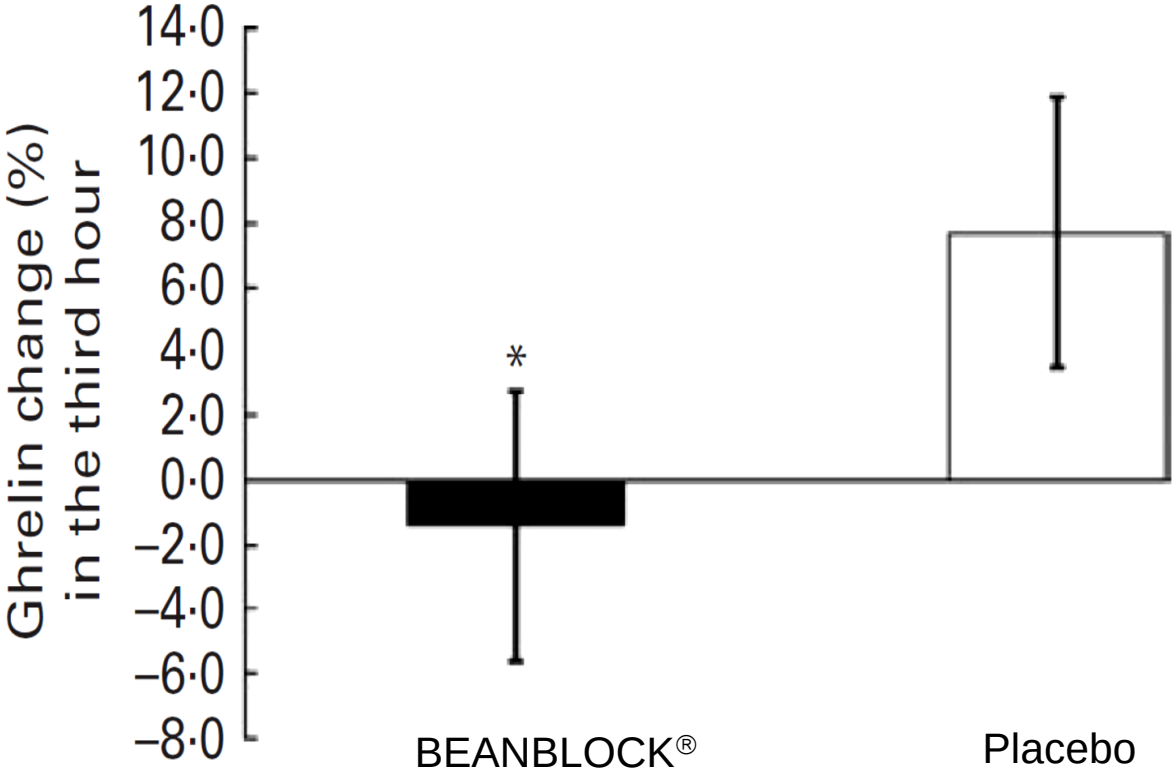


The desire to eat decreased immediately after both tests, more profoundly with BEANBLOCK® than placebo (27.4 cm vs 26.3 cm, P=0.06), remaining significantly lower than baseline until 180 min (P<0.05).

indena®

BEANBLOCK® employed as supplement in a Mediterranean meal positively affected appetite control

Fasting and postprandial plasma levels of ghrelin



Plasma ghrelin, the stomach secreted orexigenic peptide, decreased similarly in both groups but with BEANBLOCK® did not rebound as in placebo thereafter (P=0.04).

indena®

BEANBLOCK®

Relevant conclusions in healthy volunteers

- BEANBLOCK® employed as supplement in a mixed Mediterranean balanced meal positively affected glucose metabolism in healthy volunteers.

- BEANBLOCK® suppresses ghrelin secretion and induce a longer duration of satiety in healthy volunteers suggesting a potential use for the control of excessive food intake.

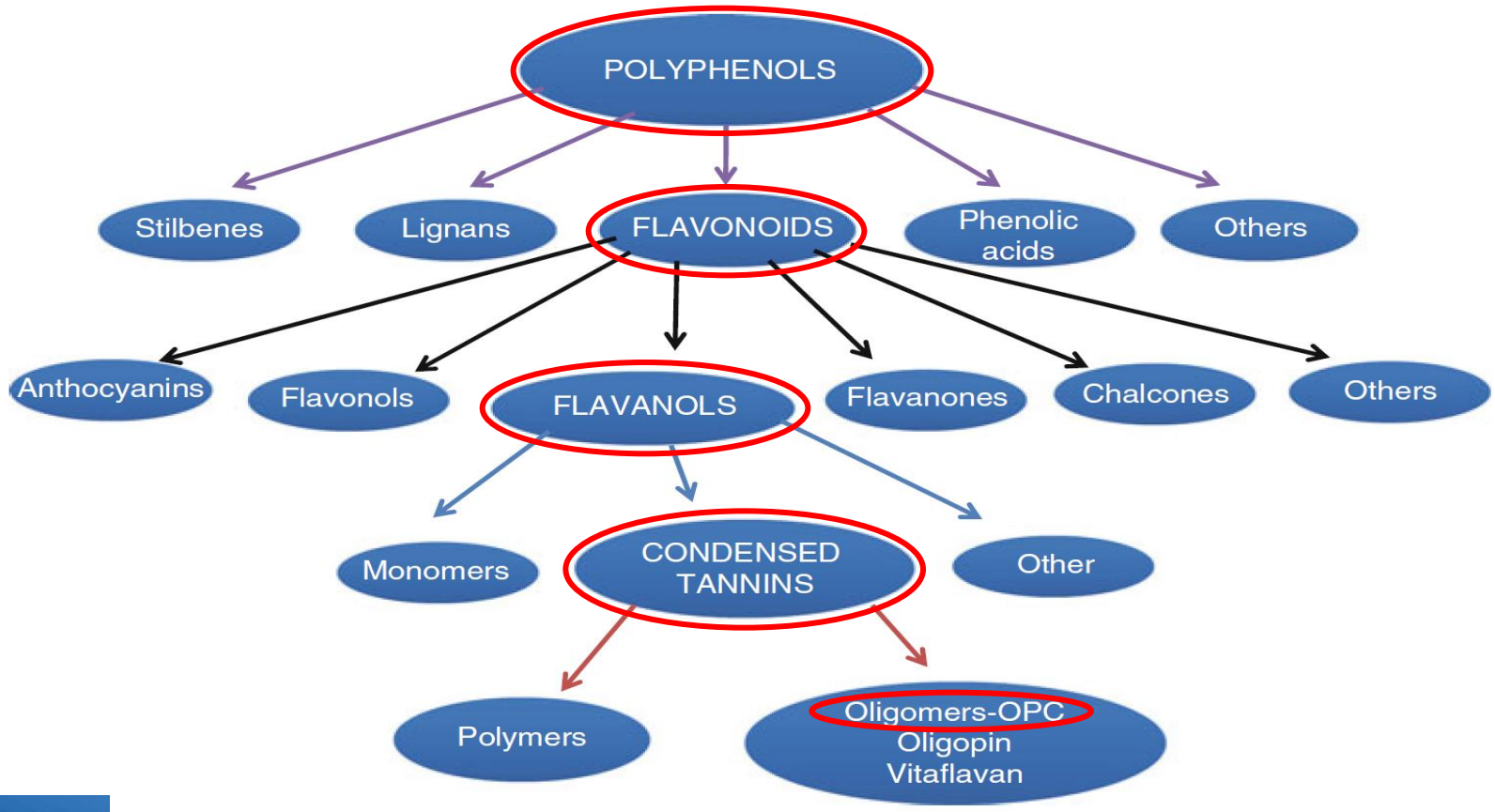
indena®

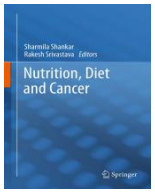
ENOVITA ®

Vitis vinifera L.

indena®

OLIGOMERIC PROANTHOCYANIDINS:
ONE OF THE MOST CHARACTERIZING GROUPS OF POLYPHENOLS IN *Vitis vinifera* L.





Modified from:
Sharmila Shankar, Brahma N. Singh, and Rakesh K. Srivastava, in: Nutrition, Diet and Cancer, Chapter 10, Plant Polyphenols and Their Role in Cancer Prevention and Chemotherapy, p 209, S. Shankar and R.K. Srivastava (Eds.), Springer, 2012

indena®

…AND MODERN INSIGHTS INTO **OPC HEALTH BENEFITS**

THERAPY

- PHARMACEUTICAL PRODUCTS
(Mostly concerned with vascular protection)

PREVENTION/RISK REDUCTION

- DIETARY SUPPLEMENTS
(Mostly in the area of CVDs and stimulated by the "French Paradox"* induced cascade of literature)

*S. Renaud and M. de Lorgeril, *Lancet 339*, 1523 (1992);
M. de Lorgeril *et al*., *Cardiovas. Res. 54*, 503 (2002).

indena®

ENOVITA®

OPC rich grape seeds extract is made **exclusively with grape seeds from white wine production**.
Using only water as extraction solvent, ENOVITA® is a **food grade grape seed extract** whose development has capitalized on Indena's 40 years experience in grape seed extract production.

ENOVITA® is standardized to contain: **>95% of proanthocyanidins** (spectrophotometry); **5% -15% catechin/epicatechin** (HPLC)

ENOVITA® is produced according to **Indena 30 Quality system** and under **HACCP conditions** in a **GMPs and ISO 14001 certified facility**, ensuring full traceability from grape harvest to the finished product.

Furthermore, ENOVITA® is **Halal and Kosher certified** and its environmental friendly **production process is designed to minimize the production of waste**.

EFSA allowed risk – reduction claims

5.2. Claims on the reduction of blood pressure

Maintenance of normal blood pressure is a beneficial physiological effect. The scientific evidence for the substantiation of health claims on the maintenance of normal blood pressure can be obtained from human intervention studies showing a short-term (e.g. three to four week) reduction in systolic blood pressure, or a reduction in diastolic blood pressure if accompanied by a reduction in systolic blood pressure as compared to a food/constituent which is neutral with respect to the claimed effect, or exceptionally to no treatment (e.g. control group on usual diet). In this context, also reductions in blood pressure within the normal range are considered beneficial physiological effects. Blood pressure should be measured using well-accepted protocols.

With respect to the study population, results from studies conducted in hypertensive subjects treated with lifestyle measures only (e.g. diet) could be used for the scientific substantiation of these claims.

However, the rationale for extrapolation of results obtained in hypertensive subjects under treatment with blood pressure-lowering medications (e.g. ACE-inhibitors, blockers of beta adrenergic receptors, calcium channel blockers and diuretics) to the target population for the claim should be provided, and will be considered on a case-by-case basis (e.g. evidence for a lack of interaction between the food and the medications used on the claimed effect).

EFSA Journal 2011; 9 (12):2474

indena®

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2013, Article ID 313142, 5 pages
http://dx.doi.org/10.1155/2013/313142

Research Article

Grape Seed Procyanidins in Pre- and Mild Hypertension: A Registry Study

Gianni Belcaro, Andrea Ledda, Shu Hu, Maria Rosa Cesarone, Beatrice Feragalli, and Mark Dugall

Department of Biomedical Sciences, Irvine3 Circulation-Vascular Labs and San Valentino Vascular Screening Project, Gabriele D'Annunzio University, SS 16 Bis 94, Spoltore, Pescara, Italy

The efficacy of a standardized grape seed procyanidins extract (GSPE, Enovita) to decrease blood pressure when associated with nondrug intervention (diet and lifestyle modifications) was investigated in a controlled registry study involving 119 healthy, pre- and mildly hypertensive subjects. Two dosages of Enovita were evaluated (150 and 300 mg/die), using blood pressure and heart rate as the primary endpoints and complementing these observations with a laser Doppler flowmetry (LDF) investigation of the microcirculation state and an evaluation of the plasma oxidative status. After four months of treatment, a statistically significant higher, and dose-dependent, improvement in all endpoints was observed in the treatment groups compared to that of the control, with blood pressure normalizing in 93% of the higher dosage (300 mg) treatment group. Taken together, these observations suggest that GSPEs have beneficial cardiovascular effects that complement current intervention strategies in the hypertension area. The effect on blood pressure adds to the beneficial effects of GSPEs on the cardiovascular disease (CVD) phenotype associated with the oxidation of membrane lipids (endothelial dysfunction, formation of oxidized LDL, and activation of phagocytic cells).

ENOVITA®: registry study in **mild hypertensive subjects** (undergoing Best Standard Management)

CONCLUSIONS

In healthy subjects bordering hypertension, **the combination of the Best Standard Management with ENOVITA® (150-300 mg/day for at least 4 weeks) can positively modulate blood pressure and blood flow at the level of microcirculation**.

This effect is paralleled by a significant reduction in heart rate.

A relevant reduction of plasma free radicals has also been observed.

ENOVITA® has been well tolerated with a global positive compliance.

indena®

NEXT STEP

A new study with an increased number of participants is under planning with the aim to fulfill EFSA requirements for claiming allowance

indena

Cancer prevention in Europe : the Mediterranean diet as a protective choice

- ✓ **Mediterranean diet represents an healthy approach to prevention of cancer, due to:**

. Abundant and variable plant foods
. High consumption of cereal
. Olive oil as the main added fat
. Moderate consumption of red wine
. Low intake of red meat

- ✓ **Mediterranean diet has been recently ‘ contaminated ‘ by ethnical food, such as Asian Food.**

Selected edible plants from Asian diets contain ‘ healthy ‘ phytochemicals such as curcumin, and EGCG

A. Giacosa, R. Barale, L. Bavaresco, P. Gatenby, V. Gerbi, J. Janssens, B. Johnston, K. Kas, C. La Vecchia, P. Mainguet, P. Morazzoni, E. Negri, C. Pelucchi, M. Pezzotti, M. Rondanelli
European Journal of Cancer Prevention 22, 1, 2013

indena®

CANCER RISK-LOWERING DIET REQUIREMENTS

INTAKE OF FRUIT/VEGETABLES

IN CONSUMPTION OF RED MEAT

WHOLE –GRAINS CARBOHYDRATES INSTEAD OF REFINED ONES

OLIVE OIL

A shift to this diet requirements for a population of a high-income country should produce 25% colorectal, 15% breast, 10% prostate-cancer reduction.

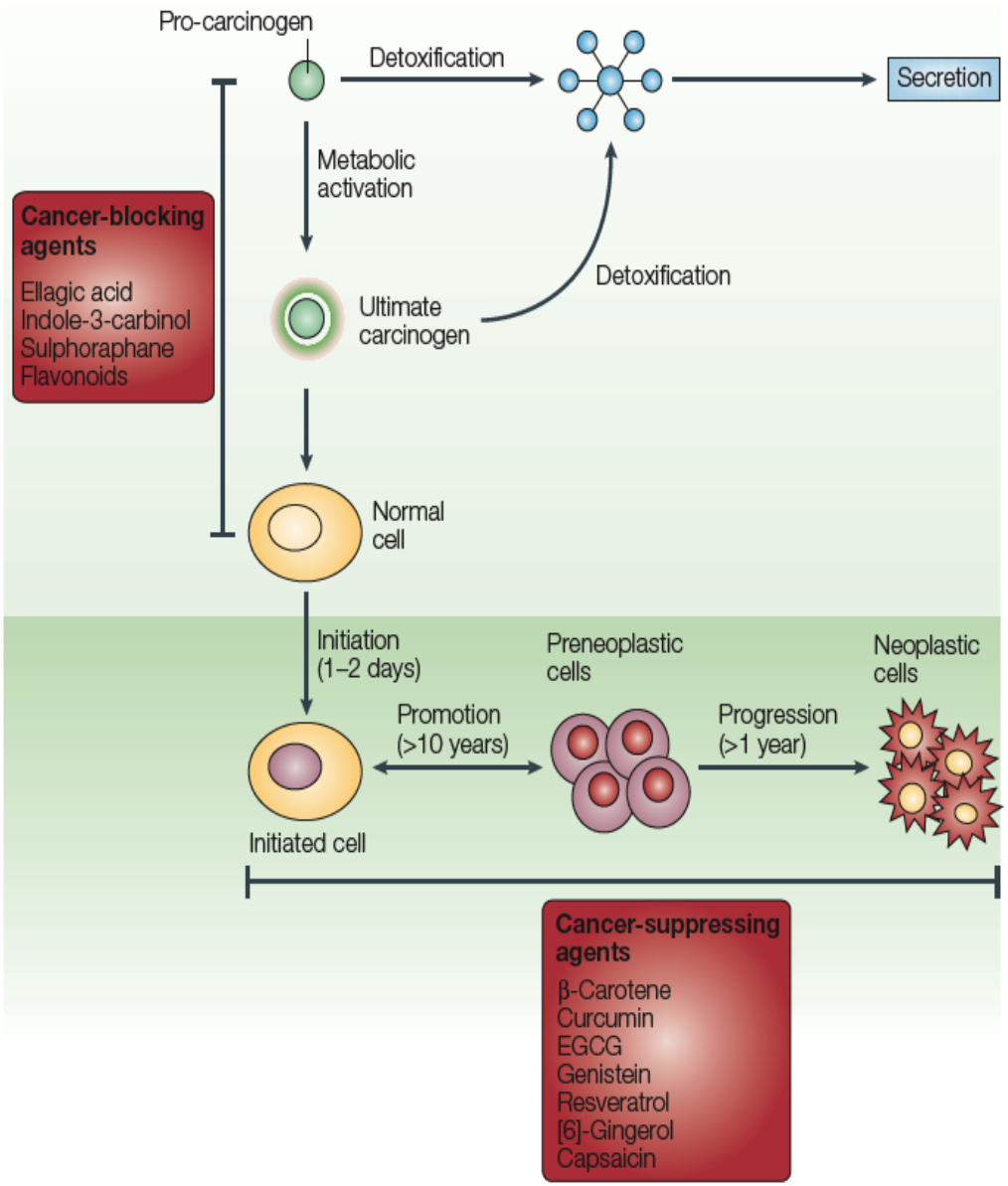
A. Trichopolou, P. Lagiou, H. Kuper, D. Trichopolou. Cancer Epidemiol. Biomarkers Prev. 9, 869, 2000

indena®

BASIC MECHANISMS UNDERLYING DIETARY PREVENTIVE EFFECTS

- Balanced ratio n-6/n-3 fatty acids
- High amount of fiber
- High amount of antioxidants and other micronutrients (especially from olive oil)
- Vitamin E
- Vitamin C
- Modulation ‘ aging genes’

PHYTONUTRIENTS AS CANCER-BLOCKING/ CANCER-SUPPRESSING AGENTS



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PHYTONUTRIENTS IN ONCOLOGY

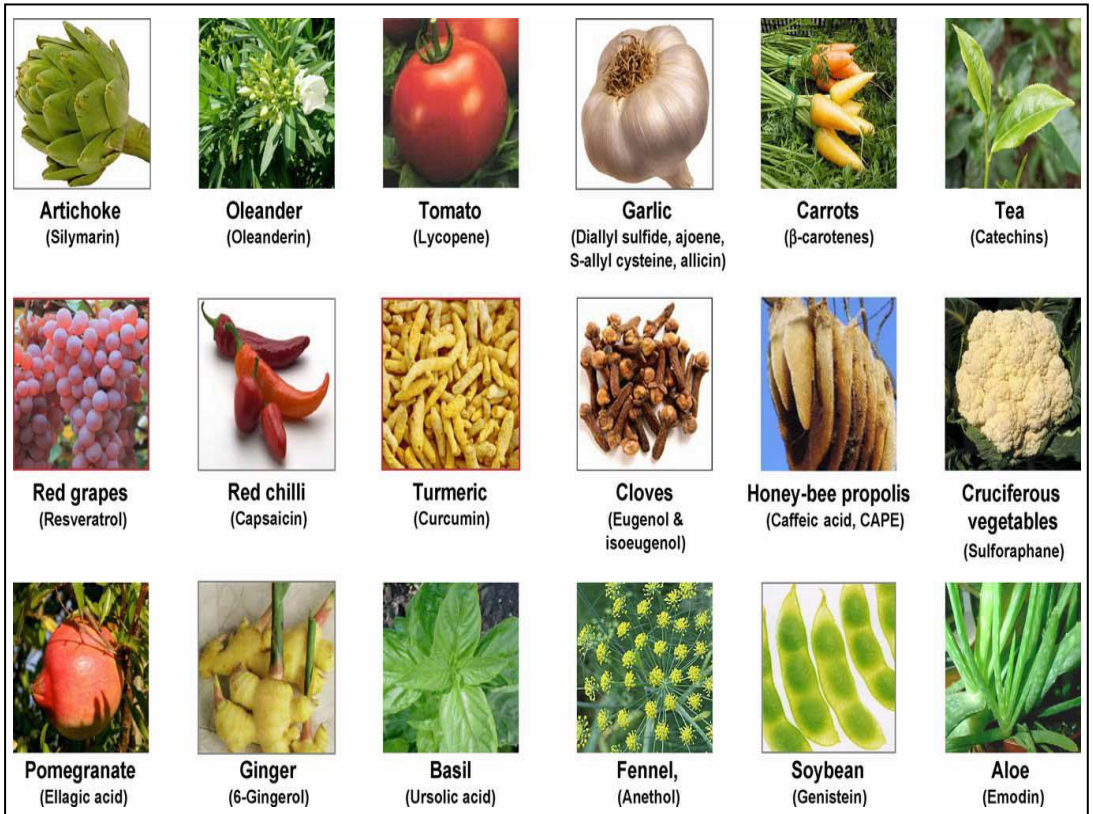


Fig. 1. Dietary agents with anti-cancer properties.

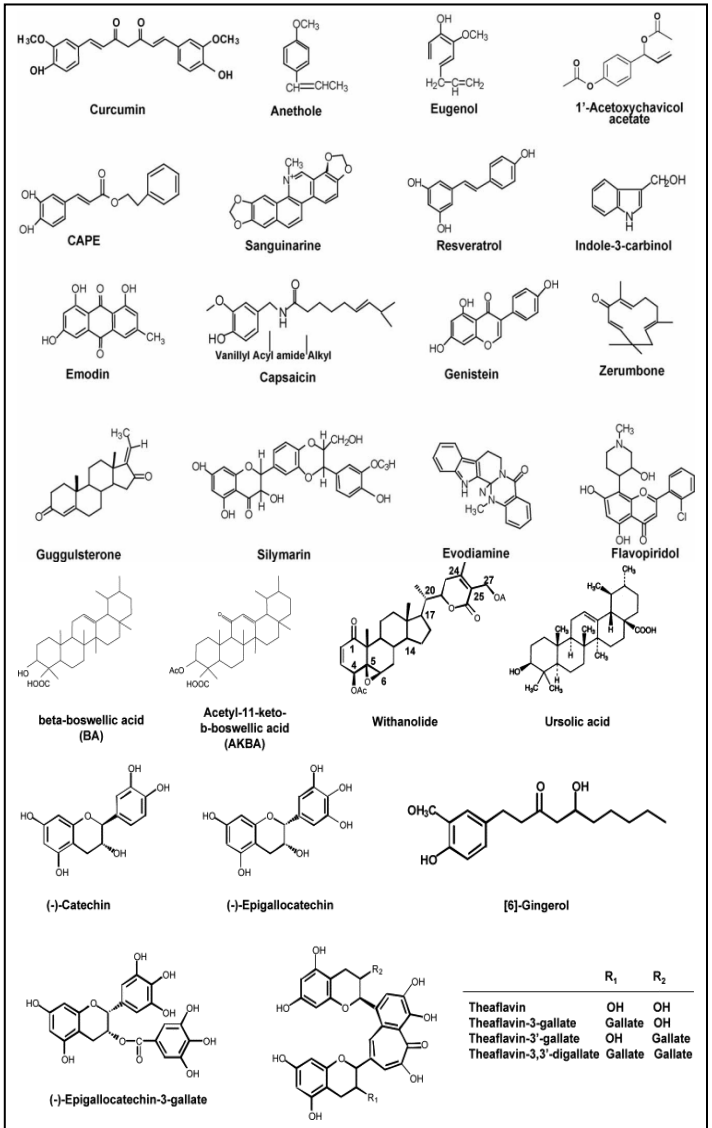


Fig. 2. Chemical structures of dietary compounds.

Molecular targets of dietary agents for prevention and therapy of cancer.

B.B. Aggarwal, S. Shishodia

Biochemical Pharmacology 71 (2006) 1397 - 1421

indena®

PLANT POLYPHENOLS

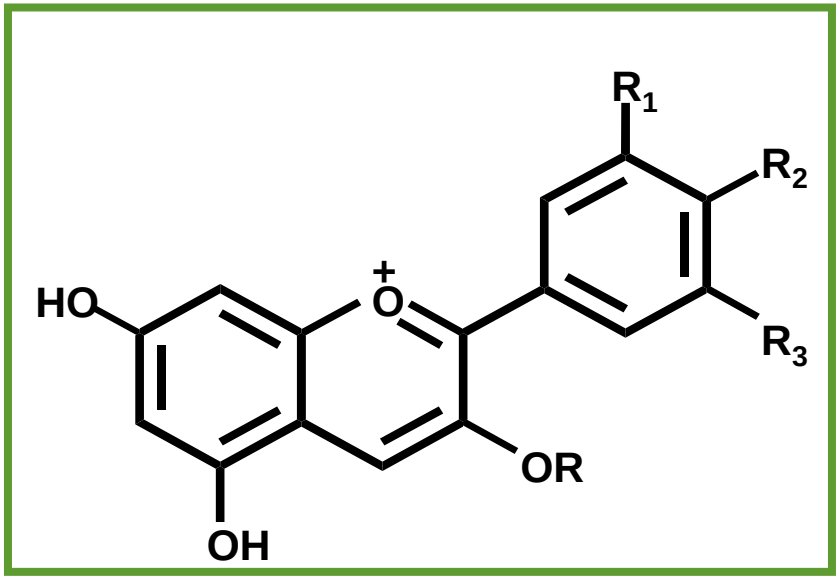
Polyphenols constitute one of the most interesting group of phytonutrients for cancer chemoprevention.

Relevant examples are represented by: anthocyanosides, curcuminoids, catechin derivatives and stilbenes.

Vaccinium myrtillus L.

indena®

MAIN ACTIVE COMPOUNDS OF *VACCINIUM MYRTILLUS* FRUIT EXTRACTS

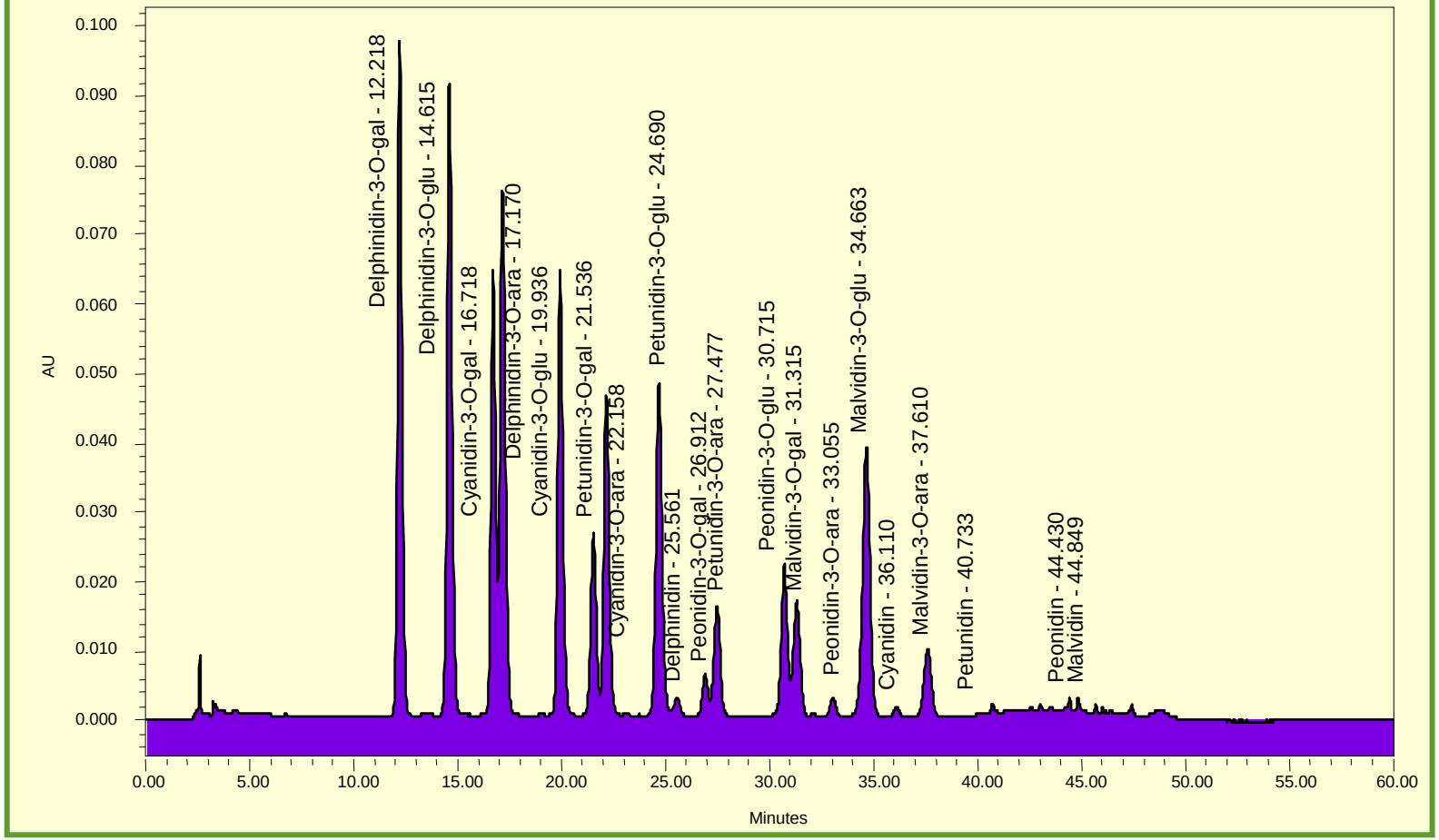


ANTHOCYANIDINS	R	R_1	R_2	R_3
DELPHINIDIN	H	OH	OH	OH
CYANIDIN	H	OH	OH	H
PETUNIDIN	H	OH	OH	OCH_3
PEONIDIN	H	OCH_3	OH	H
MALVIDIN	H	OCH_3	OH	OCH_3

ANTHOCYANINS	R	R_1	R_2	R_3
DELPHINIDIN-3-*O*-GLUCOSIDE	GLC	OH	OH	OH
CYANIDIN-3-*O*-GLUCOSIDE	GLC	OH	OH	H
PETUNIDIN-3-*O*-GLUCOSIDE	GLC	OH	OH	OCH_3
PEONIDIN-3-*O*-GLUCOSIDE	GLC	OCH_3	OH	H
MALVIDIN-3-*O*-GLUCOSIDE	GLC	OCH_3	OH	OCH_3
DELPHINIDIN-3-*O*-GALACTOSIDE	GAL	OH	OH	OH
CYANIDIN-3-*O*- GALACTOSIDE	GAL	OH	OH	H
PETUNIDIN-3-*O*- GALACTOSIDE	GAL	OH	OH	OCH_3
PEONIDIN-3-*O*- GALACTOSIDE	GAL	OCH_3	OH	H
MALVIDIN-3-*O*- GALACTOSIDE	GAL	OCH_3	OH	OCH_3
DELPHINIDIN-3-*O*-ARABINOSIDE	ARA	OH	OH	OH
CYANIDIN-3-*O*- ARABINOSIDE	ARA	OH	OH	H
PETUNIDIN-3-*O*- ARABINOSIDE	ARA	OH	OH	OCH_3
PEONIDIN-3-*O*- ARABINOSIDE	ARA	OCH_3	OH	H
MALVIDIN-3-*O*- ARABINOSIDE	ARA	OCH_3	OH	OCH_3

indena®

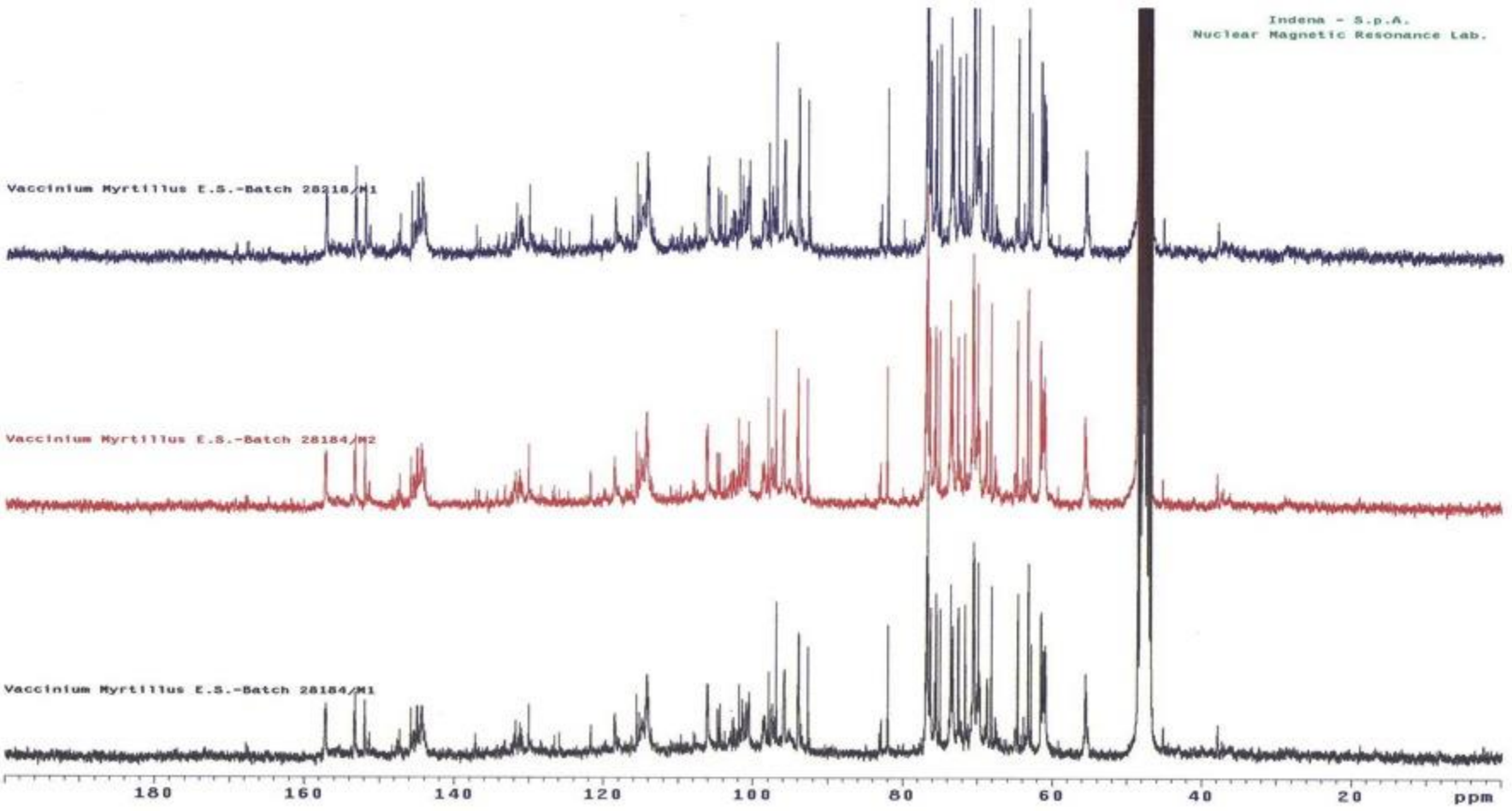
INDUSTRIALLY DEVELOPED STANDARDIZED *VACCINIUM MYRTILLUS* FRUIT EXTRACT (MIRTOSELECT®)



HPLC PROFILE

indena®

MIRTOSELECT®



^{13}C-NMR OF DIFFERENT INDUSTRIAL BATCHES

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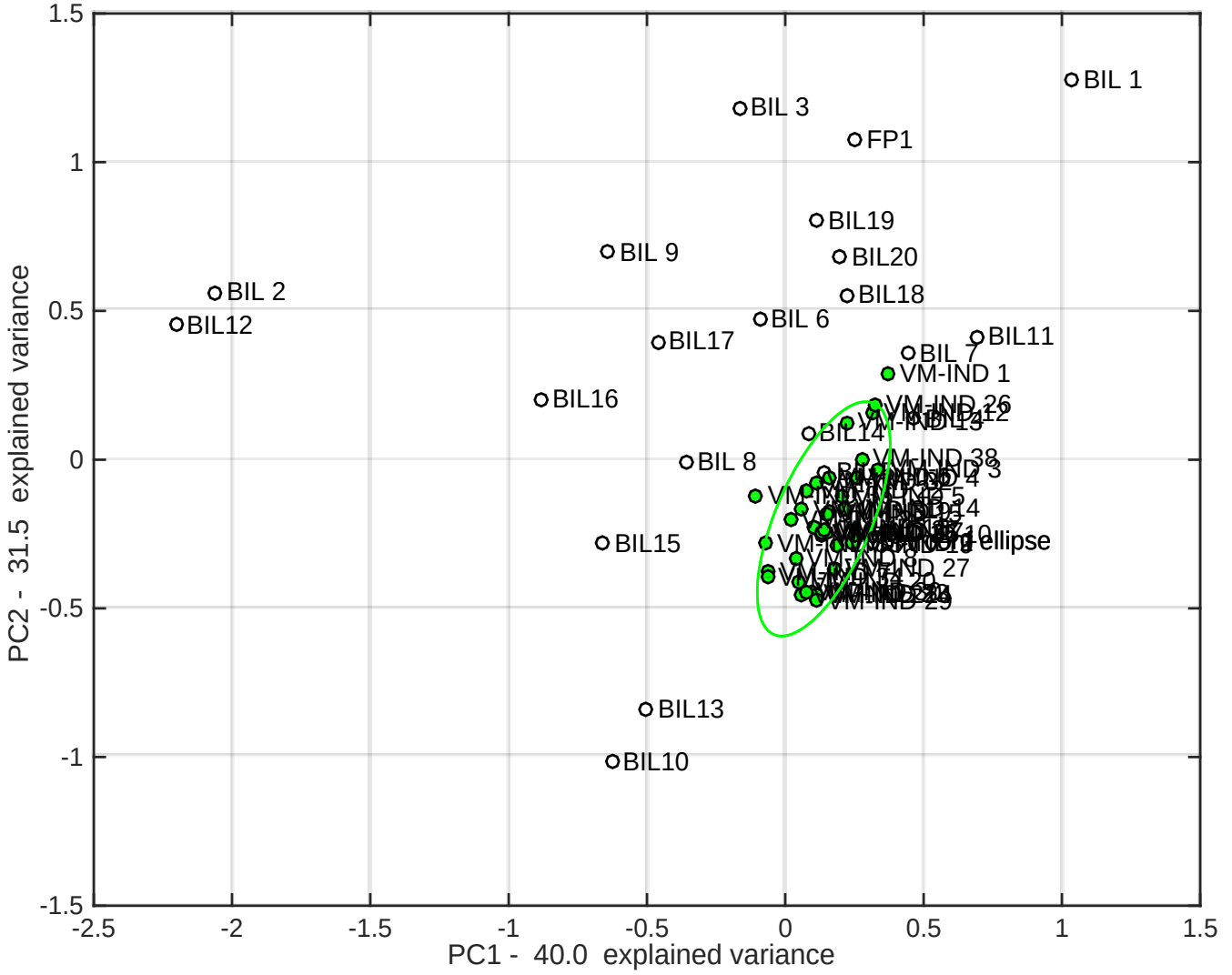
PHYTOEQUIVALENCE ISSUE



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MIRTOSELECT®

CLINICAL USE

- PERIPHERAL VASCULAR PATHOLOGY
- OPHTHALMOLOGY

- COLORECTAL CANCER CHEMOPREVENTION

indena®

COLORECTAL CANCER CHEMOPREVENTION (in rodents)

Int. J. Cancer: **119,** 2213–2220 (2006)

Effect of cyanidin-3-glucoside and an anthocyanin mixture from bilberry on adenoma development in the Apc^{Min} mouse model of intestinal carcinogenesis—Relationship with tissue anthocyanin levels

Darren Cooke[1], Michael Schwarz[2], David Boocock[1], Peter Winterhalter[2], William P. Steward[1], Andreas J. Gescher[1]* and Timothy H. Marczylo[1]

[1]*Cancer Biomarkers and Prevention Group, Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, United Kingdom*

[2]*Institute of Food Chemistry, Technical University of Braunschweig, Braunschweig, Germany*

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COLORECTAL CANCER CHEMOPREVENTION (in humans)

Cancer **Prevention** Research

Pilot Study of Oral Anthocyanins for Colorectal Cancer Chemoprevention

Sarah Thomasset,[1] David P. Berry,[2] Hong Cai,[1] Kevin West,[3] Tim H. Marczylo,[1] Debbie Marsden,[1] Karen Brown,[1] Ashley Dennison,[2] Giuseppe Garcea,[2] Andrew Miller,[4] David Hemingway,[4] William P. Steward[1] and Andreas J. Gescher[1]

Cancer Prev Res 2009;2:625-633. Published online July 7, 2009.

indena®

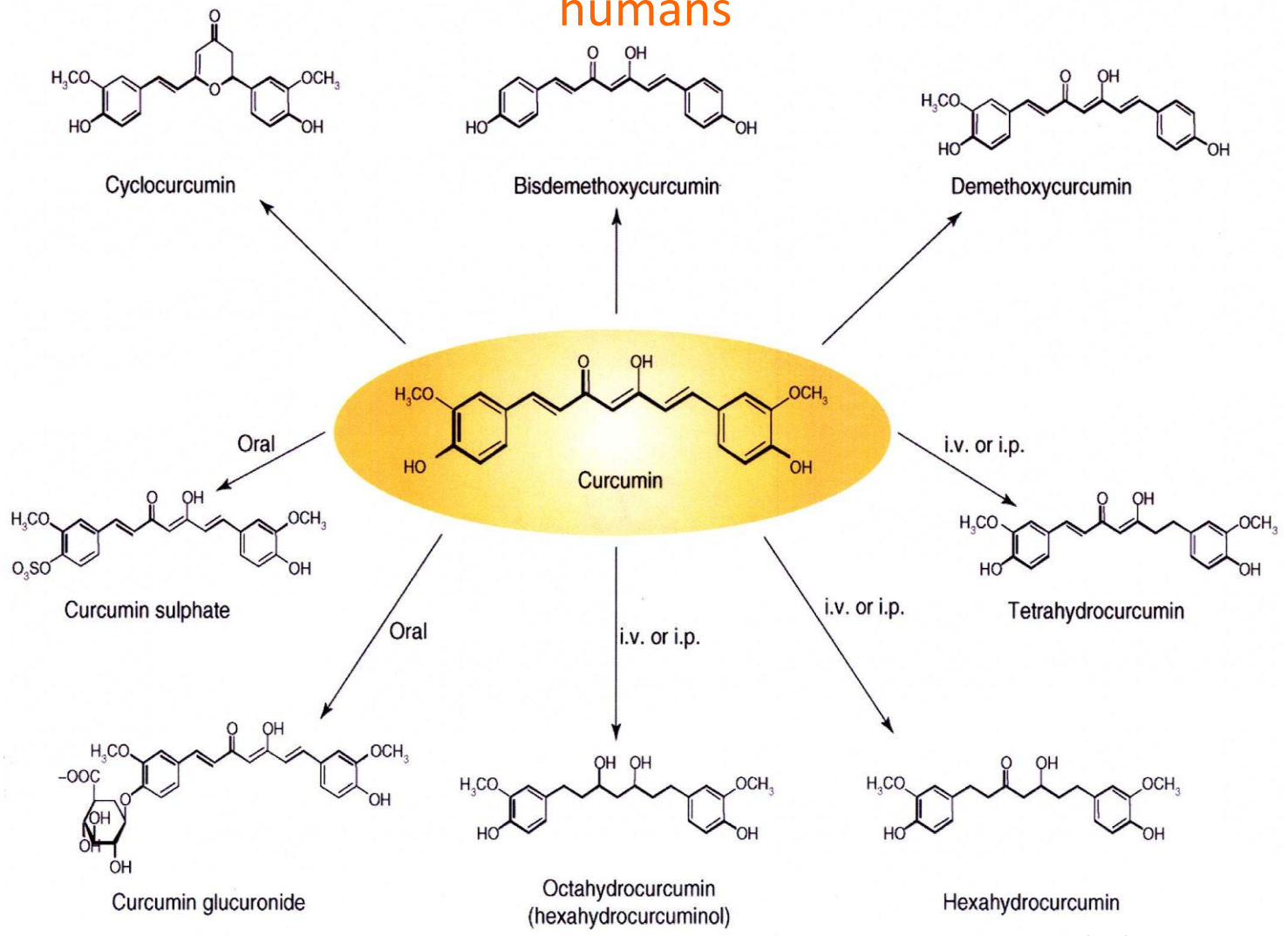
MERIVA®

BIOAVAILABLE CURCUMIN

indena®

CURCUMIN

Natural analogs and its most important metabolites in rodents and humans



B.B. Aggarwal and B. Sung, *TIPS 30*, 85-94 (2009)

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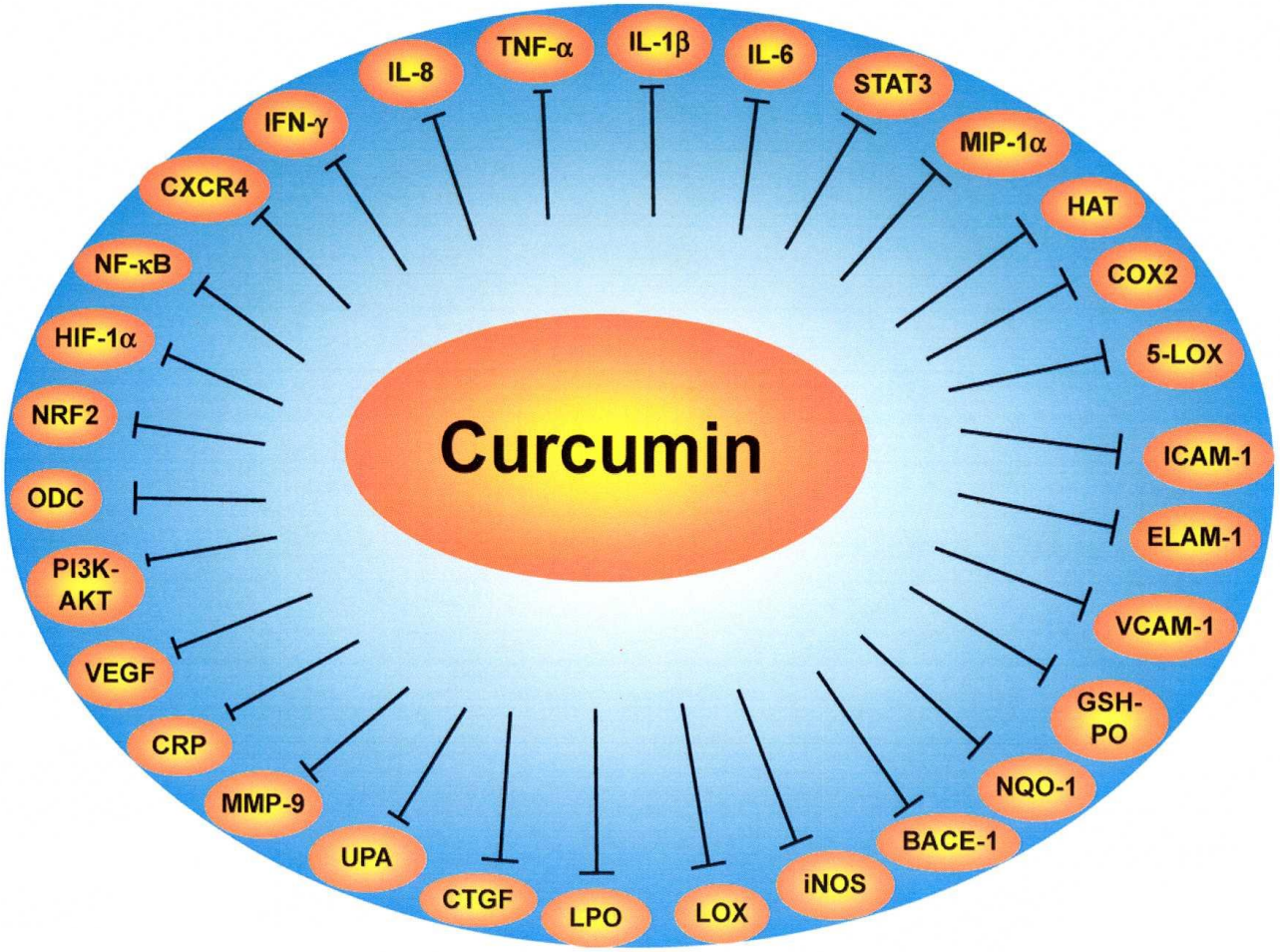
Inhibition of inflammatory pathways by curcumin



BACE-1, beta-site APP-cleaving enzyme 1; CRP, C-reactive protein; CTGF, connective tissue growth factor; ELAM-1, endothelial leukocyte adhesion molecule-1; HAT, histone acetyl transferase; HIF, hypoxia inducible factor; ICAM-1, intracellular adhesion molecule-1; LPO, lipid peroxidation; MMP, matrix metalloprotease; NF-κB, nuclear factor kappa B; ODC, ornithine decarboxylase; STAT, signal transducers and activator of transcription protein; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

B.B. Aggarwal, K.B. Harikumar / The International Journal of Biochemistry & Cell Biology 41 (2009) 40–59

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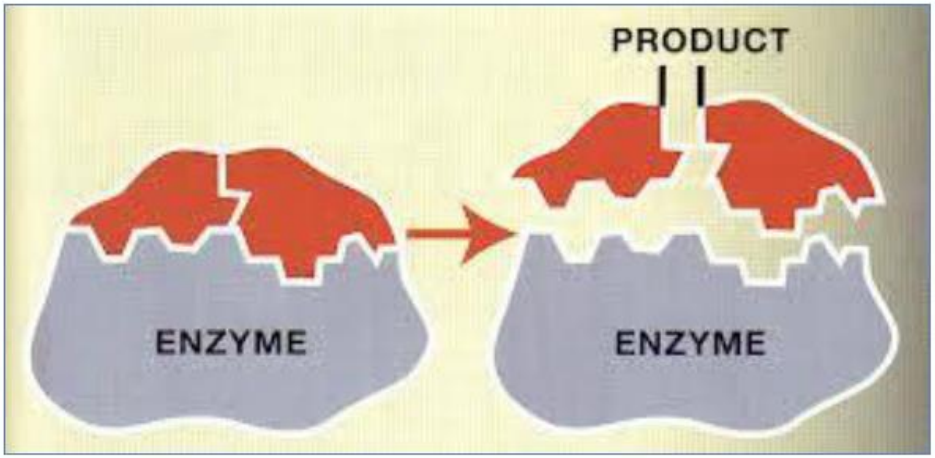
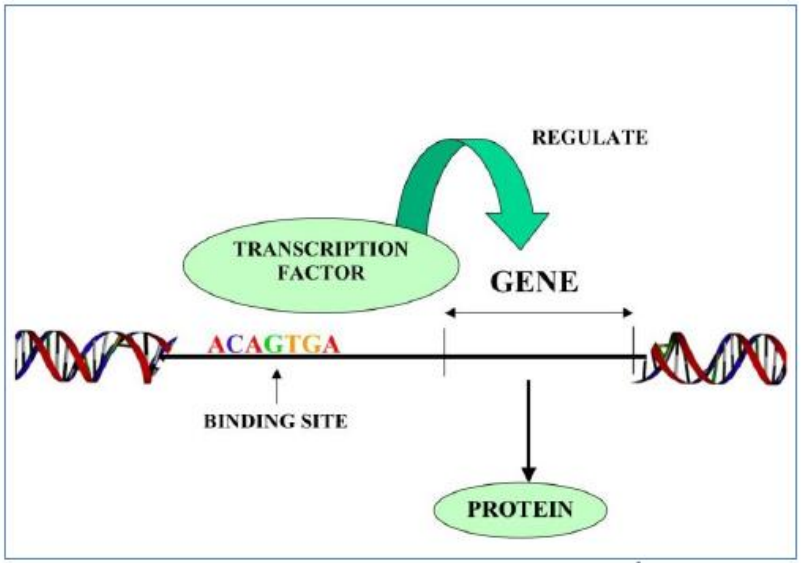
Curcumin: an *intellingent* NSAID-SAID combination?

Curcumin interrupts pro-inflammatory signals and increases anti-oxidant protection by acting at across-time-domain targets:

Short time-domain targets: enzymes (MAPKs, COX2, LO), ion channels (TRPV1, TRPA1)
Long time-domain targets: transcription factors (NF-κB, AP1, STAT, PPAR-γ)

NET RESULT: inhibition of the expression of inflammatory cytokines (TNF-α, IL-1β, IL-6)and of the expression and function of inducible inflammatory enzymes (COX2 and mPG2S)





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Cancer Letters 269 (2), 199-225 (2008)

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Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins

Ajaikumar B. Kunnumakkara, Preetha Anand, Bharat B. Aggarwal *

Cytokine Research Laboratory, Department of Experimental Therapeutics,

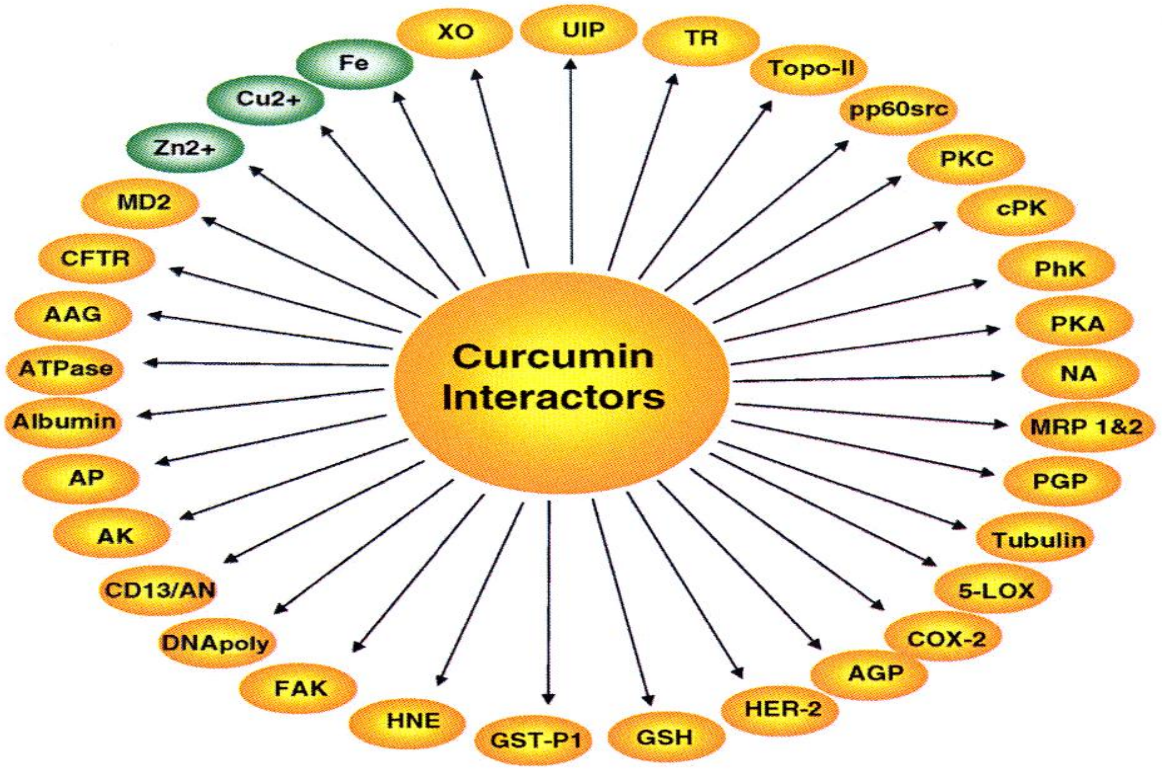

Fig. 3. Curcumin has been shown to bind to numerous molecules. AGP, human alpha1-acid glycoprotein; AK, autophosphorylation-activated protein kinase, AP, amyloid protein; CD13/AN, CD13/aminopeptidase N; CFTR, cystic fibrosis transmembrane conductance regulator; COX-2, cyclooxygenase; cPK, protamine kinase; DNA poly, DNA polymerase; FAK, focal adhesion kinase; GSH, glutathione; HER-2, human epidermal growth factor receptor; HNE, 4 hydroxy-2-nonenal; NA, nucleic acid; LOX, lipoxygenase; PGP, P-glycoprotein; PkA, protein kinase A, PkC, protein kinase C, PhK, phosphorylase kinase; pp60src, pp60c-src tyrosine kinase; TR, thioredoxin reductase; Topo-II, topoisomerase II; UIP, ubiquitin isopeptidase; XO, xanthine oxidase.

THE **CLINICAL PK CONFIRMATION**

JOURNAL OF NATURAL PRODUCTS

ARTICLE

pubs.acs.org/jnp

Comparative Absorption of a Standardized Curcuminoid Mixture and Its Lecithin Formulation

John Cuomo,[*,†] Giovanni Appendino,[*,‡] Adam S. Dern,[†] Erik Schneider,[†] Toni P. McKinnon,[†] Mark J. Brown,[†] Stefano Togni,[§] and Brian M. Dixon[†]

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[§]Indena S.p.A., Viale Ortles 12, 20139 Milano, Italy

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STUDY **DESIGN**

Nature of the study.....Randomized, double blind, cross-over

Dosage.....1800 mg unformulated curcumin vs 209 and 376 mg curcumin as Meriva® (ca 1 g and 1.75 g Meriva ®)

Partecipants.....9 healty adults

Primanry End Point.....Plasma levels of the three major curcuminoid conjugates

Analytical method.....HPLC-MS

Schedule.....Overnight fasting and donation of baseline blood

Administration with light breakfast

Donation of blood and measurements

J. Nat. Prod. **2011**, *74*, 664-669

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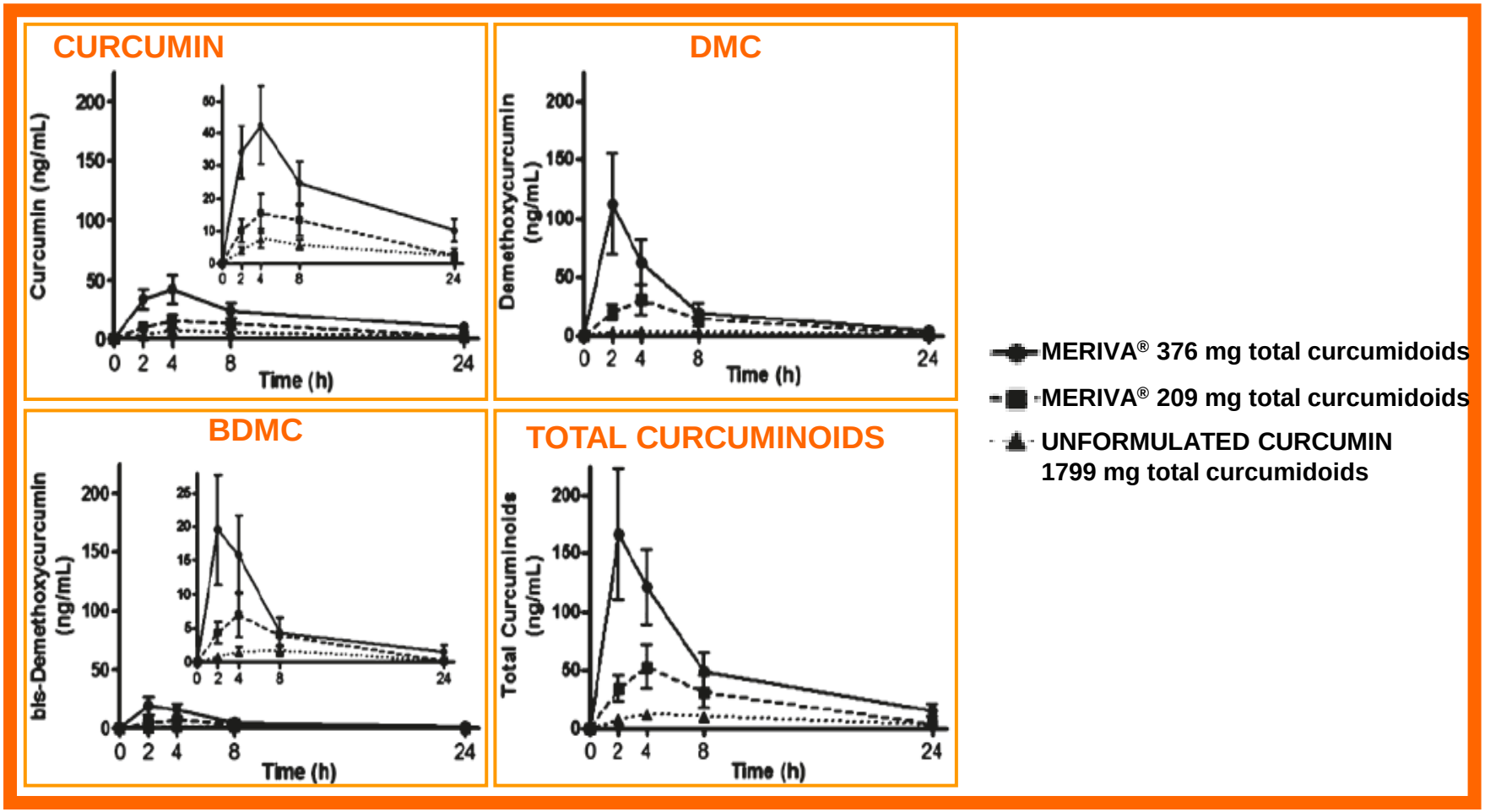
Mean plasma levels of curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC) and total curcuminoids in nine healthy volunteers after oral intake of MERIVA® vs curcumin



Cuomo et al., *J. Nat. Prod.* 74: 664 (2011)

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TAKE-HOME MESSAGES from PK

Curcumin from Meriva® is ca 18 fold **more bioavailable** than curcumin from an unformulated curcuminoid mixture.

Overall, curcuminoids as Meriva® are ca 29 fold **more bioavailable** than curcuminoids from an unformulated curcuminoid mixture.

Independently from the dosage, **DMC is the major plasma curcuminoid with Meriva®**, but not with unformulated curcumin.

Absorption of curcuminoids is faster (x2 fold) from Meriva® than from unformulated curcumin

J. Nat. Prod. **2011**, *74*, 664-669

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24 CLINICAL STUDIES AVAILABLE

THERAPEUTICAL AREA	N° OF STUDIES
OSTEOARTHRITIS	3
SARCOPENIA	1
EYES DISORDERS	4
SKIN DISORDERS (PSORIASIS)	1
DIABETES	2
BENIGN PROSTATIC HYPERPLASIA	1
PAIN MANAGEMENT	1
NEUROPATHIES	2
SPORT MEDICINE	2
DIAGNOSTIC (AD)	1

+ 1 Pharmacokinetic

+ 2 reviews

*+ **5 CLINICAL STUDIES in the cancer field***

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Randomized double-blind trial of a standardized bilberry extract and bioavailable curcumin in subjects with colorectal adenomas - MIRACOL study -

A57

Alessandra Argusti[1], Matteo Puntoni[1], Gianni Coccia[1], Matteo Clavarezza[1], Cristiano Crosta[2], Emanuele Meroni[3], Giuseppe De Roberto[2], Daniela Branchi[1], Beatrice Gatteschi[4], Roberto Benelli[4], Paolo Morazzoni[5], Andrea DeCensi[1]

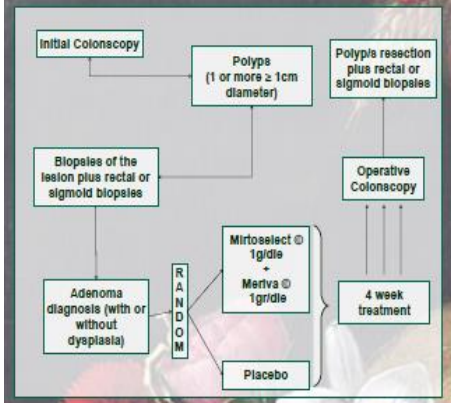
[1]E.O. Ospedali Galliera, Genoa, Italy, [2]European Institute of Oncology, Milan, Italy, [3]Istituto Nazionale Tumori Foundation, Milan, Italy, [4]National Cancer Institute, Genoa, Italy, [5]Indena S.p.A., Milano, Italy.

Tenth AACR International Conference on
FRONTIERS IN CANCER PREVENTION RESEARCH
October 22-25, 2011 • Boston, MA

RATIONALE

Colorectal cancer (CRC) is one of the most frequent malignancies in developed countries. Colorectal carcinogenesis is a multistage process that occurs over a period of 10-20 years. Colorectal adenomas (CA) are well recognized as CRC risk markers as removal of CA decreases the incidence of CRC. Chemoprevention with aspirin, COX-2 inhibitors, sulindac and DFMO have proven to be effective in reducing recurrence from colorectal adenoma, but toxicity is an important issue and overall acceptability by the lay community represents a real barrier to the large use of these agents.

Inflammation and oxidative stress appear to play a crucial role in the development of CRC; NF-kB activation has been associated with multiple pathways of oncogenesis, including apoptosis, cell cycle control, differentiation, angiogenesis and cell migration; interference with these mechanisms may represent a strategy in CRC chemoprevention.



Anthocyanins and curcumin represent, so far, the two most reliable candidates mainly due to their integrated capacity of modulating key steps of inflammatory processes, cell proliferation and tumor progression.

Anthocyanins are a group of natural occurring pigments responsible for the red-blue color of many fruits and vegetables and are provided with antiproliferative, apoptogenic, antiinflammatory and antioxidant effects and with the capacity of inhibiting tumor progression in experimental models of gastrointestinal cancerogenesis.

In a recent pilot study in CRC patients, anthocyanins administered for 7 days were dose-dependently effective in reducing the proliferation index Ki-67.

Mirtoselect® is a standardized bilberry extract containing 36% anthocyanins.

Curcumin is a polyphenolic compound obtained from turmeric (Curcuma longa L.) endowed with marked anti-inflammatory, antioxidant and antineoplastic effects; due to its peculiar proximal carbonyls.

Curcumin is also effective in interacting with the intracellular redox status contributing to modulate main steps of cellular activation and proliferation. Curcumin acts as a master switch of inflammation at enzymes and transcription factors levels (COXs and NF-kB), as well as at their genomic expression.

Meriva® is a patented formulation of curcumin with soy lecithin, complexed with phospholipids to led to a marked increase in the concentration of the plasma curcuminoids boosting its cellular capitation

We propose to test a rational combination of a natural enriched source of anthocyanins from bilberry (Vaccinium myrtillus L.), MIRTOSELECT© (standardized to contain 36 % anthocyanins) with a bioavailable form of curcumin, MERIVA©, to assess the effects of Mirtoselect © and Meriva© on beta catenin expression in both adenomatous and unaffected colonic tissue.

Based on previous experience in humans, the proposed daily dosages of 1g of MIRTOSELECT© and 1g of MERIVA© would assure an effective concentration of anthocyanins and curcumin in the target tissue and at plasma level.

We designed a presurgical, double-blind, placebo-controlled, randomized phase I/II trial in patients with colorectal adenomatous polyps. After complete colonoscopy and biopsy of the index polyp, 100 subjects with histologically confirmed CA will be assigned (50 per arm) to either placebo or Mirtoselect© 1g/d + Meriva© 1gr/die treatment for 4-6 weeks before polyp removal.

The primary endpoint will be the effect of the combination of anthocyanins and curcumin on β-catenin in adenoma and unaffected colorectal tissue.

Secondary endpoints include treatment modulation of biomarkers of oxidative activation (NF-kB), proliferation and apoptosis (Ki67, Topoisomerase.II-alpha and TUNEL), inflammation (u-CRP), circulating IGFs (IGF-1, IGFBP-3), genetic expression profile.

Pharmacokinetic of the combination of anthocyanins and curcumin will be evaluate by HPLC, Cmin (o Cmax?) will be measured at steady state.

SAMPLE SIZE

Recent results from a similar study population (APAC study, allopurinol for CR adenoma, presented at the 9th AACR, Nov 7-10, 2010, Philadelphia, PA, USA, abstract #A69) allow us to postulate a 25±35% mean expression of β-catenin in adenomas.

Using ANCOVA (i.e. adjusting for baseline levels) and assuming a pre-post correlation in β-catenin levels equal to 0.9, 50 subjects per arm will provide 85% power to detect an absolute difference between arms of 10% in the post-treatment mean levels of β-catenin on adenoma tissue. We assume a 10% of lost to follow-up and a two-sided alpha-error=5%.

CONCLUSIONS

An increasing number of cancer prevention trials are investigating the potential of natural compounds to interfere with cancer development and progression, although the majority are still in early clinical phase. Curcumin and blueberry extracts are among the most interesting candidates for CRC chemoprevention strategies in humans. The demonstration of a chemopreventive activity in humans could provide a strong rationale for the use of derivatives of curcumin and blueberries in a phase III trial to reduce the incidence of colon cancer in individuals at increased risk.

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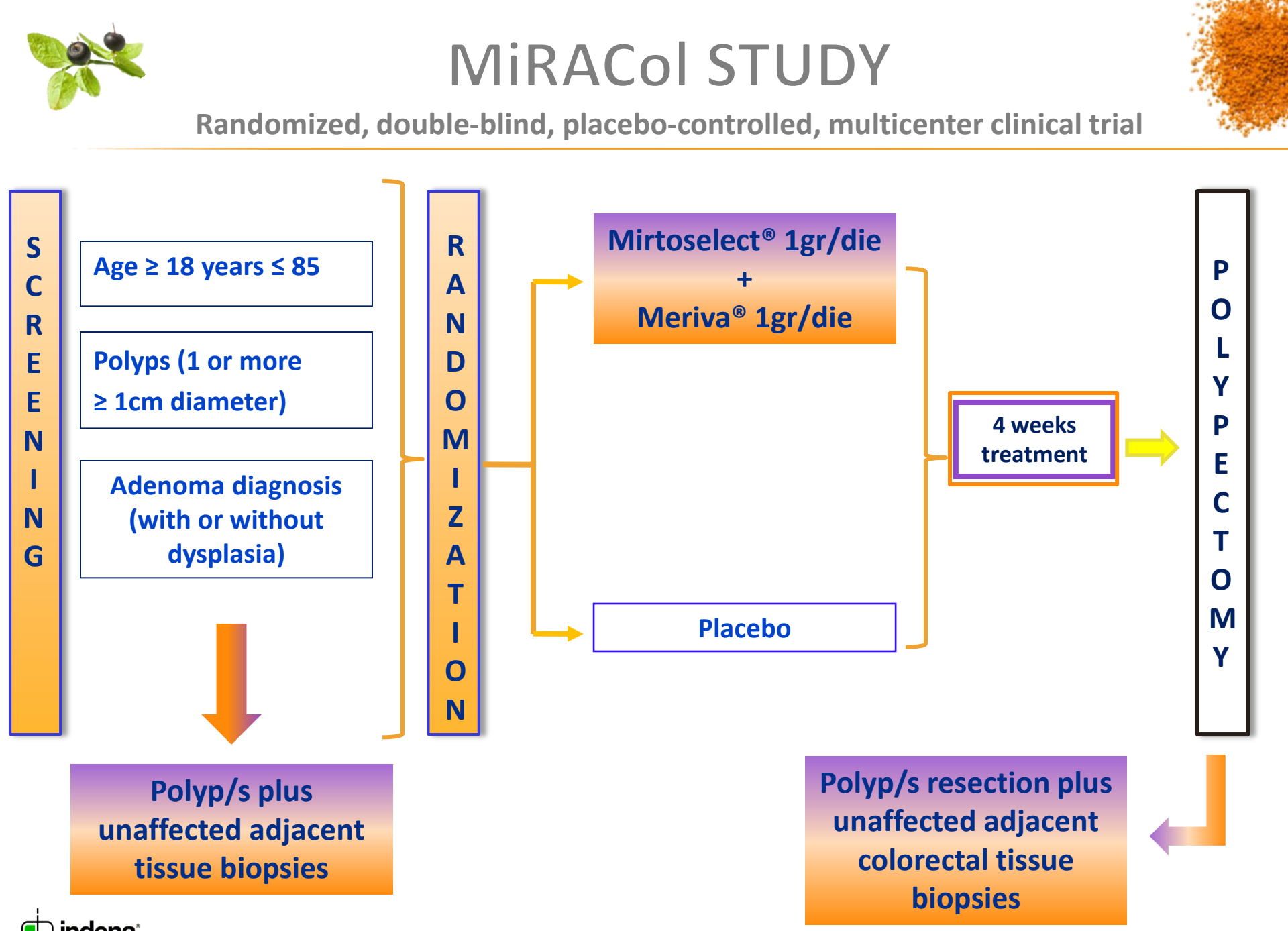
Nancy Gavert and Avri Ben-Ze'ev. β-catenin Signaling in Biological Control and Cancer Journal of Cellular Biochemistry 102:820–828 (2007)

MiRACol STUDY

Randomized, double-blind, placebo-controlled, multicenter clinical trial



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STUDY ENDPOINTS

Primary endpoint

✓ β-catenin expression in adenomatous tissue as key element in APC mediate colon cancerogenesis.

Secondary endpoints

- In adenomatous and unaffected tissue:

✓ Inflammation and oxidative stress biomarker (NFkβ)

✓ Cell proliferation biomarker (Ki67)

✓ DNA damage biomarker (P53)

✓ Circulating growth factors (IGF-I, IGFBP-3, IGF-I/IGFBP-3, EGFR)

- Evaluation of toxicity/side effects
- Plasma concentration of the active compounds (in a subgroup of subjects)

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SAMPLE SIZE

With a sample size of 100 subjects (50 per arm) the study is 85% powered to detect an absolute difference of 10% between arms in the change (pre-post treatment) of β- catenin expression levels, in adenoma tissue. Power calculation take into account a 10% of lost to follow-up patients and a two-sided alpha error equal to 5%.

Recruitment period: 48 months

30 subjects enrolled until May 2016

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TAKE HOME MESSAGES

- Plant kingdom continues to represent a large source of therapeutical products covering most relevant pathologies

- Plant kingdom and particularly edible plants are also precious containers of biologically active phytonutrients (e.g. primary and secondary metabolites) which can explain partly epidemiological highlights related to pathologies risk- reduction and dietary intake.

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TAKE HOME MESSAGES

- Combination of predictive preclinical models and controlled clinical studies (by means of surrogate end-points) with high - quality standardized botanical products are needed for confirming basic epidemiological evidences

- Examples of clinically tested standardized botanical products obtained from edible plants are nowadays available and can constitute for the future an important contribute in the strategic approach to optimize nutrition and public health conditions

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