ESEMPI DI ESTRATTI STANDARDIZZATI ATTIVI DA PIANTE COMMESTIBILI SULLA MODULAZIONE DEI RISCHI NEI DISORDINI METABOLICI <u>P. Morazzoni</u>, A. Riva - Indena SpA - Milano





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

CAUSE OF DEATH	(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

N° OF DEATH /100.000



CVDs FIRST CAUSE OF MORTALITY IN WESTERN COUNTRIES

KEY FACTS

- CVDs are the number one cause of death globally: more people die annually from CVDs than from any other cause
- An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke
- Low- and middle-income countries are disproportionally affected: over 80% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women
- The number of people who die from CVDs, mainly from heart disease and stroke, will increase to reach 23.3. million by 2030 CVDs are projected to remain the single leading cause of death
- Most cardiovascular diseases can be prevented by addressing risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity, high blood pressure, diabetes and raised lipids.

ndena 🖒

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.



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)!



eil pl	ogetto	CUOLO NONTERIOR DE
livello di rischi	o a 10 anni	High Global Risk
rischio MCV VI	oltre 30%	(>20%)
rischio MCV V	20% - 30%	Statins are reimbursed
rischio MCV IV	15% - 20%	
rischio MCV III	10% - 15%	Moderate Global Risk
rischio MCV II	5% - 10%	(<20%) Dietary intervention
rischio MCV I	meno 5%	

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

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





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

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

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. © 2014 Elsevier B.V. All rights reserved.



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
- \rightarrow About one in ten suggested claims has been approved



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



Art.14(1)(B <u>a)</u>	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.	h	Q-2011-00799	Commission Regulation (EU) 1048/2012 of 08/11/2012	Authorised	N/A
Art.14(1)(B <u>a)</u>	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)	Dat 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



					<u> </u>		
Art.14(1)(<u>a)</u>	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	Plant sterols have been shown to lower/reduce	Information to the consumer that the beneficial effect is obtained with a daily	Q-2008-085, Q-2009-530 and Q-2009	Commission Regulation (EC) 983/2009 of 21/10/2009	Authorised	N/A
<u>a)</u>	or esterified with food	blood cholesterol. High	intake of 1.5-3 g plant sterols	-718.	Amended by Commission		
	grade fatty acids.	cholesterol is a risk	Reference to the magnitude of the	Q-2011-01241	Regulation (EC) 376/2010 of		
		factor in the	effect may only be made for foods		03/05/2010,		
		development of	within the following categories: yellow		Amended by Commission		
		coronary heart disease.	fat spreads, dairy products,		Regulation (EU) No 686/2014 of		
			mayonnaise and salad dressings.		20/06/2014		
			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				
			be consumer				
1				-			



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.

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



Indena strategic approaches for the development of edible plant-derived products

• Revalorization of plants from Mediterranean area

Phaseolus vulgaris, Cynara cardunculus...

• Improvement of extract "characteristics" (bioavailability, standardization, new formulation) *Curcuma longa, Vitis vinifera.....*

• Targeted combinations Appetite control, cholesterol lowering formulation....



EFSA allowed risk – reduction claims

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 appropriate period of time (i.e. at least two hours) and no increase in insulin concentrations in comparison to the reference food.

EFSA Journal 2012;10(3):2604



EFSA allowed risk – reduction claims

5.1.2. Claims related to blood HDL-cholesterol concentration

Maintenance of normal HDL-cholesterol concentration is a beneficial physiological effect as long as LDL-cholesterol concentration is not increased.

The scientific evidence for the substantiation of health claims on the maintenance of normal HDL-cholesterol concentration can be obtained from human intervention studies showing a short-term (e.g. three to four week) increase in fasting HDL-cholesterol concentration (without a concomitant increase in LDL-cholesterol concentration) as compared to an appropriate 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 an increase in HDL-cholesterol concentration within the normal range is considered a beneficial physiological effect. Evidence for a sustained effect with continuous consumption of the food/constituent over longer periods of time (e.g. eight weeks) should also be provided.

EFSA Journal 2011; 9 (12): 2474



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).



STANDARDIZATION PROCEDURES

- 1. PLANT MATERIAL QUALITY (GACP)
- 2. MANUFACTURING PROCESS (GMP)
- 3. IN PROCESS CONTROLS

The respect of GACP and GMP Guidelines keeps the challenge for quality criteria of dietary supplements ingredients as close as possible to "phytotherapic drugs" and assure complete batch to batch reproducibility. With this approach a number of highly standardized extracts could be setup as potential candidates in the consumer health field.



Phaseolus vulgaris L.





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)

 $\begin{array}{ll} & \alpha \mbox{-Amylase inhibitor} \\ & (\mbox{HPLC} - \% \mbox{ w/w}) \geq 6\% & \leq 14\% \\ & (\mbox{Inhibiting activity} - U/mg) \geq 1000 & \leq 1600 \\ & \mbox{Phytohemoagglutinins} \\ & (\mbox{Haemagglutinating activity} - HAU/g) \geq 8000 & \leq 30000 \end{array}$



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



Beanblock[®] in Humans



British Journal of Nutrition, page 1 of 7 © The Authors 2012

2013; 109 (10): 1789-1795

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

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

Abstract

British Journal of Nutrition

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). 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 excusions, suppressed 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





Beanblock[®] employed as supplement in a Mediterranean meal positively affected glucose metabolism

Fasting and postprandial glucose



Compared with placebo^{\Box}, Beanblock[®] • resulted in lower increments in glucose (+15.4% vs 26.1%, P=0,04 at 30 min)



Beanblock[®] Employed As Supplement in a Mediterranean Meal Positively Affected Appetite Control

Fasting and postprandial satiety sensations



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).



$Beanblock^{\circledast}$

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.



Cynara cardunculus L. subsp. scolymus (L.) Hegi







Protective and curative effects of artichoke leaves extract in different pathologies



Modified from: K. Kraft, Phytomedicine 4, 369 (1997)





Cochrane Database Syst. Rev. 2013

Cochrane Database Syst Rev. 2013 Mar 28;3:CD003335. doi: 10.1002/14651858.CD003335.pub3.

Artichoke leaf extract for treating hypercholesterolaemia.

Wider B, Pittler MH, Thompson-Coon J, Ernst E.

Institute of Health Services Research, University of Exeter Medical School, Exeter, UK. b.wider@exeter.ac.uk

Abstract

BACKGROUND: Hypercholesterolaemia is directly associated with an increased risk for coronary heart disease and other sequelae of atherosclerosis. Artichoke leaf extract (ALE) has been implicated in lowering cholesterol levels. Whether ALE is truly effective for this indication is still a matter of debate. This is an update of a review first published in 2002 and last updated in 2009.

OBJECTIVES: To assess the efficacy and safety of ALE in the treatment of hypercholesterolaemia.,





Cochrane Database Syst. Rev. 2013

SEARCH METHODS: We updated searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library) (2012, Issue 5); MEDLINE Ovid (1966 to May Week 2, 2012); EMBASE Ovid (1980 to 2012 Week 19); and CINAHL Ebsco (1982 to May 2012) on 17 May 2012. CISCOM was last searched until June 2001, and AMED until June 2008. We checked reference lists of articles, and contacted manufacturers of preparations containing artichoke extract, and experts on the subject. No language restrictions were applied.

SELECTION CRITERIA: We included randomised controlled trials (RCTs) of ALE monopreparations compared with placebo or reference medication for patients with hypercholesterolaemia. We excluded trials assessing ALE as one of several active components in a combination preparation or as a part of a combination treatment.

DATA COLLECTION AND ANALYSIS: Data were extracted systematically and risk of bias was evaluated using the Cochrane 'Risk of bias' tool. Two authors independently performed the screening of studies, selection, data extraction and assessment of risk of bias. Disagreements in the evaluation of individual trials were resolved through discussion.





Cochrane Database Syst. Rev. 2013

MAIN RESULTS: We included three RCTs involving 262 participants. The trials were of adequate methodological quality but had some shortcomings. One trial was at low quality of risk, one at medium and one of unclear risk of bias. One trial is available as abstract only and includes a small sample. In the first trial the total cholesterol level in participants receiving ALE decreased by 4.2% from 7.16 (0.62) mmol/L to 6.86 (0.68) mmol/L after 12 weeks, and increased from 6.90 (0.49) mmol/L to 7.04 (0.61) mmol/L in patients receiving placebo, the total difference being statistically significant (P = 0.025). In the second trial ALE reduced total cholesterol levels by 18.5% from 7.74 mmol/L to 6.31 mmol/L after 42 ± 3 days of treatment, whereas placebo reduced cholesterol by 8.6% from 7.69 mmol/L to 7.03 mmol/L (P = 0.00001). The third trial, which is available as abstract only and provides limited data, stated that ALE significantly reduced blood cholesterol compared with placebo in a subgroup of patients with baseline total cholesterol levels of more than 230 mg/dL (P < 0.05). Trial reports indicate mild, transient and infrequent adverse events.

AUTHORS' CONCLUSIONS: Data from three clinical trials assessing ALE for treating hypercholesterolaemia are available. Athough the trials are of adequate methodological quality they have some shortcomings and one is available as abstract only. There is an indication that ALE has potential in lowering cholesterol levels, but the evidence is, as yet, not convincing. The limited data on safety suggest only mild, transient and infrequent adverse events with the short term use of ALE.





Most relevant RCTs with artichoke leaves extract

2008 - Bundy R. et al., Phytomedicine 15, 668

Mean changes in total cholesterol concentration -4.2% for the active group and +1.9% for the placebo group, total difference (6.1%). Statistically significant (P = 0.025). No further statistically significant differences in HDL, LDL, TAG between groups.

2000 - Englisch W. et al., Arzneimittel-Forsch. 50, 260

Mean reduction of total cholesterol was 18.5% (1.43 mmol/L) for the treatment group and 8.6% for the placebo group (0.66 mmol/L), difference of means 9.9%. Statistically significant. LDL-cholesterol decreased by 22.9% in the ALE group and 6.3% in the placebo group. Difference 16.6%. Statistically significant.

LDL/HDL ratio decreased by 20.2% in ALE group and 7.2% in placebo group. Difference between group 13%.

No statistically significant differences between groups for HDL cholesterol and triglycerides.

1997 - Petrowicz O. et al., Atherosclerosis 129, 147

Total cholesterol reduction

No effect in total patient population. Sub-group analysis in patients with initial total cholesterol levels of above 210 mg/dL showed that ALE significantly reduced total cholesterol compared with placebo. But this was on few patients therefore data are of limited power, n=7 Control/placebo arm and n=10 in the treatment arm.





Artichoke leaves extracts composition of the products utilized in randomized clinical trials (Cochrane's)

Bundy et al. (2008)

Cynara Artichoke, Lichtwer Pharma (UK); Acqueos extract (4-6:1) containing 2.5% caffeoylquinic acids and 0.1% luteolin-7-O-glucuronide.

Englisch et al. (2000)

Artichoke dry extract , Novartis Consumer Health (Germany); Acqueous extract (25-35:1), batch #349738.





ARTICHOKE ON THE U.S.A. MARKET



Total Caffeoylquinic acids: 3.24% Total Flavonoids: 0.07% Cynaropicrin: absent





ARTICHOKE USE IN THE UE MARKET, PLOS ONE 2014

OPEN O ACCESS Freely available online

Usage of Plant Food Supplements across Six European Countries: Findings from the PlantLIBRA Consumer Survey

Alicia Garcia-Alvarez¹, Bernadette Egan², Simone de Klein³, Lorena Dima⁴, Franco M. Maggi⁵, Merja Isoniemi⁶, Lourdes Ribas-Barba^{1,7}, Monique M. Raats², Eva Melanie Meissner³, Mihaela Badea⁴, Flavia Bruno⁵, Maija Salmenhaara⁶, Raimon Milà-Villarroel¹, Viktoria Knaze¹, Charo Hodgkins², Angela Marculescu⁴, Liisa Uusitalo⁶, Patrizia Restani⁵, Lluís Serra-Majem^{1,7,8}*

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Botanicals used

A total of 491 botanicals -used in at least one PFS- were reported across the six participating countries. An overview of all the reported botanicals -clustered by intervals of frequency of intake (number of consumers ranging from 194 to 5)- is shown in Table 12. Based on the survey results, the eleven most frequently used botanicals (numbers of consumers ranging from 194 to 100) in descending order are *Ginkgo biloba* (ginkgo), *Oenothera biennis* (evening primrose), *Cynara scolymus* (artichoke), *Panax ginseng* (ginseng), *Aloe vera* (aloe), *Foeniculum vulgare* (fennel), *Valeriana officinalis* (valerian), *Glycine max* (soybean), *Melissa officinalis* (lemon balm), *Echinacea purpurea* (echinacea) and *Vaccinium myrtillus* (blueberry) (Table 12).

3rd MOST FREQUENTLY USED BOTANICALS





Main components of artichoke leaves and their reported biological activities: are we sure to maintain all of them (and in the proper quantity) in the final products ?





A patented artichoke leaves standardized extract



PYCRINIL[®]

Caffeoylquinic acids: >20%

Flavonoids: >5%

Cynaropicrin: >5%





PYCRINIL[®]: A NEW STANDARDIZED ARTICHOKE LEAVES EXTRACT

Are we expecting an

"improved" clinical response

in respect of the already

described modulating effect

of "classical artichoke leaves extracts"

on dyslipidemia?





CLINICAL DOCUMENTATION AVAILABLE

2 studies published:

- Int. J. Food Sciences and Nutr. 64, 7 (2013)
- Fadoi 2014







PYCRINIL® AND HDL-C

Beneficial effects of artichoke leaf extract supplementation on increasing HDL-cholesterol in subjects with primary mild hypercholesterolaemia: a double-blind, randomized, placebo-controlled trial

MARIANGELA RONDANELLI¹, ATTILIO GIACOSA², ANNALISA OPIZZI¹, MILENA ANNA FALIVA¹, PATRIZIO SALA¹, SIMONE PERNA¹, ANTONELLA RIVA³, PAOLO MORAZZONI³, & EZIO BOMBARDELLI³

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Int. J. Food Sciences and Nutr. 64, 7 (2013)





PYCRINIL[®] AND HDL-C

TARGET:

Effect of PYCRINIL[®] on main glycolipidic metabolic parameters in 92 overweight subjects with mild hypercholesterolemia (Total cholesterol: 5.4-7.0 mmol/l).

STUDY DESIGN:

Subjects: 46 (PYCRINIL[®]) + 46 (Placebo) Dosage: 1 tablet (250 mg) twice daily Duration of treatment: 2 months

PRIMARY END-POINT:

Change in HDL-C levels between the baseline and the end of treatment

SECONDARY END-POINTS:

Change in lipidic parameters (TC, LDL-C, TG, TC/HDL-C, LDL-C/HDL-C) and glycemia between the baseline and the end of treatment

Int. J. Food Sciences and Nutr. 64, 7 (2013)





PYCRINIL® AND HDL-C

Statistically significant percent variations (vs baseline) in lipidic parameters

Primary end-point

HDL-C ∆ +12% P<0.001

Secondary end-points

ТС	LDL-C	TC/HDL	LDL/HDL
Δ -5%	Δ -13%	Δ -14%	Δ -20%
P=0.019	p<0.001	p<0.001	p<0.001

Triglycerides showed a not statistically significant decrease in PYCRINIL[®] group and a not statistically significant increase in the placebo group.

These opposite patterns were statistically significant in female (p=0.013).

Int. J. Food Sciences and Nutr. 64, 7 (2013)





THE NEW CLINICAL TRIAL WITH 200 mg/day – FADOI 2014

Confirmation of efficacy on HDL-C with a "omega 3 vegetable" (soft-gel capsules 200 mg) in Caucasian subjects

The dose is 1 cps/day before evening, equivalent to 200 mg/day.

15 subjects have been enrolled with two check points, at 15 and 30 days.

HDL-C: basal parameters ranging from 35 to 84 mg/dL.





FADOI 2014









XIX Congresso Nazionale della Società Scientifica FADOI, Bologna 10-13 maggio 2014

Pilot study on the efficacy of once a day dosage (200 mg) of *Cynara scolymus* L. leaf extract on HDL-cholesterol and on lipidic pattern in a group of adult subjects with mild hypercholesterolemia

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Introduction: A twice-daily administration of highly standardized extract from Cynara scolymus leaves derivatives (Pycrinil[®]) has shown to increase HDL-C in subjects with mild hypercholes-terolemia. This study aimed at assessing the effect of once-daily dosage (200 mg) of the same extract on the pattern over time of lipid metabolism.

Materials and Methods: In this pilot study participated 11 adults with mild hypercholesterolemia (F/M 7/4). The group received 200mg\die of Pycrinil[®] supplementation. The trend of raw data of lipidic parameters from baseline to days 15 and 30 was analyzed by the repeated measurements analysis of variance.

Results: Statistically significant decreases have been observed for: Total Cholesterol (T-CHL) at day 15, in female -6.4% (p=0.007) and in whole sample (w.s) -4.5% (p=0.007);LDL-C (females) -11.6%(p=0.041); T-CHL/HDL-C (w.s) -9.8% (p=0.009). Statistically significant increases have been observed for: APOA: (w.s), day 15:+10.2% (p=0.045); day 30:+18.8% (p=0.003);APOA/APOB: (w.s), day 15: +18.12% (p=0.036);day 30: +18.73% (p=0.034); APOA/HDL: (w.s) at day 30:+11.08% (p=0.036). As concerns HDL-CHL the outcomes are more favourable in the sample of subjects with baseline values <=median:+7.7 (p=0.120)+16.3% (p=0.075) at day 15;+5.2 (p=0.239)+12% (p=0.165) at day 30.

Conclusions: The results evidenced that parameters of lipids metabolism showed statistically significant changes in the course of the treatment. This study evidenced, for the first time, a specific effect on relevant parameters connected with HDL-C regulation such as APOA, APOA/APOB, APOA/HDL.



[Italian Journal of Medicine 2014; 8(s2)]

[page 113-114]





FADOI 2014 TRIAL WITH 200 mg/day

Confirmation of efficacy on HDL-C with a "omega 3 vegetable" (soft-gel capsules 200 mg) in Caucasian subjects

Small pilot study designed as «a stressed study condition» (no strong subjects selection + 30 days of treatment instead of 2 months).

Results:

- Increase of HDL-C confirmed (more favourable in low HDL subjects)
- Decrease of TC confirmed (4.5% p=007)
- ✓ Decrease of LDL-C confirmed (females -11.6% p= 0.041))
- Decrease of TC/HDL-C confirmed (-9.8% p=0.009)

New!!

- Increase of APO A-1 (+ 18.8% p=0.003)
- Increase of APO A/ APO B (+ 18.73% p=0.0034)



BIOSYNTHESIS AND CATABOLISM OF HDL-C AS' PYCRINIL[®] TARGETS ?

Lipid-free apoA-I is secreted by the liver and intestine and acquires phospholipids and free cholesterol via hepatic and intestinal ABCA-1.

Nascent HDL takes up further phospholipids (via PLTP) as well as free cholesterol from peripheral tissues and triglyceride-rich lipoproteins. HDL-associated LCAT esterifies part of the free cholesterol to cholesterol esters, thereby forming the hydrophobic core of the HDL particle ('HDL maturation'). HDL-associated cholesterol is either directly transferred to the liver via hepatic SR-BI or following **CETP-mediated** transfer to VLDL/LDL via the hepatic LDL receptor.



C. Besler et al., EMBO Mol Med 4, 251 - 268 (2012)



Vitis vinifera L.



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



...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).



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**.



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

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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, preand 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.



Curcuma longa L.





Curcumin: natural analogs and the most important metabolites





Curcumin and proinflammatory diseases



Aggarwal and Harikumar, The International Journal of Biochemistry & Cell Biology 41: 40 (2009)



Schematic representation of epigenetic factors modulated by curcumin







Promises and problems

The beneficial effects of curcumin are mostly

- Suggested by epidemiological studies
- Extrapolated from studies in vitro
- Supported by studies in animal models

But have not yet been clinically validated

Limited curcumin bioavailability continues to be highlighted as a major concern in clinical trials





Curcumin has critical pharmacokinetics in humans



- Extremely poor oral absorption
- High rate of metabolic conjugation (sulphation and glucuronidation) and reduction
- Rapid clearance from the body



The development of MERIVA®





MERIVA[®] is the natural way to deliver a food related dosage of curcuminoids (3 mg/kg/die according to EFSA) with the proper bioavailability.



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[†]

ABSTRACT: The relative absorption of a standardized curcuminoid mixture and its corresponding lecithin formulation (Meriva) was investigated in a randomized, double-blind, crossover human study. Clinically validated dosages were used for both products, and plasma levels of all three major curcuminoids [curcumin (1a), demethoxycurcumin (1b), and bisdemethoxycurcumin (1c)] were evaluated. Total curcuminoid absorption was about 29-fold higher for Meriva than for its



corresponding unformulated curcuminoid mixture, but only phase-2 metabolites could be detected, and plasma concentrations were still significantly lower than those required for the inhibition of most anti-inflammatory targets of curcumin. Remarkably, phospholipid formulation increased the absorption of demethoxylated curcuminoids much more than that of curcumin (1a), with significant differences in plasma curcuminoid profile between Meriva and its corresponding unformulated curcuminoid mixture. Thus, the major plasma curcuminoid after administration of Meriva was not curcumin (1a), but demethoxycurcumin (1b), a more potent analogue in many in vitro anti-inflammatory assays. The improved absorption, and possibly also a better plasma curcuminoid profile, might underlie the clinical efficacy of Meriva at doses significantly lower than unformulated curcuminoid mixtures.



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

Mean plasma levels of curcumin, demethoxycurcumin, bisdemethoxycurcumin and total curcuminoids in nine healthy volunteers after oral intake of MERIVA[®] vs curcumin





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



Key concepts from the human PK study



Curcumin as MERIVA[®] is ~18-fold more bioavailable than curcumin from the unformulated total curcuminoids.

Overall, curcuminoids as MERIVA[®] are ~29-fold more bioavailable than curcuminoids from the unformulated total curcuminoids.

Demethoxycurcumin is the major plasma curcuminoid after MERIVA[®] administration; DMC is the most potent curcuminoid in several assays of antiinflammatory activity.

Absorption of curcuminoids is faster (~2-fold) from MERIVA[®] than from unformulated total curcuminoids.



Clinical Areas where Meriva® is under investigation





Aggarwal and Harikumar, The International Journal of Biochemistry & Cell Biology 41: 40 (2009)



LIVER DISORDERS





NAFLD



SPECTRUM OF NONALCOHOLIC FATTY LIVER DISEASE SIMPLE STEATOSIS NONALCOHOLIC CIRRHOSIS (Nonalcoholic Fatty Liver) **STEATOHEPATITIS** (NASH) A liver blopsy shows A liver biopsy shows Scarring has total fat content > 5%. excessive fat. In addition, occurred throughout About 25% of patients there is inflammation, liver the liver, affecting progress to the next cell damage and some scar liver function and stage, NASH tissue (fibrosis) present. structure. About 20% of patients with NASH progress to cirrhosis, usually over 20-30 years. LEAST SEVERE-MOST SEVERE









indena[®]

Marczylo et al., Cancer Chemother Pharmacol, 60: 171 (2007)

CURCUMIN MECHANISM OF ACTION AND POTENTIAL EFFECT ON INITIAL STEPS OF LIVER DAMAGES





MERIVA[®] for NAFLD

A Phase II, Randomized, double – blind, placebo controlled trial is under planning at Ospedale Gradenigo (TO)





OVERALL CONCLUSIONS

- Diet is an important modulator of main intermediate risk factors in CVDs, the number one killer in most developed countries
- Maintenance of an healthy diet, even through a costant intake of phytonutrients contained in edible plants can contribute in the positive modulation of some intermediate risk factors for CVDs, such as i.e. : blood lipid profile (TC, LDL-C, HDL-C,...) blood glucose (including post – prandial peaks levels) and blood pressure
- Rigourosly standardized extracts obtained from edible plants verified for their effectiveness in controlled clinical studies, according to EFSA (and other agencies) requirements, can contribute to a general strategy of optimizing nutrition and reduction of major risks for CVDs

