

TECHNOLOCY

INTEGRATORE NUTRIZIONALE

I BOTANICALS NEGLI INTEGRATORI ALIMENTARI E NEI PRODOTTI COSMETICI:

ASPETTI SCIENTIFICI E REGOLATORI

20 NOVEMBRE 2019 Mi.Co Milano



Sviluppo industriale di nuovi integratori con derivati botanici: esempi recenti

Paolo Morazzoni

Scientific Advisor Indena S.p.A. Milano

MERCATO ITALIANO DEGLI INTEGRATORI:

DINAMICHE DISTRIBUTIVE AGGIORNATE A MARZO 2019

	VOLUMI		VALORI			
	ANNO TERMINANTE (milioni di confezioni)	QUOTA (%)	± % (vs 2018)	ANNO TERMINANTE (milioni di Euro)	QUOTA (%)	± % (vs 2018)
TOTALE MERCATO*	256	100	2,5	3468	100	4,3
FARMACIA	184	72	3,1	2892	83	4,9
PARAFARMACIA	20	8	-0,9	290	8	0,3
SUPER/IPER NO CORNER	37	14	3,6	172	5	3,4
SUPER/IPER CORNER	15	6	-1,6	114	3	0,1

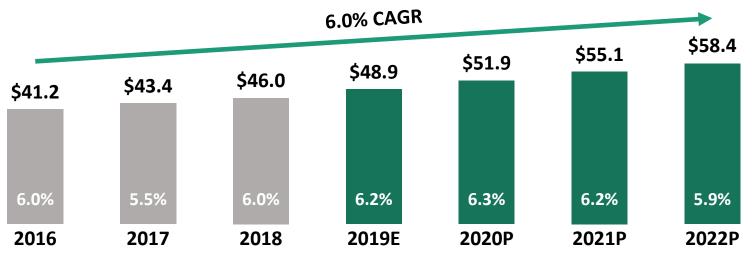
*gli integratori erbali hanno rappresentato circa il 50% del valore totale del comparto

Fonte: Elaborazione dati IQVIA SOLUTIONS Italy



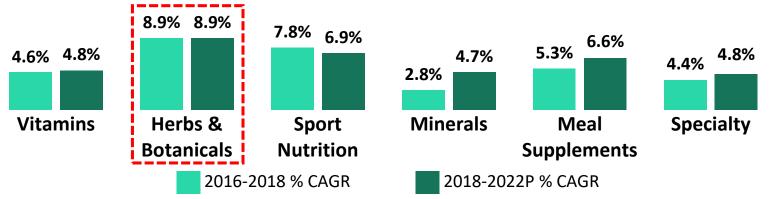
U.S. Supplement Sales

(\$ in billions, % growth)



U.S. Supplement Growth by End Market

Herbs & Botanicals is the strongest performing category and is projected to maintain its current growth trajectory at an 8.9% CAGR from 2018-2022P



Source: Nutrition Business Journal 2019, Nielsen, Panel 52 weeks ended 9/20/18



Herbal Supplement Sales in US Increase by 9.4% in 2018

Record growth driven by sales of CBD, mushrooms, and immune-health products

By Tyler Smith,^a Michelle Gillespie,^b Veronica Eckl,^b Jake Knepper,^b and Claire Morton Reynolds^c

^a American Botanical Council; Austin, Texas ^b SPINS; Chicago, Illinois ^c Nutrition Business Journal; Boulder, Colorado

Herbal supplement sales in the United States experienced record growth in 2018, increasing by an estimated 9.4% from 2017, according to the *Nutrition Business Journal* (NBJ). Consumers spent a total of \$8.842 billion on herbal supplements across all market channels in 2018 — an increase of roughly \$757 million in sales from the previous year. This marks the strongest US sales growth of herbal supplements since 1998.¹

62 • ISSUE 123 • 2019 • www.herbalgram.org



Table 1. To	Table 1. Total US Retail Sales of Herbal Supplements*				
Year	Total Sales % Change				
2018	\$8.842 billion	9.4%			
2017	\$8.085 billion	8.5%			
2016	\$7.452 billion	7.7%			
2015	\$6.922 billion	7.5%			
2014	\$6.441 billion	6.8%			
2013	2013 \$6.033 billion 7.9%				
2012	\$5.593 billion 5.5%				
2011	\$5.302 billion 4.5%				
2010	\$5.049 billion	3.3%			
2009	\$5.037 billion	5.0%			
2008	008 \$4.800 billion 1.0%				
2007	\$4.756 billion 4.4%				
2006	006 \$4.558 billion 4.1%				
2005	05 \$4.378 billion 2.1%				
2004	\$4.288 billion 3.4%				
2003	\$4.146 billion –2.3%				
2002	\$4.275 billion –2.8%				
2001	\$4.361 billion 3.2%				
2000	o \$4.225 billion 2.9%				
Source: Nutrition Business Journal					

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* Includes sales in all channels. NBJ primary research includes NBJ surveys of supplement manufacturers, distributors, multilevel marketing firms, mail order, internet, and raw material and ingredient supply companies, as well as interviews with major retailers (Walmart, Costco, etc.), manufacturers, suppliers, and industry experts. Secondary sources include IRI, SPINSscan Natural, Nielsen, *Natural Foods Merchandiser*, Insight, The Hartman Group, company data, and other published material.



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Table 4. Top-Selling Herbal Supplements in 2018 — US Mainstream Multi-Outlet Channel

Rank	Primary Ingredient	Latin Binomial	Total Sales	% Change from 2017
1	Horehound	Marrubium vulgare	\$146,624,255	4.1%
2	Echinacea ^a	Echinacea spp.	\$110,331,569	15.1%
3	Turmeric ^b	Curcuma longa	\$93,312,677	30.5%
4	Elderberry	Sambucus nigra	\$50,979,669	138.4%
5	Green tea	Camellia sinensis	\$45,160,552	14.2%
6	Ginger	Zingiber officinale	\$38,714,413	2.0%
7	lvy leaf	Hedera helix	\$37,838,209	10.8%
8	Garlic	Allium sativum	\$37,723,155	-0.1%
9	Fenugreek	Trigonella foenum-graecum	\$32,498,548	9.2%
10	Black cohosh	Actaea racemosa	\$31,673,127	-6.0%

^a Includes three *Echinacea* species: *E. angustifolia*, *E. pallida*, and *E. purpurea*.

^b Includes standardized turmeric extracts with high levels of curcumin.

^c Excludes over-the-counter laxative drugs containing senna or sennosides.



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Table 5. Top-Selling Herbal Supplements in 2018 — US Natural Channel				
Rank	Primary Ingredient	Latin Binomial	Total Sales	% Change from 2017
1	Cannabidiol (CBD)	Cannabis spp.	\$52,708,488	332.8%
2	Turmeric ^a	Curcuma longa	\$51,213,502	0.4%
3	Elderberry	Sambucus nigra	\$25,374,666	93.9%
4	Wheatgrass / Barley grass	Triticum aestivum / Hordeum vulgare	\$19,484,470	-3.3%
5	Flax seed / Flax oil	Linum usitatissimum	\$13,903,851	-7.5%
6	Aloe vera	Aloe vera	\$13,788,574	-1.0%
7	Ashwagandha	Withania somnifera	\$12,426,468	16.9%
8	Milk thistle	Silybum marianum	\$10,419,926	3.5%
9	Echinacea ^b	Echinacea spp.	\$9,979,769	11.0%
10	Oregano ^c	Origanum vulgare	\$9,925,727	9.9%

^a Includes standardized turmeric extracts with high levels of curcumin.

^b Includes three *Echinacea* species: *E. angustifolia*, *E. pallida*, and *E. purpurea*.

^c Includes products labeled as containing oregano oil and oregano leaf tinctures.





A RESEARCH BASED COMPANY - SETTALA

Process Research: design, optimization and scaling up of advanced industrial manufacturing processes

Analytical Research: design, optimization and validation of methods for complex mixtures





A RESEARCH BASED COMPANY - MILANO

Formulative Research: design, optimization and scaling up of botanical ingredients formulations

Product Research: discovery and development of new active products derived from plants for health & nutrition (H&N), pharmaceuticals and cosmetics



More than 120 patent families and 700 scientific papers





Indena R&D focus is to identify phytonutrients

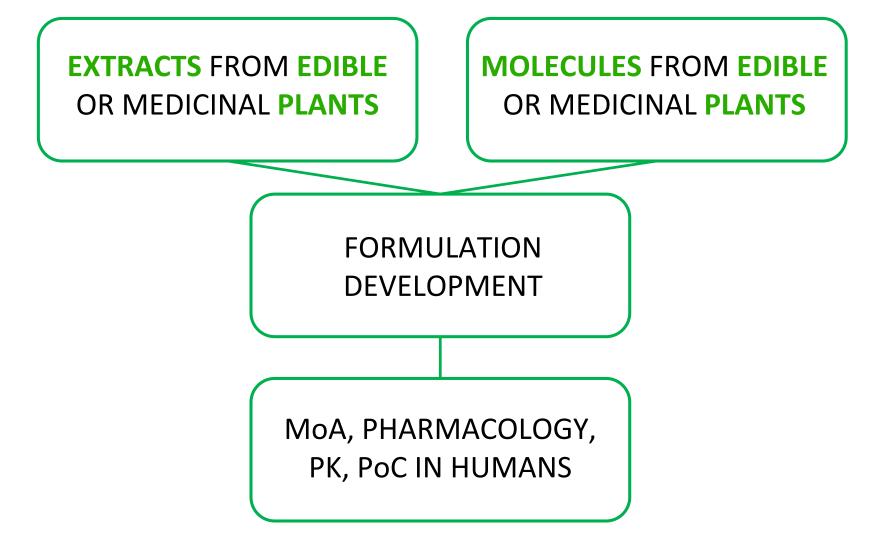
provided with a **solid scientific background**

and to develop these ingredients by **optimizing**

their biological benefits for improving quality of life



INDENA RESEARCH APPROACH IN H&N





RECENT INDENA RESEARCH DEVELOPMENT IN H&N



Focus on plants that:

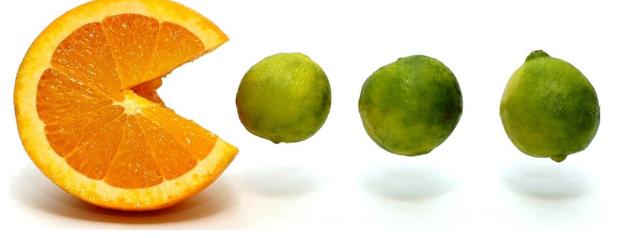
- are traditionally used as food (edible plants)
- can benefit from the use of proprietary extraction and formulation technologies



RECENT INDENA RESEARCH DEVELOPMENT



Main reasons for focusing on edible plants:

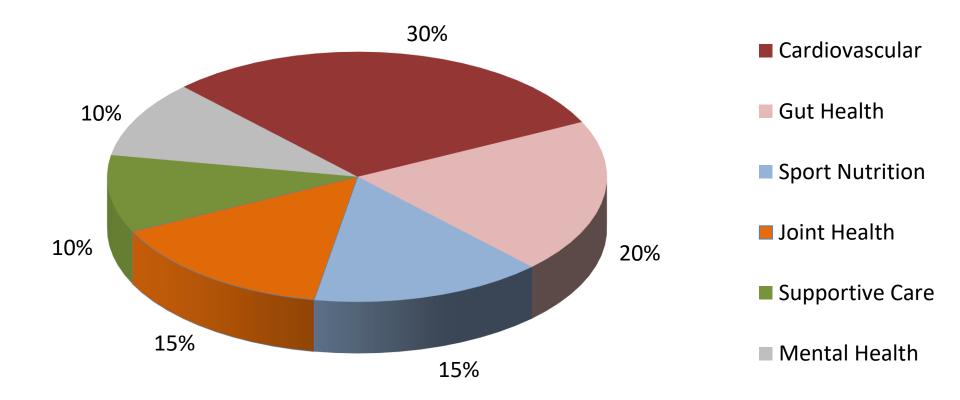


- Safe use tradition, rediscovery of ancient varieties
- Epidemiological data linked to the consumption of a food
- Basic biomedical evidence for specific constituents



INDENA RESEARCH IN H&N: AREAS







INDENA RESEARCH IN H&N: ENDPOINTS

CARDIOVASCULAR	Blood glucose Cholesterol Blood pressure	
GUT HEALTH	Functional dyspepsia IBS/IBD Microbiota	
MENTAL HEALTH	Cognitive decline	
SPORT NUTRITION	Healthy inflammation Performance Recovery	
JOINT HEALTH	Inflammation Pain Cartilage	
SUPPORTIVE CARE (ONCOLOGY)	Supportive care Chemioprevention	



INDENA RESEARCH IN H&N: EXAMPLES OF RECENT INGREDIENTS LAUNCHED WORLDWIDE

CARDIOVASCULAR	Vazguard™	
CANDIOVASCOLAN	(Bergamot phytosome [®])	
GUT HEALTH	Casperome®	
GUT HEALTH	(Boswellia phytosome [®])	
SPORT NUTRITION	Quercefit™	
SPORTNOTRITION	(Quercetin phytosome®)	
JOINT HEALTH	Meriva®	
(INFLAMMATION)	(Turmeric phytosome®)	



Phytosome[®] technology

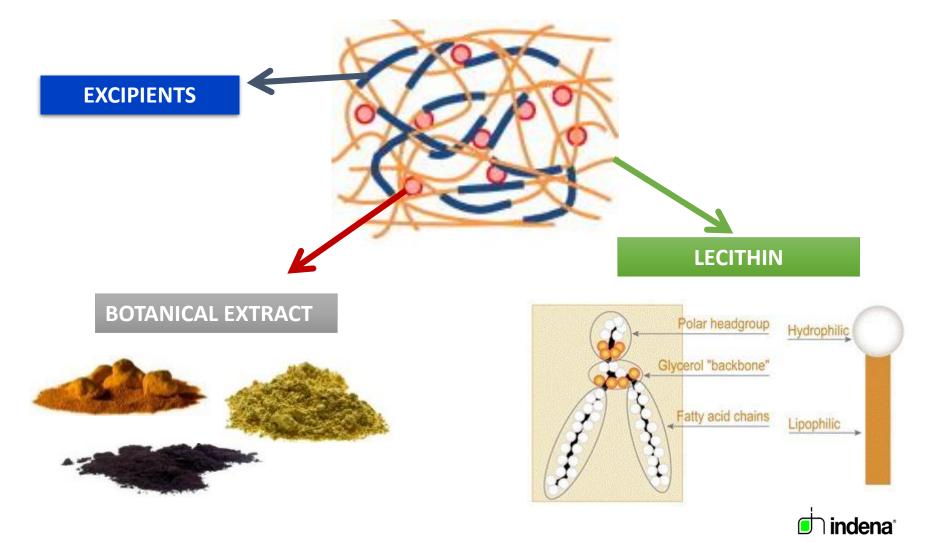


WHAT IS A PHYTOSOME[®]?



In that contest Phytosome[®] was born as a dispersion of botanicals into lecithin,

a dietary surfactant in typical ratio BNs/lecithin from 1:1 to 1:3



HOW DOES PHYTOSOME® WORK?



Lecithin is an amphipatic molecule consisting of a positively charged head group and two neutral tail acyl moieties.

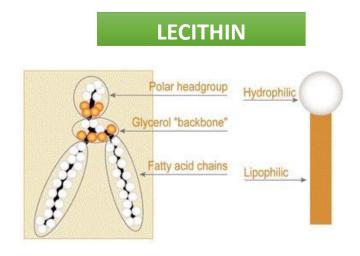
The presence of « ultra-interacting » moieties makes lecithin an inhibitor of self-aggregation,

dispersing sparingly soluble compounds into a sort of solid-state emulsion.

Lecithin is poorly soluble in water,

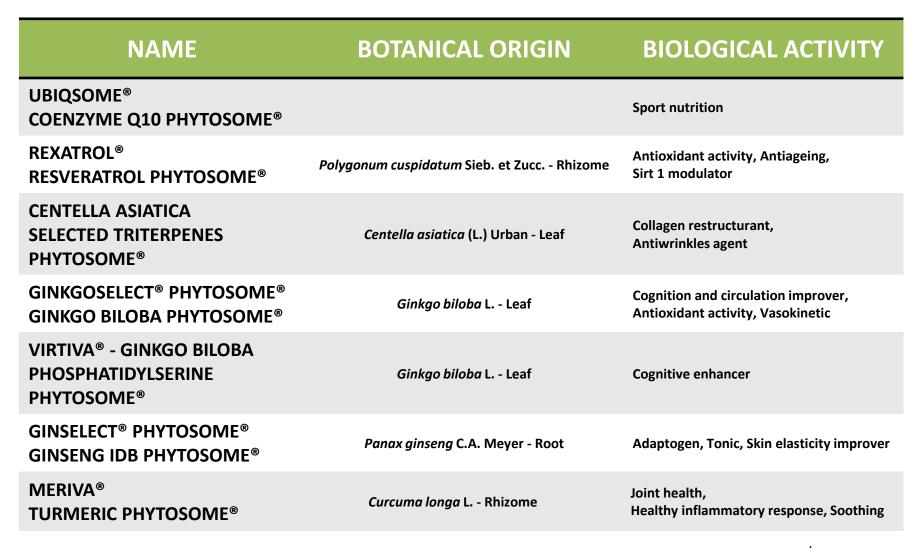
but is readily absorbed e.g. from the intestine,

leaving phytochemicals into a dispersed state more readily absorbed.





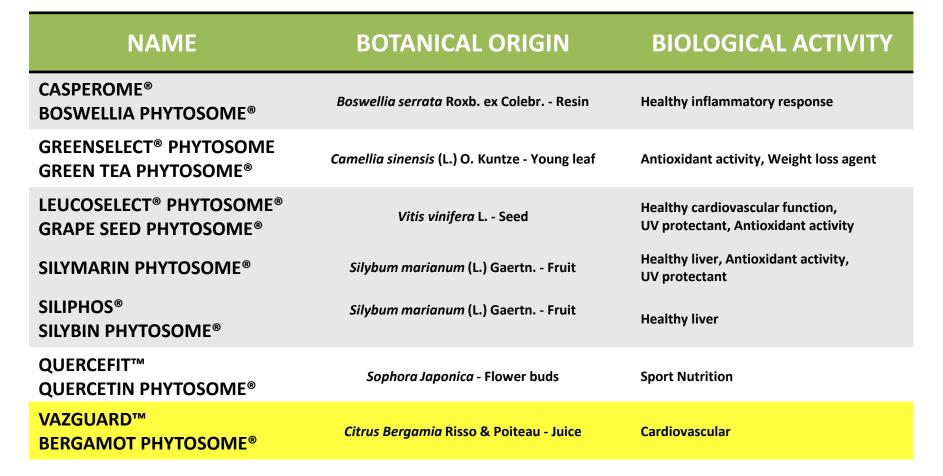
PHYTOSOME[®]: SOME EXAMPLES OF A SUCCESSFUL STORY (1)





PHYTOSOME

PHYTOSOME[®]: SOME EXAMPLES OF A SUCCESSFUL STORY (2)





PHYTOSOME



THE NEW NATURAL INGREDIENT FOR CARDIOVASCULAR HEALTH



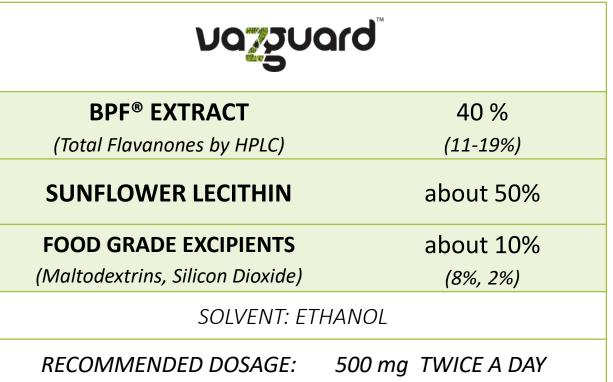
WHAT IS VAZGUARD™?

VAZGUARD[™] is the innovative purified Bergamot Polyphenols Fraction (BPF[®]) formulated with Indena Phytosome[®] technology to improve bioavailability and optimize biological absorption of bergamot polyphenols.

VAZGUARD[™] is a new patented and standardized delivery system of bergamot polyphenols proven to be effective in supporting cardiovascular health.



BERGAMOT PHYTOSOME® COMPOSITION







BERGAMOT EXTRACT SUPPLY CHAIN

CULTIVATIONS OF *CITRUS BERGAMIA RISSO & POITEAU* CALABRIA, ITALY - **THE UNIQUE SOURCE**





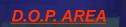


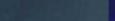




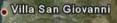
THE UNIQUE SOURCE













eggio di Calabria

Palmi 👩

Image NASA © 2008 Tele Atlas Image © 2008 DigitalGlobe © 2008 Europa Technologies Streaming ||||||||| 100%

Polistena

Cittanova

Siderno

. Locri

Provide State

Taurianova 💿





Duomo in Florence



****C000





UNIQUE CONTROLLED SUPPLY-CHAIN CALABRIA (ITALY)

- Bergamot supply-chain is under direct and continuous quality control by Indena:
- Indena's Audit in order to ensure improved traceability of source, extraction, manufacturing
- The *Declaration of Authenticity* of BERGAMOT POLYPHENOL FRACTION (BPF[®]) by H&AD srl (RC, Italy) is available



PHYTOCHEMICAL CHARACTERIZATION

AGRICULTURAL AND FOOD CHEMISTRY

Cite This: J. Agric. Food Chem. 2019, 67, 3159–3167

pubs.acs.org/JAFC

Article

Detailed Phytochemical Characterization of Bergamot Polyphenolic Fraction (BPF) by UPLC-DAD-MS and LC-NMR

Carmen Formisano,[†] Daniela Rigano,[†] Annalisa Lopatriello,[†] Carmina Sirignano,[†] Giuseppe Ramaschi,[‡] Lolita Arnoldi,[‡] Antonella Riva,[‡] Nicola Sardone,^{*,‡} and Orazio Taglialatela-Scafati^{*,†}

[†]Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Via D. Montesano 49, 80131 Naples, Italy

[‡]INDENA SpA, Via Don Minzoni 6, 20090 Settala, Milan, Italy

S Supporting Information

ABSTRACT: Bergamot (*Citrus bergamia*) is cultivated in Southern Italy almost exclusively to produce the prized essential oil, a top note in several perfumes. The juice of bergamot, until recently poorly studied, is the object of a growing scientific interest due to its claimed activity to treat metabolic syndrome. The aim of this investigation was a detailed characterization of bergamot juice polyphenolic fraction (BPF) based on a UPLC-DAD-MS analysis complemented by preparative chromatographic separations, followed by NMR characterization of the isolated compounds. The combination of these techniques efficiently covered different classes of secondary metabolites, leading to the identification of 39 components, several of which had never been reported from bergamot. One of them, bergamjuicin (**35**), is a new flavanone glycoside, whose structure has been determined by MS and NMR techniques. The reported results could provide a guide for future routine analyses of BPF, a material of great nutraceutical and industrial interest.

KEYWORDS: Citrus bergamia, bergamot polyphenolic fraction, NMR analysis, flavanones, limonoids, metabolic syndrome



BPF® EXTRACT UNIQUE PHYTOCHEMICAL PROFILE



BPF[®] phytochemical profile has been estensively **studied and chatacterized** by Indena

BPF[®] is characterized by a **unique** phytochemical profile in terms of both flavonoids *composition* and *content*

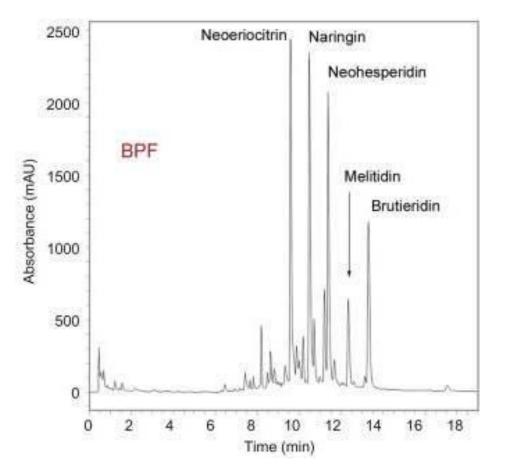
BPF[®] has the same phytochemical profile of natural **bergamot juice**

BPF[®] distances itself from all other bergamot extracts on the market



BPF[®] EXTRACT PHYTOCHEMICAL CHARACTERIZATION

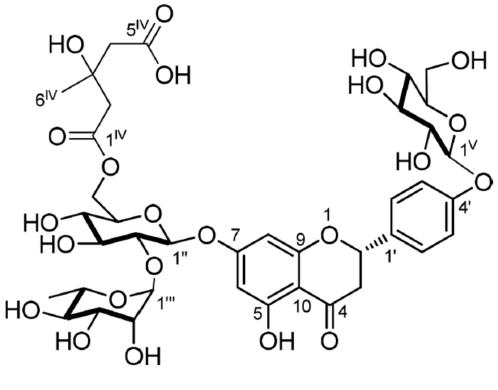
BERGAMOT POLYPHENOL FRACTION (BPF®) composition



- High content of flavanones: the main flavonoids of BPF[®] are naringin, neoeriocitrin and neohesperidin.
- 2. Exclusive content of statin-like glycosidic flavonoids: **melitidin** and **brutieridin**.
- 3. Other flavones are: rutin, neodiosmin, rhoifolin, poncirin.
- 4. Presence of ascorbic acid and other vitamins.



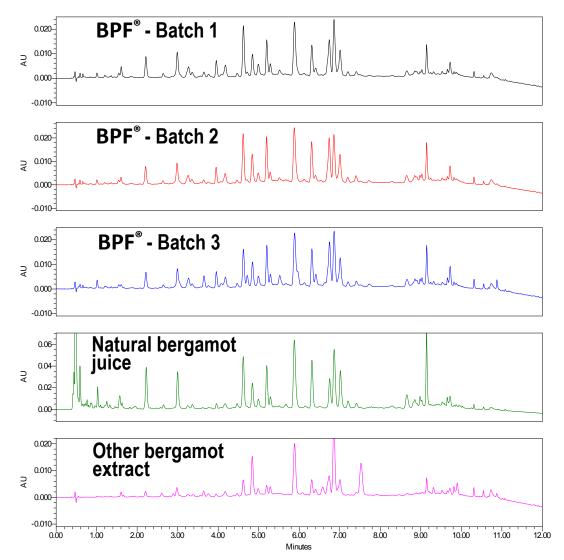
BPF® EXTRACT PHYTOCHEMICAL CHARACTERIZATION (A NEW FLAVANON IDENTIFIED) J. Agric. Food Chem. 2019, 67, 3159–3167



Bergamjuicin



SAME PHYTOCHEMICAL PROFILE AS NATURAL JUICE



HPLC Profile comparison (@254 nm) between:

- 3 BPF[®] batches
 - 1 Natural bergamot juice
- 1 Bergamot extract competitor's batch

HIGH REPRODUCIBILITY AMONG DIFFERENT BPF[®] BATCHES

BPF® HAS SAME PROFILE OF NATURAL JUICE

indena

VAZGUARD[™]: THE SCIENTIFIC RATIONALE

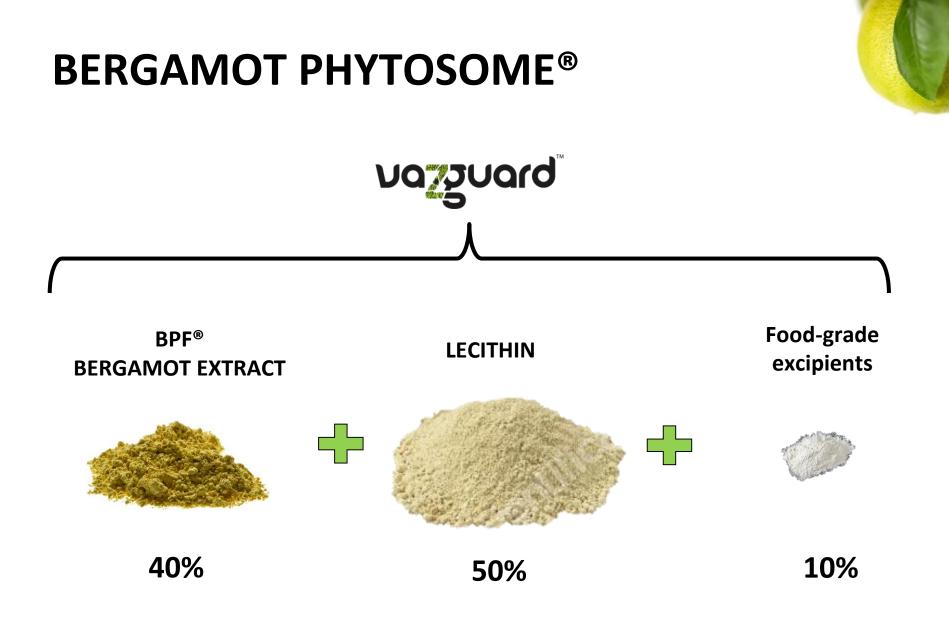


Active components of Bergamot (BPF[®] flavonoids) are characterized by low bioavailability

Necessity to consolidate the clinical benefit of bergamot with a more efficient formulation and lower dosages









CLINICAL EVIDENCES ON



vazzuard THE FIRST CLINICAL EVIDENCE OF EFFICACY

Endocrine, Metabolic & Immune Disorders - Drug Targets, 2019, 19, 136-143

RESEARCH ARTICLE



Hypoglycemic and Hypolipemic Effects of a New Lecithin Formulation of Bergamot Polyphenolic Fraction: A Double Blind, Randomized, Placebo-Controlled Study



Vincenzo Mollace^{1*}, Miriam Scicchitano¹, Sara Paone¹, Francesca Casale¹, Carla Calandruccio¹, Micaela Gliozzi¹, Vincenzo Musolino¹, Cristina Carresi¹, Jessica Maiuolo¹, Saverio Nucera¹, Antonella Riva², Pietro Allegrini², Massimo Ronchi², Giovanna Petrangolini² and Ezio Bombardelli²

ets

¹Institute of Research for Food Safety & Health (IRC-FSH), Department of Health Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy; ²Research and Development Unit, Indena S.p.A., Milan, Italy



CLINICAL STUDY: DESIGN PLACEBO (N=20) BPF[®] EXTRACT 1300 mg/day (N=20) RANDOMIZATION **vazzuard** 1000 mg/day (N=20) corresponding to 400 mg of BPF® extract 30 days 0

- ✓ SPONSOR: Prof. Mollace (University of Catanzaro) and Indena S.p.A.
- ✓ STUDY TYPE: Double blind, randomized, placebo-controlled
- ✓ STUDY POPULATION: 60 subjects with dyslipidemia associated with/without hyperglycemia
- ✓ ENDPOINTS: total cholesterol (TC), Low-Density Lipoproteins (LDL-C), triglycerides (TG), High-Density lipoproteins (HDL-C) and blood glucose





CLINICAL STUDY: ADMINISTERED DOSAGES

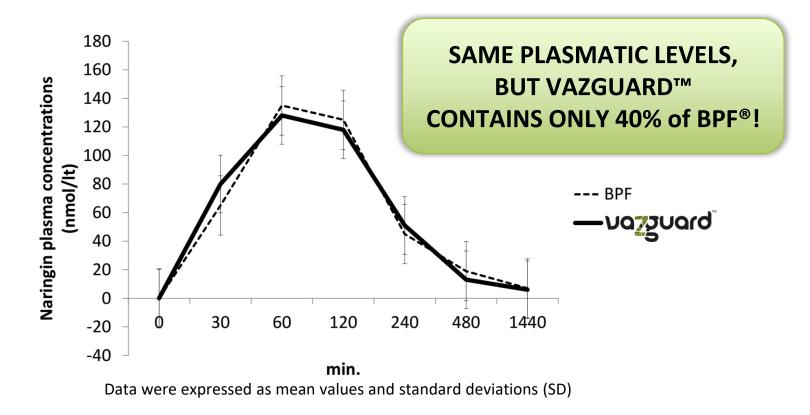
	BPF [®] EXTRACT	nasionarg	
DAILY DOSE (mg)	1300	1000	-30 %
DAILY DOSE <i>as</i> <i>BERGAMOT EXTRACT</i> (mg)	1300	400	-70 %

VAZGUARD™ IS ADVANTAGEOUS COMPARED TO BPF® EXTRACT IN TERMS OF BOTH WEIGHT (-30%) AND EXTRACT CONTENT (-70%)



CLINICAL STUDY: BIOAVAILABILITY IN HUMAN PLASMA

TIME VS PLASMA CONCENTRATION CURVES FOR NARINGIN AFTER RECEIVING **1300 mg of BPF[®] extract** *vs* **1000 mg of vazguard**[™]







CLINICAL STUDY: MOST RELEVANT EFFECTS

Varguard 1000 mg/day

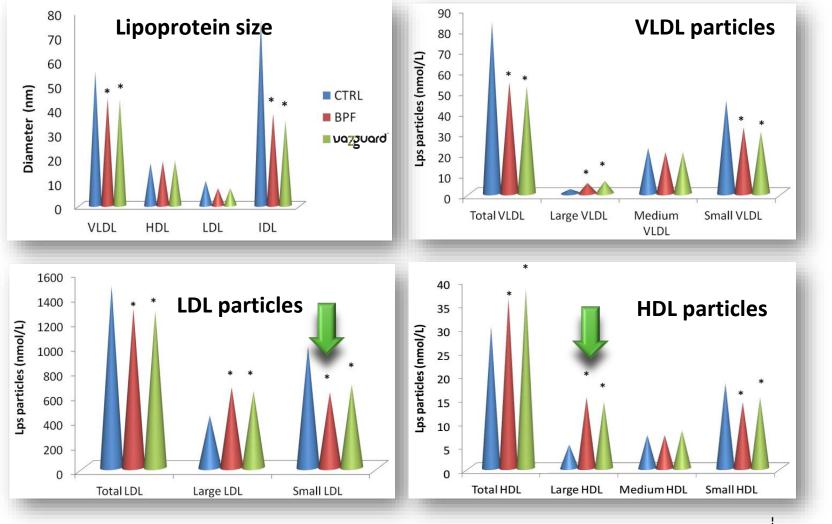
VARIATION OF GLUCIDIC AND LIPIDIC PROFILES AFTER 30 DAYS

Serum Lipids (p<0.05)	TC LDL-C HDL-C Triglycerides	- 24% - 35% +14% - 31%
Fasting Glucose (p<0.05)		-23%

DESPITE OF THE LOWER CONTENT OF BPF® EXTRACT, VAZGUARD™ RESULTED IN PROMISING OUTCOMES AS SUPPORT IN CARDIOVASCULAR HEALTH



CLINICAL STUDY: REMODULATION OF LIPOPROTEIN SIZE





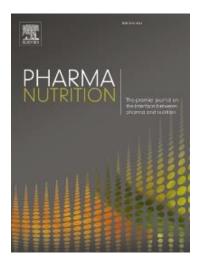




PLEIOTROPIC

MECHANISM OF ACTION



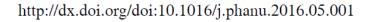




Molecular mechanisms of lipid- and glucose-lowering activities of bergamot flavonoids

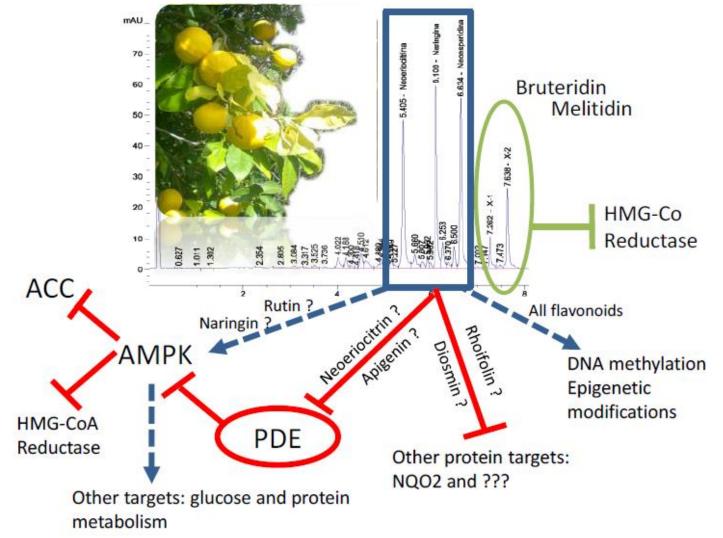
Elzbieta Janda^{a,b}*, Antonella Lascala^{a,b}, Concetta Martino^{a,b}, Salvatore Ragusa^b, Saverio Nucera^{a,b}, Ross Walker^{a,c}, Santo Gratteri^a and Vincenzo Mollace^{a,b}

^a Institute of Research for Food Safety & Health (IRC-FSH), ^bHealth Sciences Department, University "Magna Graecia", Campus Germaneto, Catanzaro, Italy; ^c Sydney Adventist Hospital, Sydney, Australia





Innovative and pleiotropic MoA at the base of lipid- and glucose-lowering effects







ADDITIONAL AND RECENT EVIDENCES

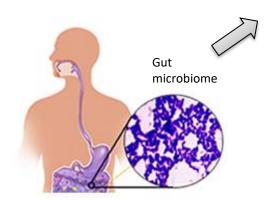
ON MoA:

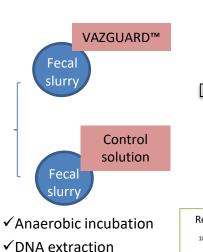
MODULATION OF MICROBIOTA



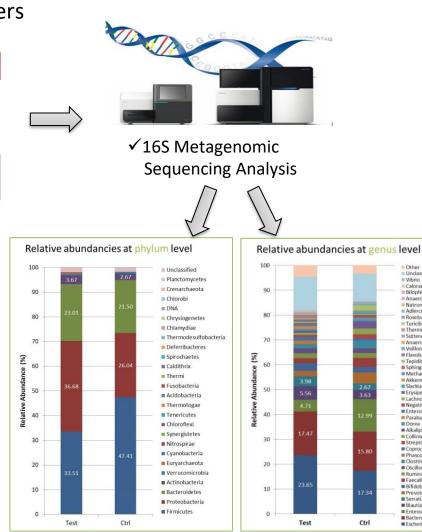
MICROBIOME DIVERSITY AFTER VAZGUARD[™] TREATMENT

Experimental design: three healthy volunteers





✓ Library preparation for Illumina sequencing





Other

■ Vibrio Caloramator

Bilophila

Unclassified

Anaerobranca Natronincola

Adlercreutzia

Thermicanus Sutterella

Veillonella Flavobacterium

Tepidibacter

Akkermansia

Erysipelothrix

Lachnospira Negativicoccus

Enterobacter

Parabacteroides

Slackia

Dorea Alkaliphilus

Collinsella

Streptococcus

Coprococcus

Clostridium

Oscillospira

Prevotella Serratia

Enterococcus

Bacteroides

Escherichia

Blautia

Ruminococcus Faecalibacterium

Bifidobacterium

Phascolarctobacterium

Sphingobacterium Methanobrevibacter

Anaerotruncus

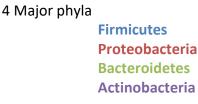
Roseburia Turicibacter

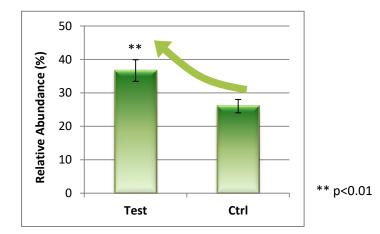
MICROBIOME DIVERSITY AFTER VAZGUARD™ TREATMENT

Proteobacteria decrease are associated with CVD¹



25 Different **phyla** identified





¹ Dinakaran et al. PLOS ONE 9(8) (2014)

Major area of interest: Obesity and CVD associated with changes in microbioma composition

418 Different genera identified

8 Major genera (62%) Escherichia Serratia Bacteroides Prevotel

Bacteroides Prevotella Enterococcus Bifidobacterium Blautia Faecalibacterium

Area of interest	Taxonomy level	Name	Disease Outcome	VAZGUARD™ Outcome
CVD	Genus	Bacteroides	\downarrow	\uparrow
	Genus	Eubacterium	\checkmark	\uparrow
	Genus	Streptococcus	\uparrow	\checkmark
	Genus	Collinsella	\uparrow	\checkmark
Obesity	Genus	Bifidobacterium	\downarrow	\uparrow
	Genus	Methanobreviba cter	\downarrow	\uparrow
	Genus	Blautia	\checkmark	\uparrow
	Genus	Flavobacterium	\checkmark	\uparrow
	Genus	Akkermansia	\checkmark	\uparrow



Varguard IN A NUTSHELL



- Unique Italian origin and based on Mediterranean dietary tradition
- Complete control of the supply chain from fruit to Phytosome[®]
- Full phytochemical characterization available
- Same natural profile of bergamot juice
- Proven improved bioavailability of bergamot flavonoids
- Proprietary clinical evidences of efficacy in CV health
- Pleiotropic MoA (including evidences of positive modulation of microbiota)



CONCLUSIVE REMARKS

- 1. H&N is a fast growing and competitive area worldwide
- 2. In this scenario, herbal products represent a remarkable part of the market
- 3. Respect of the International guidelines for both botanical sourcing (cGAP) and industrial development (GMP) is a pivotal aspect
- 4. Innovation plays a strategic role for companies development and survival
- 5. Pre-clinical and clinical documentation for safety and efficacy will play an unavoidable role







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