indena®
INDUSTRIA
DERIVATI
NATURALI

MIRTOSELECT®:
THE *UNIQUE* BILBERRY EXTRACT

MIRTOSELECT™

Product Research, R&D
March 2021

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100 YEARS

MIRTOSELECT®

THE GOLDEN STANDARD

1970

- IdB initiates its research looking for a standardized bilberry extract, first named **Myrtocyan® "Bilberry 25% dry extract".**

1976

- IdB registers a **medicinal specialty** that soon becomes the world's best-selling OTC bilberry product.

1980

- Indena's product enters the dietary supplements market under the **MIRTOSELECT®** brand name and becomes the reference bilberry extract.

2005

- Indena updates the analytical method and the **new validated HPLC method** for bilberry quantifies all the anthocyanins present in both plant material and in extracts . It represents **a standard reference for the main pharmacopeias**

2007

- Indena publishes the bilberry extract **method of analysis**, applicable also to finished products. In the same year Indena underline the presence on the market of **fraudulent bilberry extracts** and not properly labeled finished products. The new **MIRTOSELECT®** website is online.

2008

- Indena's efforts **against adulterated bilberry extracts** have been welcomed by well-known authorities and **Indena actively contributes in drawing up today available bilberry extract monographs in the European, Italian and USP Pharmacopoeia.**

ESCOP MONOGRAPHS ARE BASED ON OUR CLINICAL STUDIES

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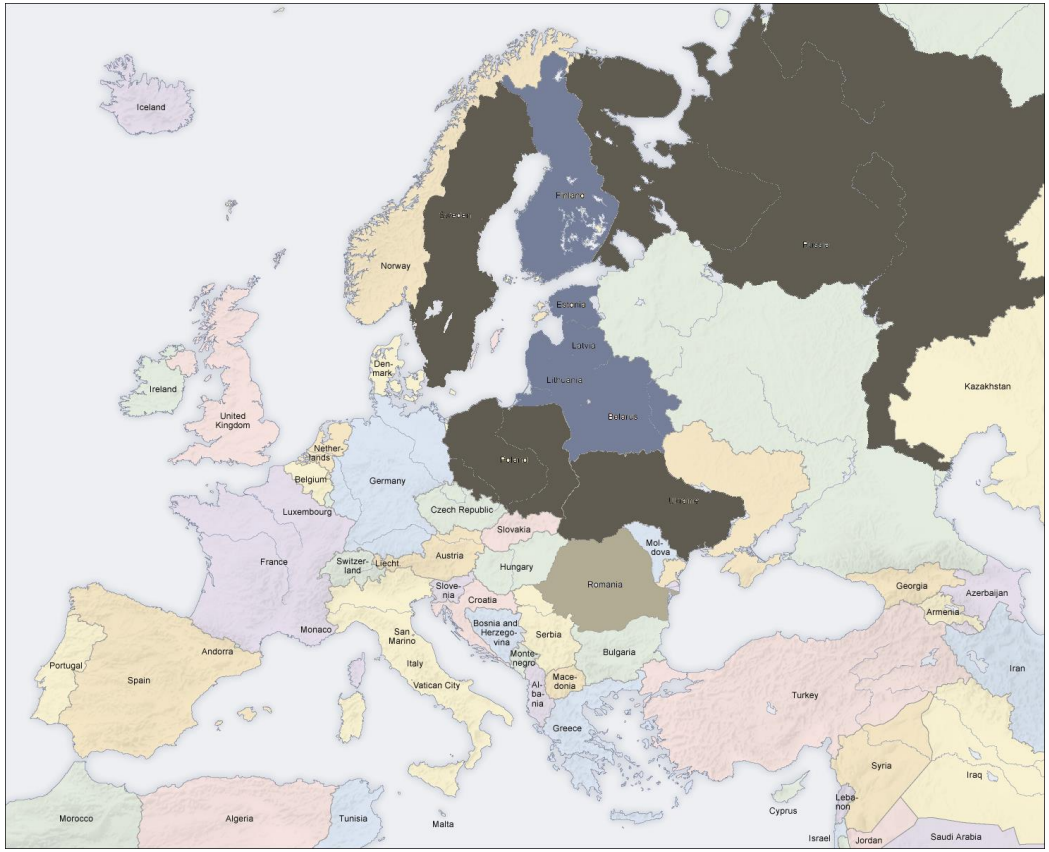
BILBERRY BIOMASS REQUIRES GREAT EXPERTISE

BILBERRIES ARE COLLECTED FROM WILD PLANTS



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VACCINIUM MYRTILLUS L.
SO UNIQUE AND SO FRAGILE

- *Vaccinium myrtillus* L. grows in acidic, nutrient-poor soils throughout the temperate and subarctic regions of Europe.
- In Southern Europe it grows mainly in the mountains, while in Northern Europe it is common in lowland forests.
- Unlike most other berries, *V. myrtillus* L.
  - is extremely difficult to grow
  - does not produce clusters of berries, but single or, more rarely, pairs of berries
  - produces only a limited number of berries compared to the plant biomass
- Bilberries are softer and juicer than most other berries, and therefore
  - more susceptible to damage using berry-picking rakes, and mostly hand-picked
  - more difficult to transport

Bilberries can not be cultivated, nor can they be processed unfrozen, since tissue damage triggers the deglycosidation of anthocyanins, with detrimental effects on their chemical stability

BILBERRY (*V. MYRTILLUS*) vs BLUEBERRY (*V. CORYMBOSUM - V. ASHEI - V. ANGUSTIFOLIUM*)

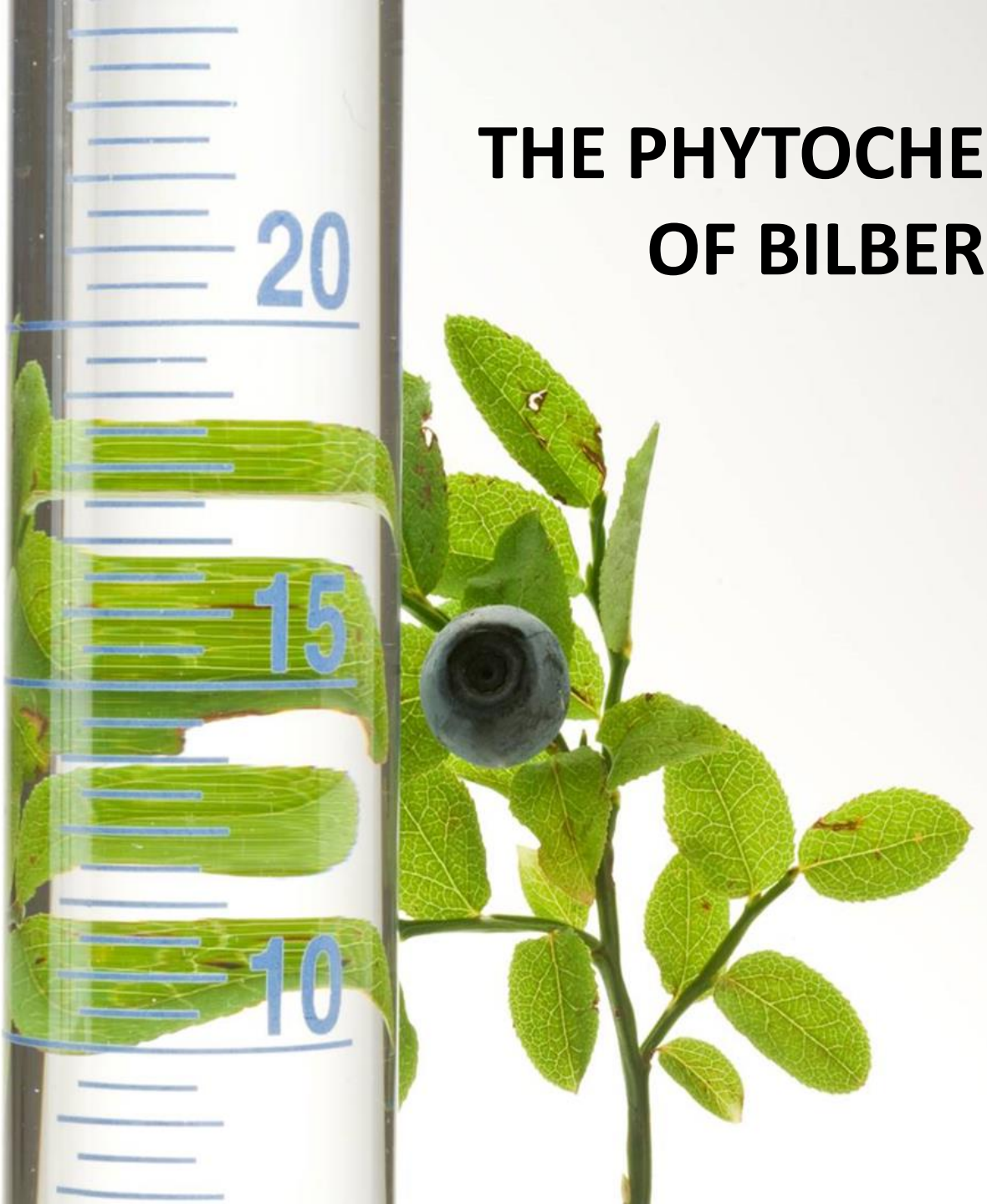
BILBERRY

- Wild European plant
- Smaller and darker berries
- Blue pulp
- Harder, less juicy and easier to transport

BLUEBERRY

- cultivated hybrid of three native American species *(V. corymbosum, V. ashei and V. angustifolium).*
- bigger and lighter berries
- The pulp is greenish
- The blueberry bush produces much more berries than the bilbery bush

THE PHYTOCHEMISTRY OF BILBERRY



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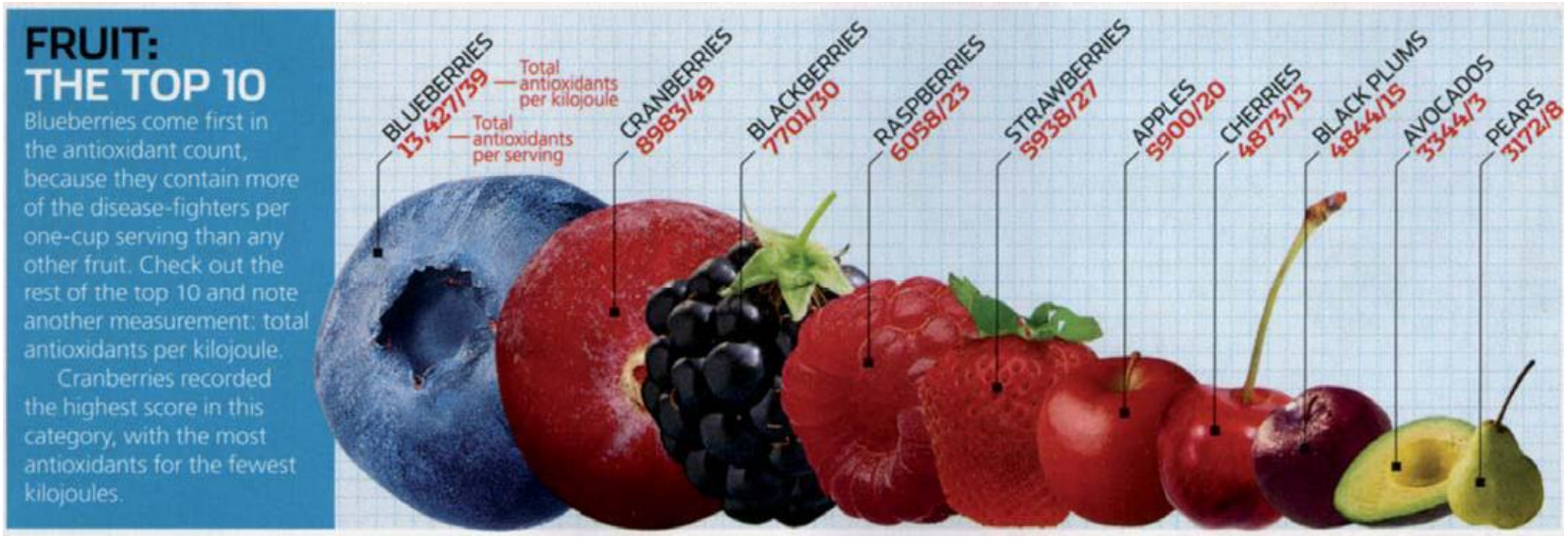
BILBERRY AS A SUPER-FRUIT: BEYOND THE TOP 10 AS ORAC VALUE



ANTHOCYANINS: THE PHYTOCHEMICAL HALLMARK OF BILBERRY

QUANTITY:

Bilberry is one of the richest sources of anthocyanins
(ca. 0.3-0.6% on fresh weight basis)

ANTHOCYANINS CONTENT OF BERRIES
(mg/100g FRESH WEIGHT)

Chokeberry (Aronia)	890
Bilberry	537
Cherry	403
Elderberry	472
Blueberry, highbush	171
Blueberry, lowbush	123
Blackcurrant	285
Cranberry	58
Raspberry	54
Blood orange	26
Blackberry	123

Source: Indena internal report 01/08/LRA 00

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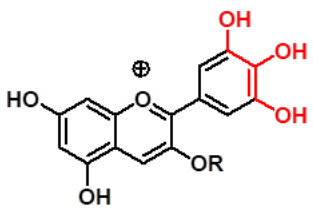
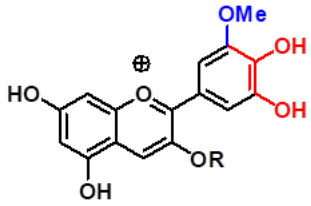
ANTHOCYANINS: THE PHYTOCHEMICAL HALLMARK OF BILBERRY

QUALITY:

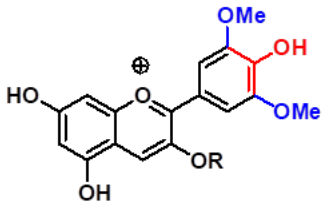
The anthocyanin profile of bilberry is **combinatorial** (5 anthocyanidins and 3 sugars), while that of all other sources is **additive**, and characterized by 1-3 major compounds



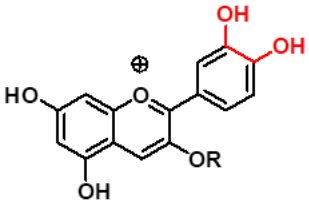
DELPHINIDIN



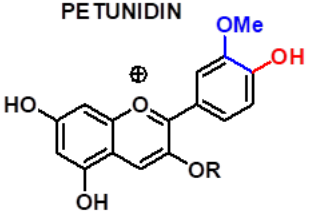
PETUNIDIN



MALVIDIN

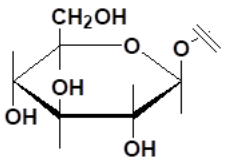


CYANIDIN

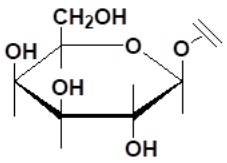


PEONIDIN

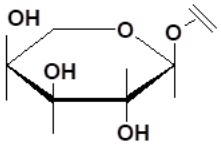
BILBERRY ANTHOCYANINS BUILDING BLOCKS



D.Glucose

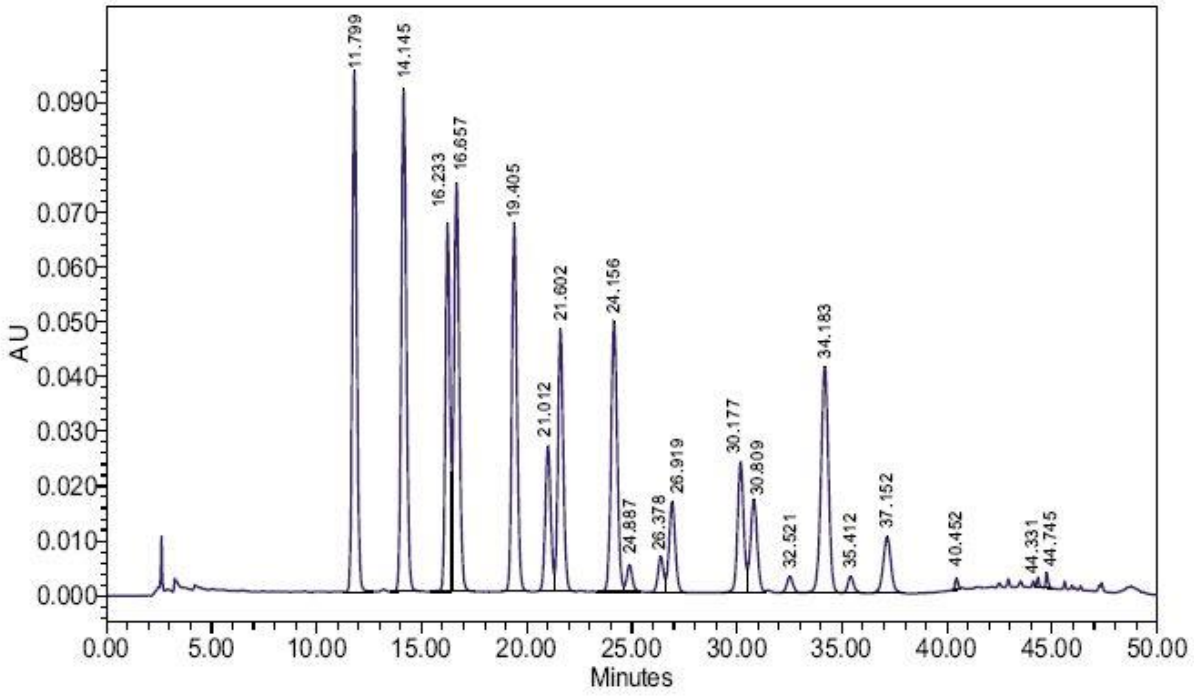


D-Galactone



L-Arabinose

BILBERRY'S COMBINATORIAL ANTHOCYANIN FRACTION

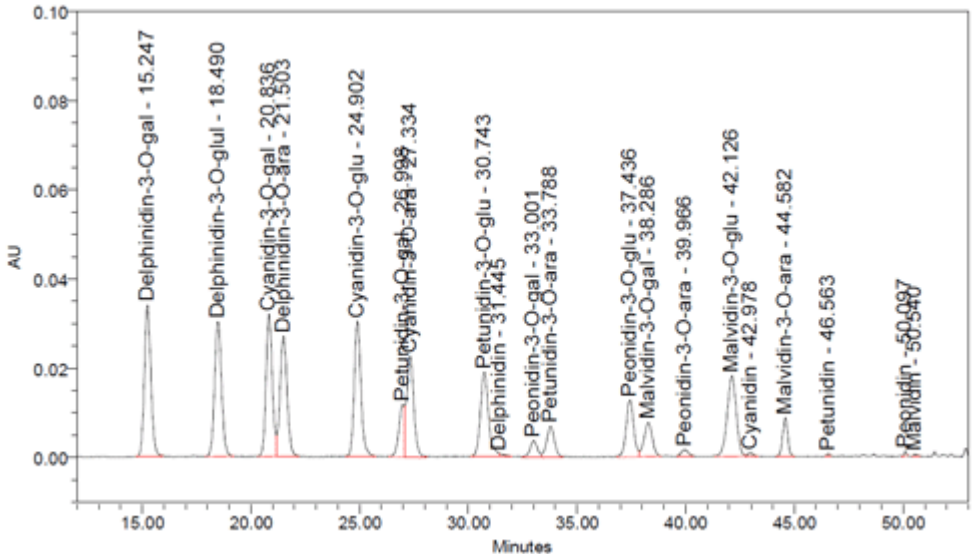


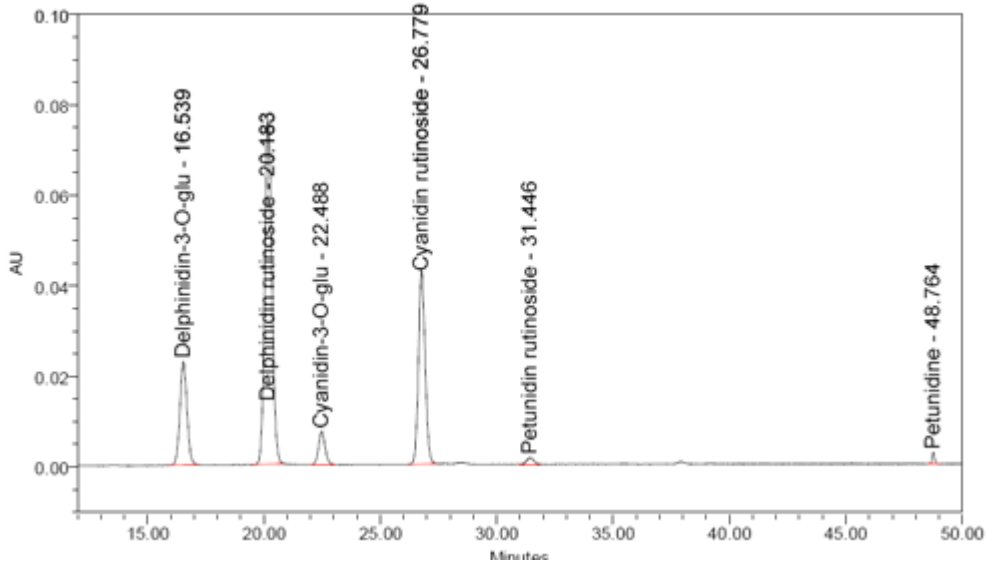
A typical HPLC profile obtained with this method.

COMPOUND	RETENTION TIME
Delphinidin-3-O-galactoside	11.8
Delphinidin-3-O-glucoside	14.15
Cyanidin-3-O-galactoside	16.23
Delphinidin-3-O-arabinoside	16.66
Cyanidin-3-O-glucoside	19.41
Petunidin-3-O-galactoside	21.01
Cyanidin-3-O-arabinoside	21.6
Petunidin-3-O-glucoside	24.16
Delphinidin	24.89
Peonidin-3-O-galactoside	26.38
Petunidin-3-O-arabinoside	26.92
Peonidin-3-O-glucoside	30.18
Malvidin-3-O-glucoside	30.81
Peonidin-3-O-arabinoside	32.52
Malvidin-3-O-galactoside	34.18
Cyanidin	35.41
Malvidin-3-O-arabinoside	37.15
Petunidin	40.45
Peonidin	44.33
Malvidin	44.75

- The structure, reactivity and polarity of anthocyanins are pH-dependent
- Current analytical techniques are aimed at the detection of the *flavilium* form, and derivatives of colorless forms are not detected

BLACKCURRANT *vs* BILBERRY





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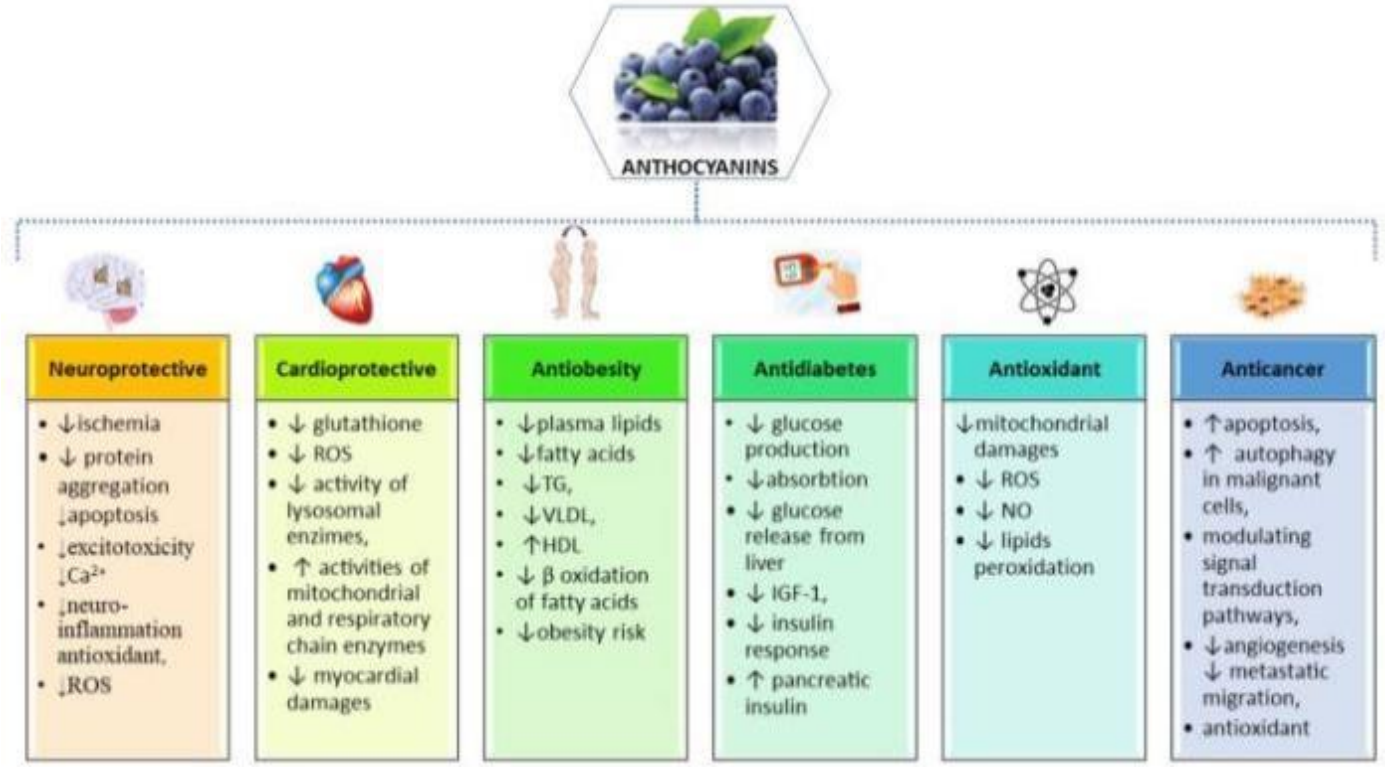
BIOLOGICAL TARGETS OF ANTHOCYANINS



Salehi, Bahare, et al. "The therapeutic potential of anthocyanins: current approaches based on their molecular mechanism of action." Frontiers in Pharmacology 11 (2020).

BIOLOGICAL TARGETS OF ANTHOCYANINS

- Antioxidant activity
- Anti-inflammatory activity:
  - Enzymatic (NF-kB, COX2, iNOsynthase)
  - Gene expression
- Endothelium protecting activity (NO bioavailability)
- Anti-atherogenic effects
- Anticarcinogenic effects (RTK)
- Immunostimulation
- Antibacterial and antiviral (herpes, influenza virus) activity
- Neuroprotection and neuroplasticity (Akt, PKC, PI3K)
- Adipocite differentiation
- Retinal cells protection

Mazza & Kay. 2007. Bioactivity, Absorption, and Metabolism of Anthocyanins. In: Recent Advances in Polyphenols Research-Vol. I. Blackwell Publishing Ltd., Oxford, UK

FROM BILBERRY TO

MIRTOSELECT®

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INDENA LONG-STANDING EXPERTISE WITH BIOMASS

- The freshly collected berries are frozen in ventilated tunnels at –35°C
- The frozen berries are processed by machinery
  - separated (in order to have the single berries)
  - selected according to dimensions (small berries are removed)
  - weighted (in order to remove stones)
  - cleaned up, eliminating leaves
- Red berries from *Vaccinium vitis-idaea* (lingonberry) are removed through a system called Niagara. A belt moves the berries up to a point where they'll fall, and color sensors detect the falling berries of "out of range color"
- A manual check is carried out before packaging, and the cleaned berries are either packed or temporarily stored in big boxes .

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MIRTOSELECT™: INDENA EXPERTISE AT THE SERVICE OF QUALITY

V. MYRTILLUS FREEZE-DRIED BERRIES

Shipment at – 20°C

INDUSTRIAL MANUFACTURE OF THE STANDARDIZED EXTRACT IN INDENA PRODUCTION SITE (Milano - Italy)

MIRTOSELECT®

36% ANTHOCYANINS

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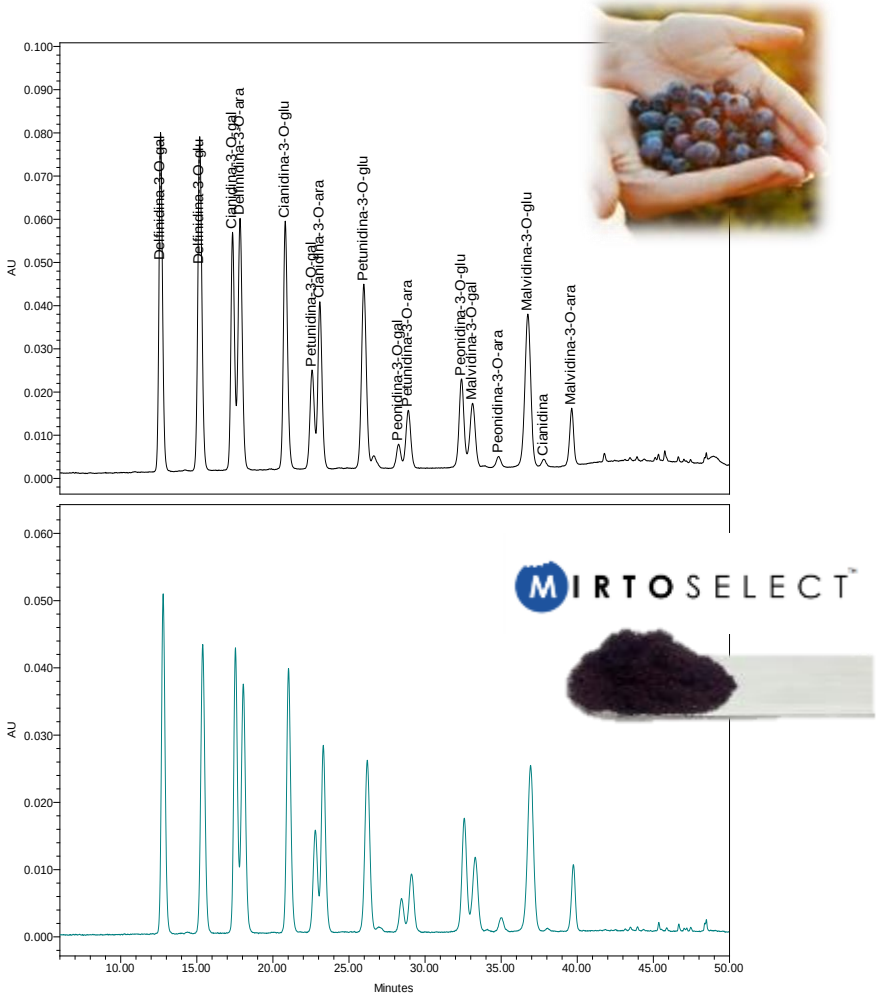
MIRTOSELECT™ RETAINS THE SAME ANTHOCYANIN PROFILE OF BILBERRY



THE DEEP LONG-STANDING KNOWLEDGE OF

- ✓ **BIOMASS**
- ✓ **SUPPLY CHAIN**
- ✓ **EXTRACTION PROCESS**
- ✓ **ANALYTICAL TECNIQUE**

ALLOWED INDENA TO DEVELOP THE MOST STUDIED BILBERRY EXTRACT ON THE MARKET

THAT

RETAINS ALL ANTHOCYANIN PATTERN OF NATURAL BILBERRY FRUIT

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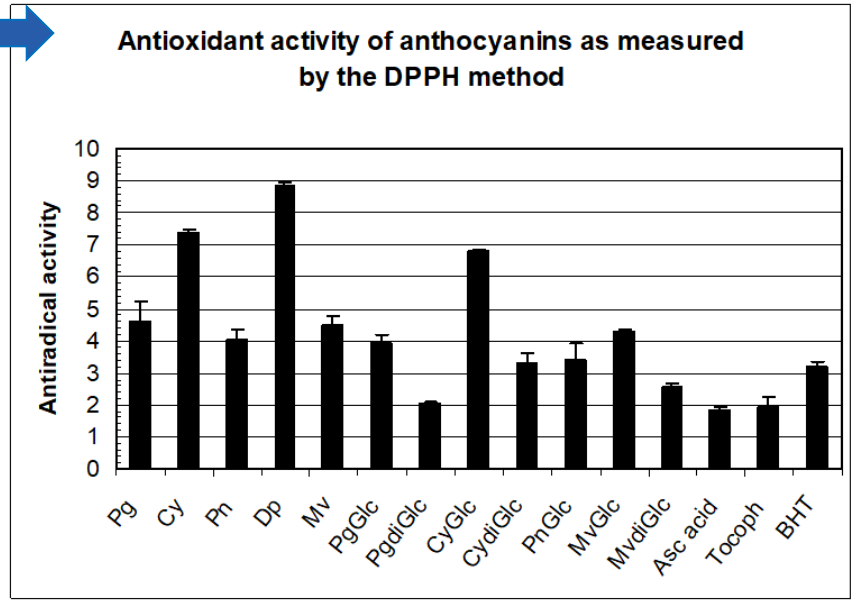
THE BIG ISSUE OF BILBERRY ADULTERATION

ANTHOCYANINS ARE NOT ALL CREATED EQUAL

- Anthocyanins have different:
  - Chemical and metabolic stability
  - PK and tissue distribution (*J. Nutr.* 2003, *133*, 4178–4182)
  - Potency in molecular assays of activity
  - Different antioxidant activity



- Anthocyanins can be adulterated even with synthetic azo dyes:

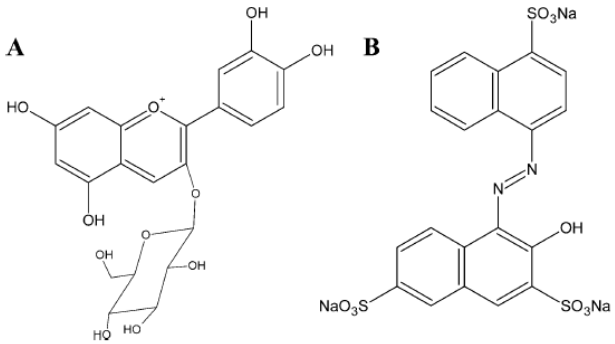


Figure 3. Representative structures of the anthocyanin cyanidin 3-glucoside (**A**) and amaranth (**B**).

J.Agric. Food Chem. 2006, 54, 7378

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BILBERRY ADULTERATION IS RAMPANT

SURVEY ON 10 FINISHED PRODUCTS ON THE MARKET

Table 2 *Summary of bilberry analysis and compliance to label: variability in bilberry extract analysis and the differences among available commercial extracts. Compliance with the declared content is not always observed*

No	Batch	Anthocyanins (HPLC) (%)	Anthocyanins (UV/Visible) (%)	Label	Compliance to label
6	0C10704	44.5	28.3	15mg/2cps (25%)	compliant
6	0L10333	41.1	28.1	15mg/2cps (25%)	compliant
10	81028	40.6	27.9	10mg (25%)	compliant
5	421101	39.0	27.3	25% - 80mg anthocyanins	compliant
9	92701	37.9	24.2	36% anthocyanosides	compliant
10	88046	37.3	25.5	25% anthocyanidins	compliant
8	90402	37.0	25.7	36% anthocyanosides	compliant
5	340435	27.7	27.8	25% - 80mg anthocyanins	compliant
1	2011616	25.8	27.0	25% anthocyanosides	compliant
2	50304	21.3	17.5	25% anthocyanidins	non compliant
3	64981-06	2.2	3.3	n.d.	not applicable
7	410127	1.7	2.2	25%anthocyanosides	non compliant
7	402178	0.7	1.3	25% anthocyanosides	non compliant
4	JJ08/A	0.0	0.0	n.d.	not appl; null

The bilberry extracts in the products we have analyzed show differences in content as well as in variations between actual and reported concentrations, with one samples even totally lacking anthocyanosides.

Artaria et al, NutraFood 2007, 6, 13-18

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AUTENTICITY IS OUR MISSION

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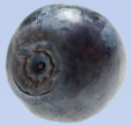
THE UNIQUENESS OF

MIRTOSELECT®



UNIQUE **PHYTOCHEMICAL PROFILE**: THE MATRIX EFFECT

UNIQUE **ANTHOCYAININS ABSORPTION**

UNIQUE **CLINICAL EFFICACY**

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1. UNIQUE PHYTOCHEMICAL PROFILE

European Review for Medical and Pharmacological Sciences 2014; 18: 3948-3953

Omne Ignotum pro Magnifico: characterization of commercial Bilberry extracts to fight adulteration

L. GIACOMELLI, G. APPENDINO[1], F. FRANCESCHI[2], S. TOGNI[2], R. PACE[2]

Independent Researcher, Milan, Italy.
[1]Department of Scienza del Farmaco, University of Piemonte Orientale "A. Avogadro", Novara, Italy
[2]Indena SpA, Milan, Italy

Chapter

Can Herbal Extracts be Essentially Similar? A Metabolomic Investigation of Vaccinium myrtillus (Bilberry) Dry Extracts

September 2016

In book: Occurrences, Structure, Biosynthesis, and Health Benefits Based on Their Evidences of Medicinal Phytochemicals in Vegetables and Fruits. Volume 5 · Chapter: Can Herbal Extracts be Essentially Similar? A Metabolomic Investigation of Vaccinium myrtillus (Bilberry) Dry Extracts · Publisher: Nova Science Publishers · Editors: Noboru Motohashi

Eric de Combarieu · Ernesto Marco Martinelli · Roberto Pace · Nicola Sardone

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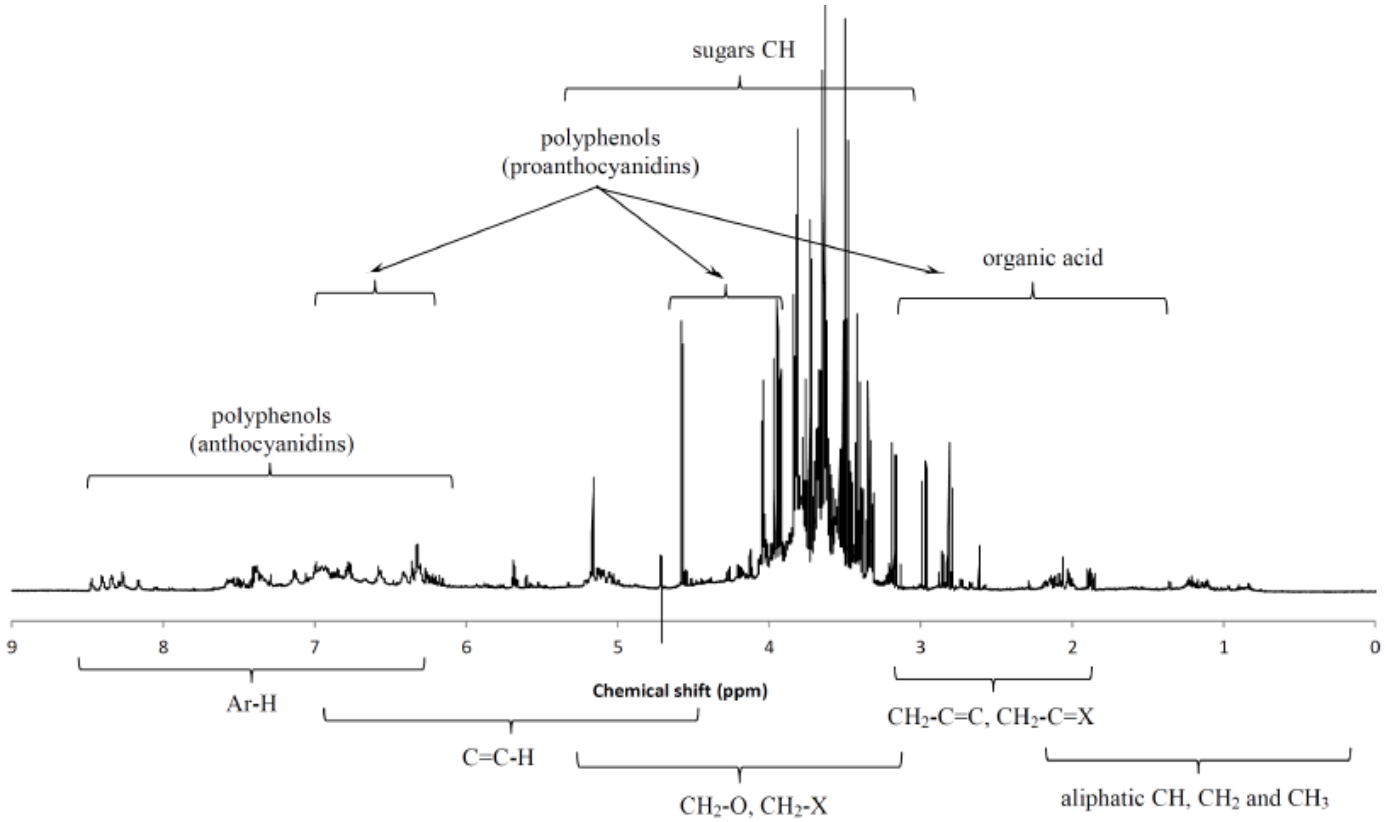
FULL SPECTRUM PROFILE

BILBERRY EXTRACT IS REGARDED AS ACTIVE IN ITS ENTIRETY



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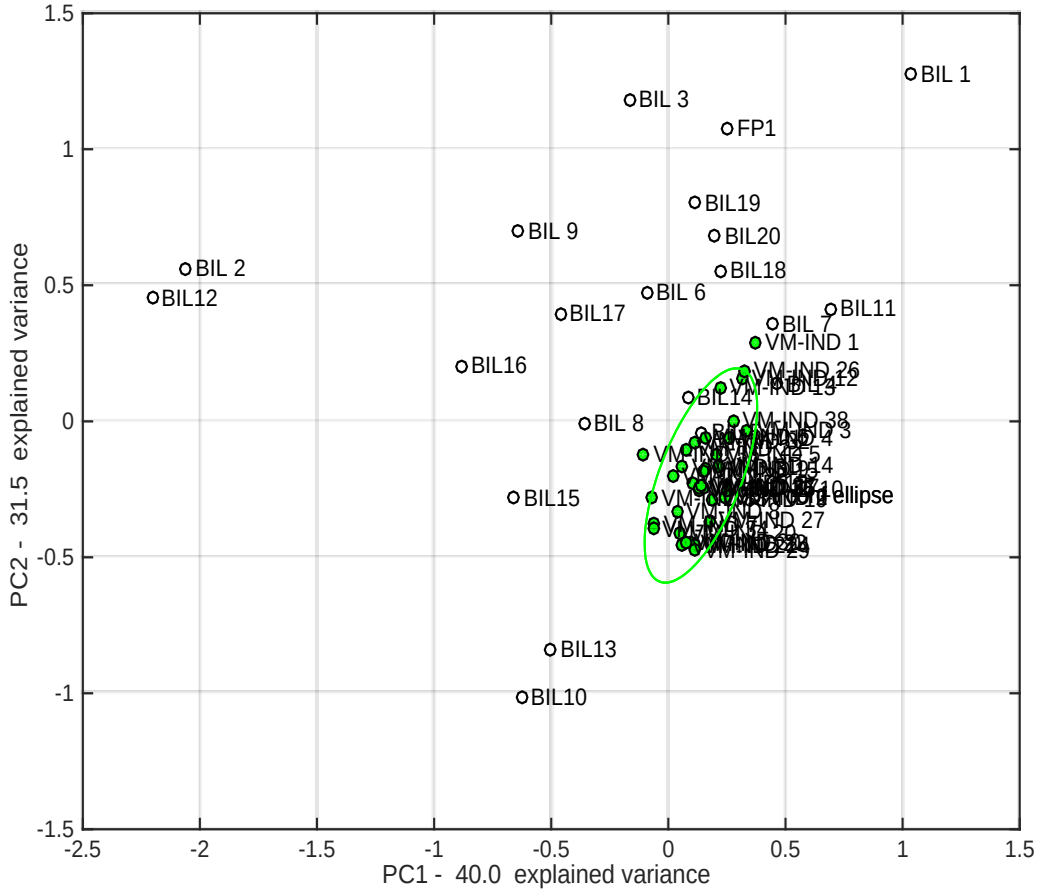
PCA – METABOLOMIC ANALYSIS WITH DIFFERENT TECNIQUES



The current best method to evaluate the batch to batch consistency is the Chemometrics (**Principal Component Analysis – PCA** – using **different available analytical variables**).

^{1}H-NMR data take into considerations all the hydrogen containing substances (i.e. all the extract constituents).

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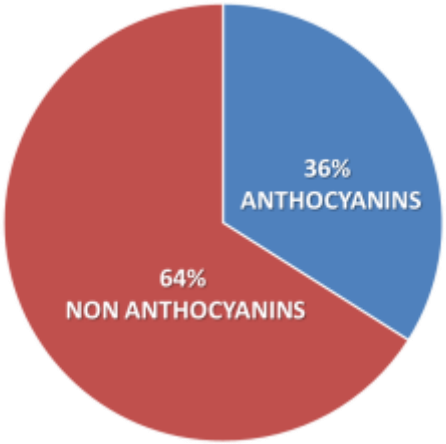
MIRTOSELECT™ HAS A UNIQUE PHYTOCHEMICAL PROFILE



***Vaccinium myrtillus* dry extracts available on the market differed from Indena extracts for the following** :

- ✓ Higher content of anthocyanidins (degradation products)
- ✓ Higher content of fibers
- ✓ High level of maltodextrins
- ✓ Lower contents of fructose and glucose, and higher content of maltose
- ✓ Lower content of organic acids

EVEN AMONG REAL BILBERRY EXTRACTS WITH 36% ANTHOCYANINS, SUBSTANTIAL DIFFERENCES EXIST IN THE REMAINING 64% MATRIX

NO EXTRACT ON THE MARKET IS PHYTOEQUIVALENT TO MIRTOSELECT®

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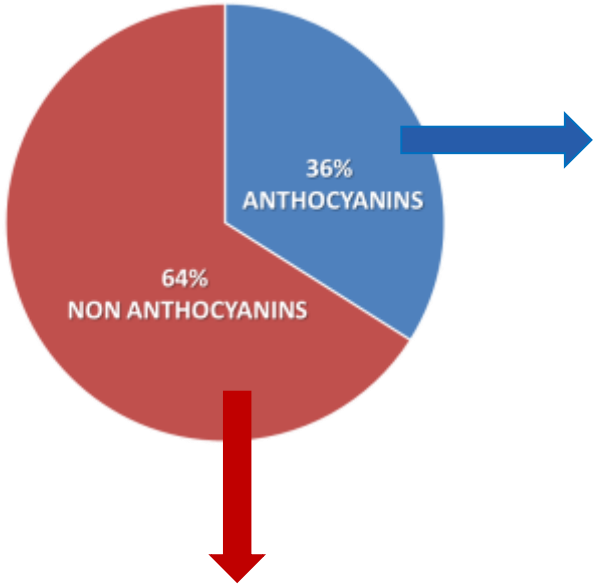
THE MATRIX EFFECT



The 36% anthocyanins titre is found in MIRTOSELECT® and other extract son the market according to Pharmacopoeias

The remaining 64% is different in MIRTOSELECT® and other extracts.

The non-anthocyanins matrix is not biologically inert (while maltodextrins are!)

The non-anthocyanins matrix has a crucial biological role

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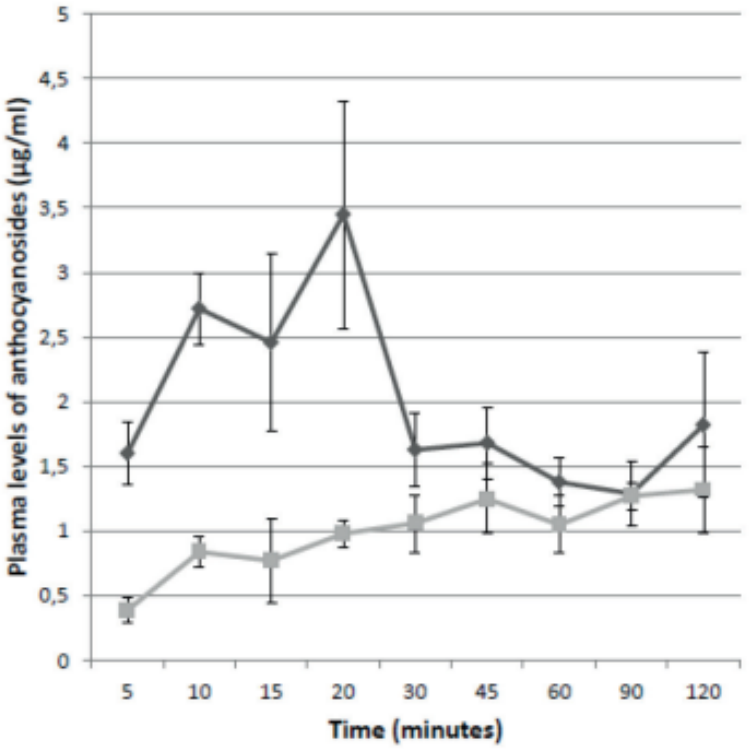
2. UNIQUE ABSORPTION OF ANTHOCYANINS



MIRTOSELECT®

> 8 fold more bioavailable

MIRTOSELECT®

Generic bilberry extract reconstructed extract (80% anthocyanins, diluted to 36% with inert carrier)

THE 64% MATRIX PLAYS A CRUCIAL ROLE IN ANTHOCYANINS BIOABSORPTION

Riva, A., et al. "The effect of a natural, standardized bilberry extract (Mirtoselect®) in dry eye: a randomized, double blinded, placebo-controlled trial." Eur. Rev. Med. Pharmacol. Sci 21 (2017): 2518-2525.

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3. UNIQUE CLINICAL EFFICACY

THE MOST EXTENSIVE PRECLINICAL AND CLINICAL PACK FOR A BILBERRY EXTRACT

No. 6	• Clinical trials in **EYE DISORDERS**
No. 6	• Clinical trials in **RETINOPATHY**
No. 25	• Clinical trials in several **others conditions** such as Type 2 Diabetes, Women's Health, Vascular/Cardiovascular protection, …

DUE TO THE DIFFERENCE IN MATRIX PROFILE, THIS CLINICAL PACK CANNOT BE ASCRIBED TO OTHER BILBERRY EXTRACTS DIFFERENT FROM


MIRTOSELECT®
IN EYES DISORDERS

MIRTOSELECT™

THE BIOLOGICAL ROLE OF THE MATRIX

European Review for Medical and Pharmacological Sciences 2016; 20: 2418-2424

Bilberry extracts are not created equal: the role of non anthocyanin fraction. Discovering the "dark side of the force" in a preliminary study

C. GIZZI[1], G. BELCARO[2], G. GIZZI[2], B. FERAGALLI[2], M. DUGALL[2], R. LUZZI[2], U. CORNELLI[2]

[1]Department SMO Biotech, [2]Irvine Labs, Circulation Sciences, Chieti-Pescara University, Italy

MIRTOSELECT™ ***VS*** **GENERIC BILBERRY EXTRACT**
(36% anthocyanins + Maltodextrins)

SAME ANTHOCYANINS CONTENT,
THE DIFFERENCE IS IN THE MATRIX

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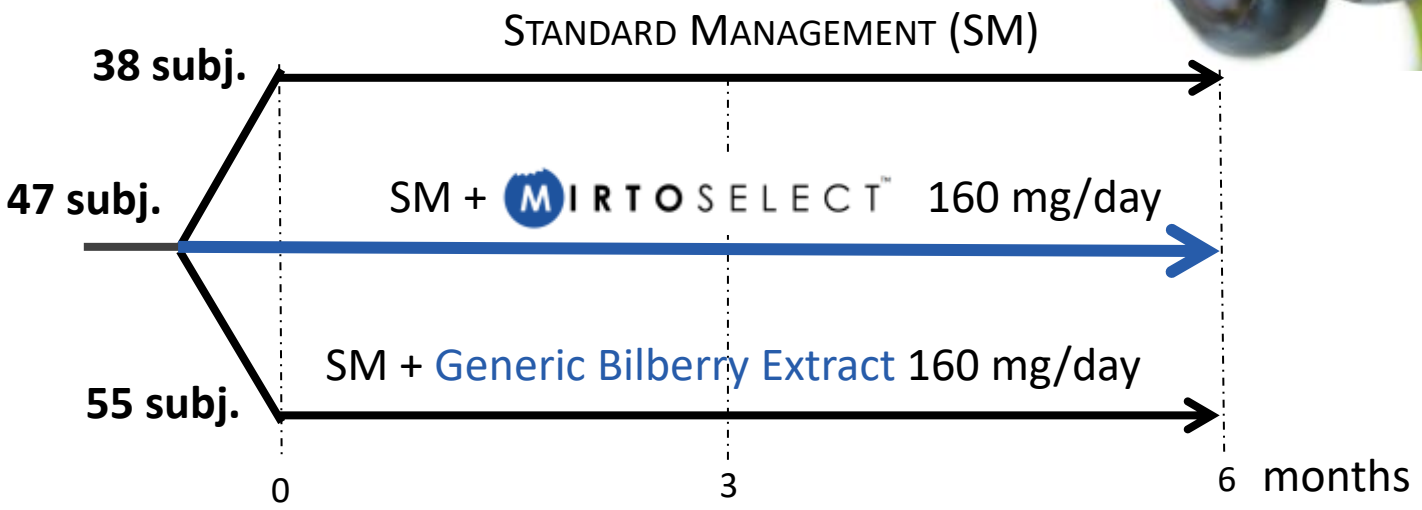
STUDY DESIGN



- ✓ **STUDY TYPE:** open label, registry
- ✓ **TREATMENTS**:
  - control (SM)
  - MIRTOSELECT® 160 mg/day
  - generic bilberry extract (36% anthocyanins + Maltodextrins): 160 mg/day
- ✓ **STUDY POPULATION**: 140 patients with different types of retinopathies
  - Hyperflow: diabetic proliferative, no-proliferative retinopathy
  - Ischemic: post-thrombotic, hypertensive, glaucoma, ischemic

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STUDY POPULATION AND ENPOINTS

	Standard Management	Standard Management + MIRTOSELECT	Standard Management + generic bilberry extract
Diabetic non proliferative	10 (6)	12 (6)	9 (5)
Diabetic proliferative	7 (4)	8 (4)	11 (4)
Retinal post-thrombosis	6 (4)	8 (3)	12 (5)
Hypertensive retinopathy	7 (3)	10 (5)	11 (4)
Glaucoma	8 (5)	9 (4)	12 (6)
Total subjects	**38**	**47**	**55**
Age, years (mean ± SD)	44.5±2.2	44.3±1	44.1±2.2

SD: standard deviation

PRIMARY ENDPOINTS:

clinical ophthalmological observations

- Macular edema
- Capillary microaneurisms
- Dot&Blot retinal hemorrage
- Hard exudates
- Soft exudates
- Arteriolar vasoconstriction
- Arteriovenous crossing
- Aterosclerosis
- Wall changes

SECONDARY ENDPOINTS:

- Flow (high res duplex)
- Snellen Chart (visual acuity)
- Edema (ultrasound)
- Blurring

MIRTOSELECT™ : EFFECTIVE IN REDUCING RETINOPATY SYMPTOMS

	SM only (n=38)		SM+MIRTOSELECT® (n=47)		SM+generic bilberry extract (n=55)	
	inclusion	6 months	inclusion	6 months	inclusion	6 months
Edema	18	16+	19	12*#+	21	18+
Capillary microaneurisms	11	11	13	7*#	14	12
Dot&Blot retinal hemorrage	8	9	8	6*+	10	7*+
Hard exudates	7	7	9	2*#+	7	3*+
Soft exudates	8	9	11	4*#+	8	5
Arteriolar vasoconstriction	8	6	12	4*#+	11	6*+
Arteriovenous crossing	8	8	11	8*#+	10	9
Aterosclerosis	12	10	13	5*#+	12	8*+

SM = standard management. *p<0.0.5 vs. SM; #p<0.05 vs. SM+generic bilberry extract; +p<0.05 vs. inclusion

Δ 25% - 77%

SIGNIFICANT IMPROVEMENT IN SEVERAL RETINAL CIRCULATORY PARAMETERS

MIRTOSELECT™

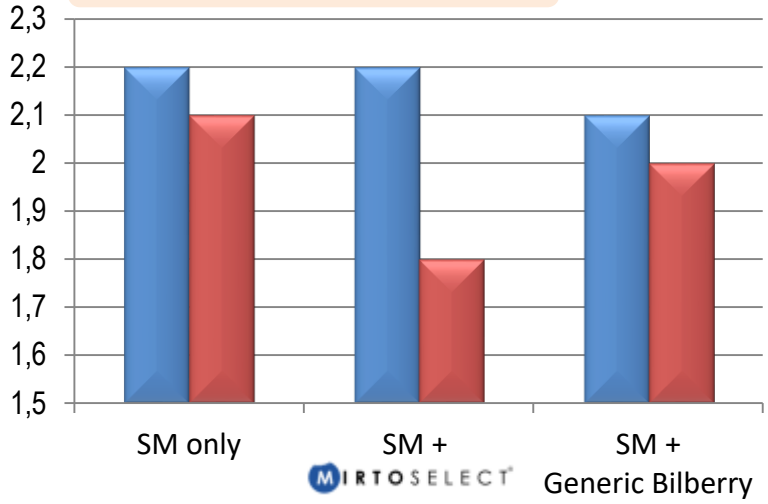
REDUCED BLOOD FLOW ALTERATION

Table III. Outcome of target test parameters investigated in this study.

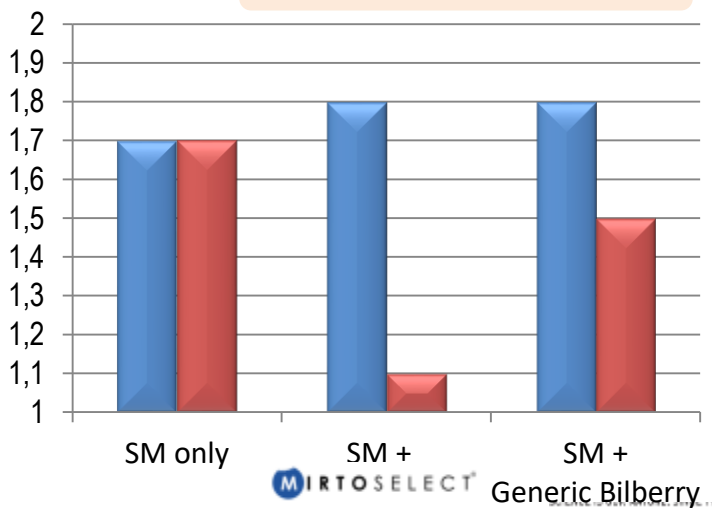
	SM only		SM+MIRTOSELECT®		SM+generic bilberry extract	
	inclusion	6 months	inclusion	6 months	inclusion	6 months
Snellen Chart score	8/10	7/10	8/10	9/10	8/10	7/10
Flow (0-3 score)	2.2±0.2	2.1±0.2	2.2±0.2	1.8±0.2$^{*\#+}$	2.1±0.3	2.0±0.2
Edema (0-3 score)	1.7±0.5	1.7±0.1	1.8±0.5	1.1±0.3$^{*\#+}$	1.8±0.1	1.5±0.2^{*+}
Blurring (0-3 score)	2.1±0.2	2±0.2	2±0.4	1.2±0.3$^{*\#+}$	2.2±0.3	1.6±0.3^{*+}

Evaluation scale: 0: normal; 1: minimal alterations; 2: important alterations; 3: severe alterations Data are reported as mean ±standard deviation. $^{*}p<0.05$ vs. SM; $^{\#}p<0.05$ vs. SM+generic bilberry extract; $^{+}p<0.05$ vs. inclusion

OCULAR FLOW ALTERATION



MACULAR EDEMA



MIRTOSELECT™ : AMELIORATION OF EYE MICROCIRCULATION

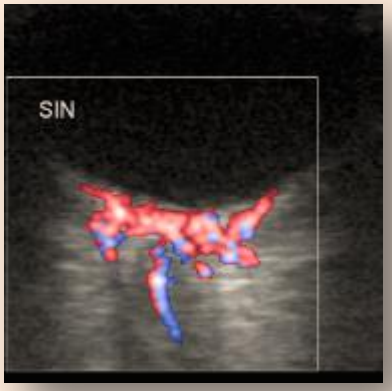
Table IV. Measurements of ocular blood flow velocity.

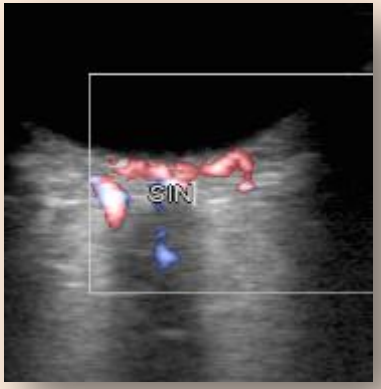
	SM only		SM+MIRTOSELECT®		SM+generic bilberry extract	
	inclusion	6 months	inclusion	6 months	inclusion	6 months
Hyperflow group	28±3/16±2	28±3/15±3	29±2/15±1	24±2/12±1*#+	28±2/17±2	28±3/16±2
Ischemic group	17±2/11±1	17±2/12±1	16±2/11±2	23±2/14±2*#+	17±2/10±1	19±2/11±1*+

Diastolic/systolic flow velocity. Data are expressed in cm/sec as mean ±standard deviation. *$p<0.05$ vs. SM; #$p<0.05$ vs. SM+generic bilberry extract; +$p<0.05$ vs. inclusion

HYPERFLOW vs ISCHEMIC RETINOPATHY

- Increased systolic and diastolic flows
- Diabetic non proliferative and proliferative retinopathy





- Decreased systolic and diastolic flows
- Post-thrombotic, hypertensive, glaucoma and ischemic retinopathy

High-resolution ultrasound color doppler

MIRTOSELECT™:

STUDY KEY MESSAGES

- Compared to the generic bilberry extract, **MIRTOSELECT®** supplementation resulted in **statistically significant and clinically relevant improvements in several retinal circulatory parameters**.

- **MIRTOSELECT®** (a naturally standardized bilberry extract, with 36% anthocyanins and the full range of non-anthocyanin components) and a commercially-available, generic bilberry extract (constituted by 36% anthocyanins with maltodextrins as carrier) **show remarkably different biological effects and clinical response.**

- The remaining non-anthocyanin fraction of natural bilberry extract can explain these differences (**the matrix effect**).

- Commercially-available generic bilberry extracts are **NOT phytoequivalent to MIRTOSELECT®.**

- **MIRTOSELECT® human studies cannot be ascribe to other bilberry extracts.**

MIRTOSELECT™

IN SEVERE DIABETIC RETINOPHATY

Minerva Oftalmol 2017 June;59(2):38-41
DOI: 10.23736/S0026-4903.17.01775-5

ORIGINAL ARTICLE

The effect of oral supplementation with standardized bilberry extract (Mirtoselect®) on retino-cortical bioelectrical activity in severe diabetic retinopathy

Fabio MAZZOLANI [1], Stefano TOGNI [2], Federico FRANCESCHI [2], Roberto EGGENHOFFNER [3], Luca GIACOMELLI [3] *

[1]Private Practitioner, Milan, Italy; [2]Indena SpA, Milan, Italy; [3]Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy

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Mazzolani, Fabio, et al. "The effect of oral supplementation with standardized bilberry extract (Mirtoselect®) on retino-cortical bioelectrical activity in severe diabetic retinopathy." Minerva Oftalmol (2017).

MIRTOSELECT™

STUDY DESIGN

- ✓ STUDY POPULATION: 9 subjects affected by type-2, non-insulin DM associated with severe pre-proliferative vascular retinopathy without macular edema

- ✓ ENDPOINTS:
  - Pattern-reversal VEP analysis (Retino-cortical bioelectrical activity as electro-physiological response of the nervous system to visual stimuli)

Mazzolani, Fabio, et al. "The effect of oral supplementation with standardized bilberry extract (Mirtoselect®) on retino-cortical bioelectrical activity in severe diabetic retinopathy." Minerva Oftalmol (2017).

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VEP TEST (VISUAL EVOKED POTENTIAL)

This is a test to determine the integrity of the nerve transmission from the eye to the brain.

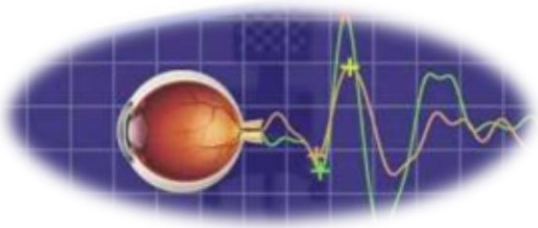
When light from an image enters the eye, it is turned into electrical energy by cells in the retina – the light-sensitive layer at the back of the eye.

These cells send the electrical energy back to the visual cortex, the part of brain where the image is processed.

Mazzolani, Fabio, et al. "The effect of oral supplementation with standardized bilberry extract (Mirtoselect®) on retino-cortical bioelectrical activity in severe diabetic retinopathy." Minerva Oftalmol (2017).

MIRTOSELECT™ : IMPROVED EYE FUNCTION

THE 45% OF PATIENTS SHOWED AN IMPROVED RETINO-CORTICAL RESPONSE TO VEP STIMULUS FOLLOWING SUPPLEMENTATION WITH MIRTOSELECT™



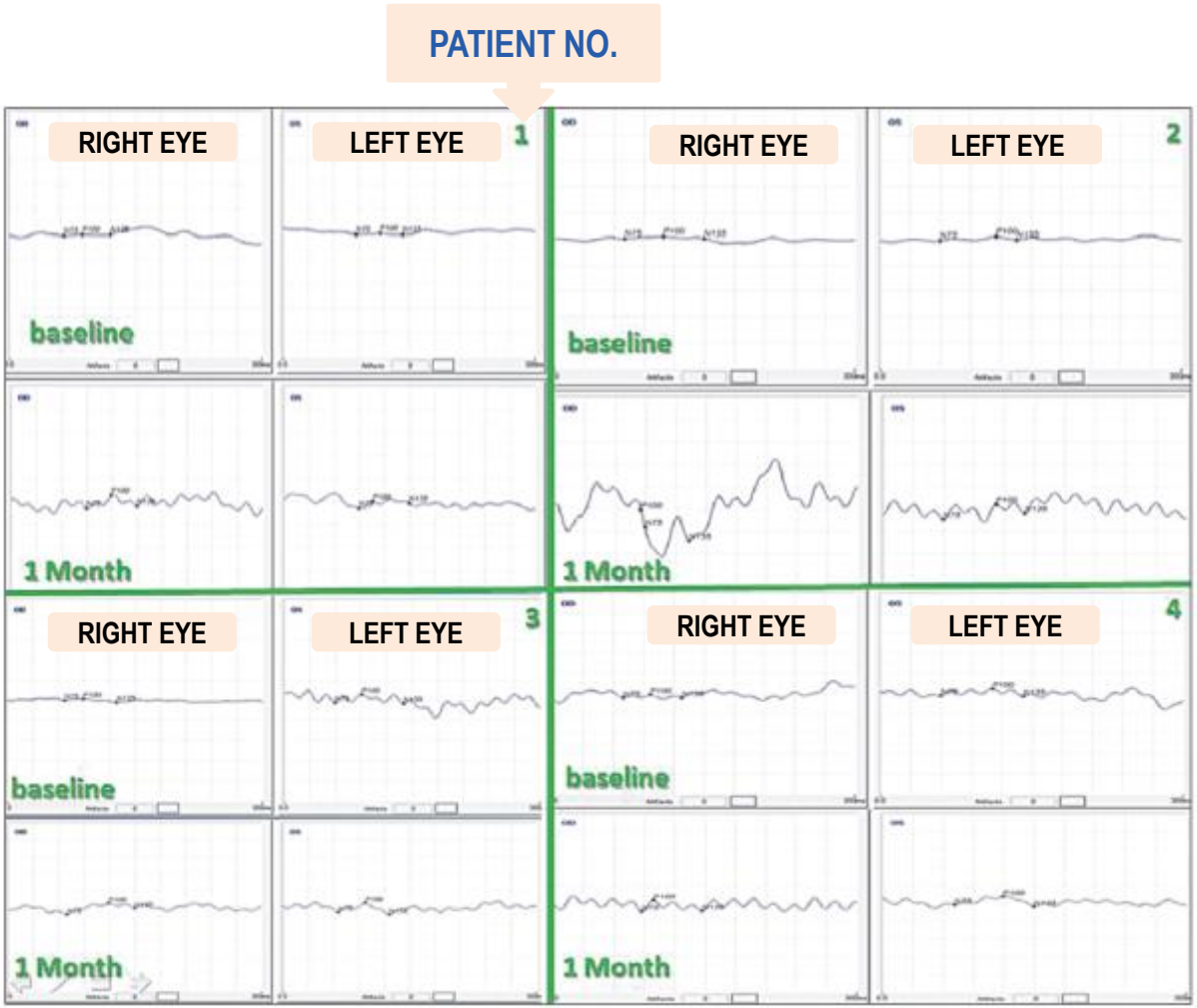


Figure 1.—Improvement of P100 amplitude, latency and wave morphology of visual evoked potential (VEP) response in 4 patients with diabetes mellitus and retinopathy, after 1-month, oral supplementation with standardized bilberry extract (Mirtoselect®).

Mazzolani, Fabio, et al. "The effect of oral supplementation with standardized bilberry extract (Mirtoselect®) on retino-cortical bioelectrical activity in severe diabetic retinopathy." Minerva Oftalmol (2017).

MIRTOSELECT™

IN DRY EYE SYNDROME

European Review for Medical and Pharmacological Sciences 2017; 21: 2518-2525

The effect of a natural, standardized bilberry extract (Mirtoselect®) in dry eye: a randomized, double blinded, placebo-controlled trial

A. RIVA[1], S. TOGNI[1], F. FRANCESCHI[1], S. KAWADA[2], Y. INABA[2], R. EGGENHOFFNER[3], L. GIACOMELLI[3]

[1]Indena SpA, Milan, Italy
[2]Indena SpA, Tokyo, Japan
[3]Department of Surgical Sciences and Integrated Diagnostics, School of Medicine, Genoa University, Genoa, Italy

Riva, A., et al. "The effect of a natural, standardized bilberry extract (Mirtoselect®) in dry eye: a randomized, double blinded, placebo-controlled trial." Eur. Rev. Med. Pharmacol. Sci 21 (2017): 2518-2525.

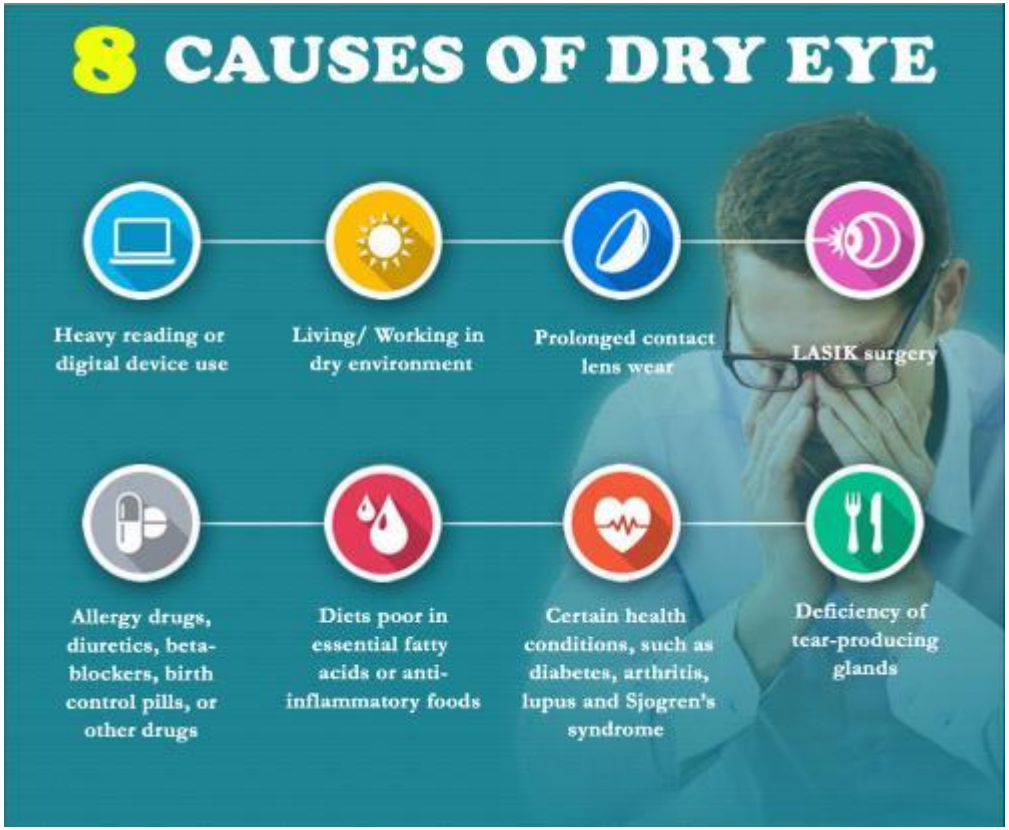
MIRTOSELECT™

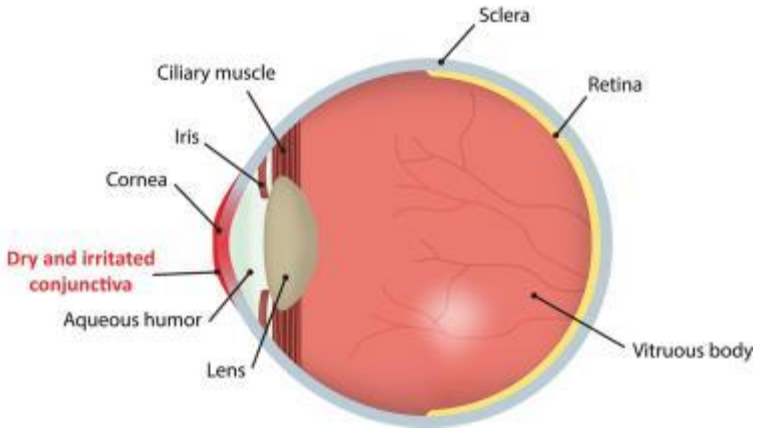
IN DRY EYE SYNDROME

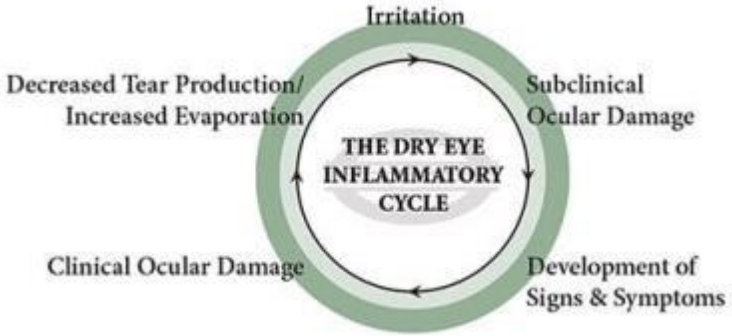
- ✓ **STUDY TYPE:** Randomized, double blinded, placebo-controlled
- ✓ **STUDY POPULATION**: 22 healthy subjects suffering from visual fatigue or eye strain (dry eye *vs* wet condition)
- ✓ **ENDPOINTS:**
  - Schirmer's Test (volume of tears secretion)
  - Oxidative stress: BAP (Biological Antioxidant Potential) and d-ROMS (diacron-reactive oxygen metabolites)

Riva, A., et al. "The effect of a natural, standardized bilberry extract (Mirtoselect®) in dry eye: a randomized, double blinded, placebo-controlled trial." Eur. Rev. Med. Pharmacol. Sci 21 (2017): 2518-2525.

THE DRY EYE SYNDROME







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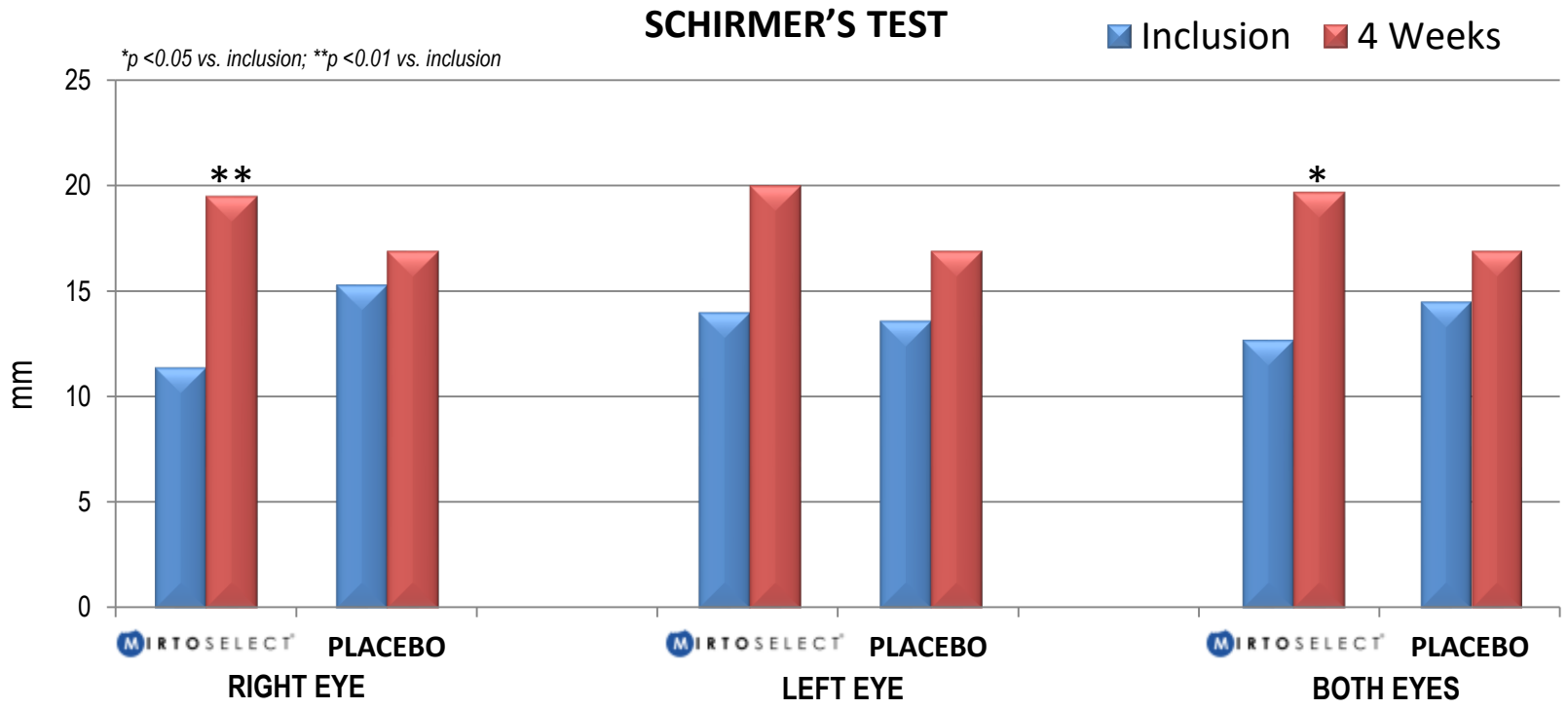
EFFICACY ON TEARS FLOW



MIRTOSELECT™ **GROUP REPORTED:**

- **SIGNIFICANT IMPROVEMENT OF TEAR FLOW PARAMETER (Δ 43% - 71%)**
- **HIGHER IMPROVEMENT RATE AMONG SUBJECTS WITH SEVERE SYMPTOMS (P = 0.015)**

Riva, A., et al. " (2017):.

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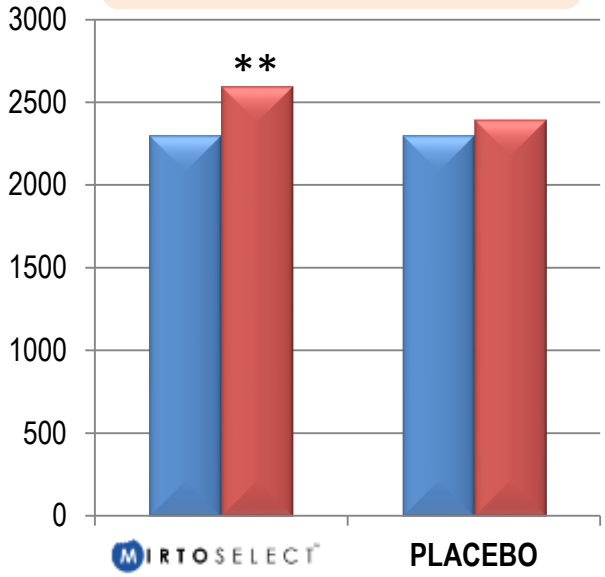
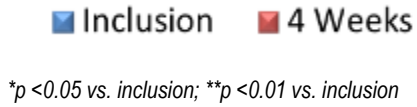
REDUCED OXIDATIVE STRESS

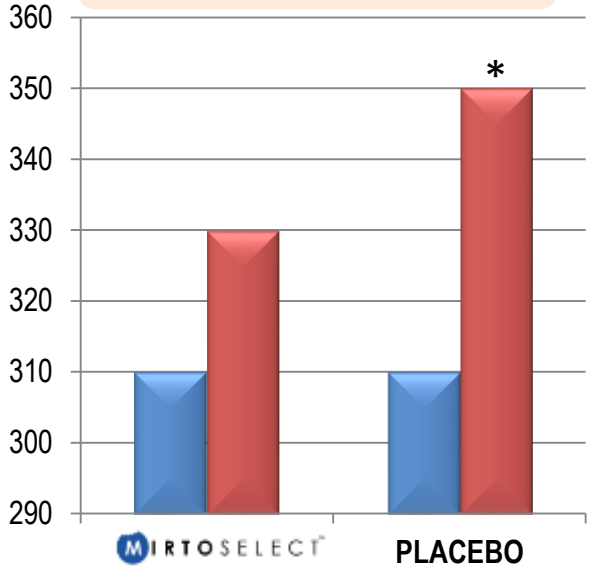
PLASMA ANTIOXIDANT BIOLOGICAL POTENTIAL (BAP)





*p <0.05 vs. inclusion; **p <0.01 vs. inclusion

PLASMA DIACRON-REACTIVE OXYGEN SPECIES (d-ROMs)



MIRTOSELECT™ **GROUP REPORTED**

SIGNIFICANT IMPROVEMENT OF OXIDATIVE STRESS PARAMETERS

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TAKE HOME MESSAGES

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MIRTOSELECT™ IS UNIQUE

- **Supply chain validated by decades** of expertise and constant production
- Recognized as the **golden standard for bilberry extracts** in regulatory terms (e.g. USP and EuPh) and within the commercial arena
- **Unique "fingerprint",** authentically **matching that of bilberries** and showing **substantial differences in the non anthocyanin fraction (64%)**
- **Not phytoequivalent** to other bilberry extracts on the market
- Best documented bilberry extract in terms of **clinical efficacy and safety,** with a clinical dossier that cannot be ascribed to other bilberry extracts
- Recent clinical evidences in **eye health**

MIRTOSELECT™ IS UNIQUE

THE FIRST BOTANICAL EXTRACT

DNA-CERTIFIED

IN DNA™
VERIFIED EXTRACT
indena

indena
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100 YEARS

WHY ANALYZE MIRTOSELECT®'S DNA?

MIRTOSELECT® IS **UNIQUE**:

Effectiveness proven by clinical studies

+

Authenticity additional verification by DNA extract testing

=

Reliable action

HOW DOES OUR DNA METHOD WORK?

1 | EXTRACTION

2 | PURIFICATION

3 | AMPLIFICATION

4 | IDENTIFICATION

= *Vaccinium myrtillus*

THE KEY TO OUR METHOD'S SUCCESS?

The amplified region must be univocal for *Vaccinium myrtillus*.

REAL TIME TESTING.
ANYTIME, ANYWHERE.

- The platform can be used anywhere.
- Same results as traditional lab-based instruments.
- Cloud-based data portal lets you access your results anywhere.

Portable PCR Thermal Cycler

Software

Reagents

WHAT MAKES MIRTOSELECT® SO SPECIAL?

DNA TESTING ON EXTRACTS' FIRST APPLICATION

DNA VERIFICATION ANYWHERE YOU ARE

IN DNA™
VERIFIED EXTRACT
indena

bCUBE® by HYRIS
GLOBAL D AGNOSTICS

INDENA TODAY

Follow us on:

MIRTOSELECT®

CLINICAL STUDIES

EYES DISORDERS

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CLINICAL STUDIES

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