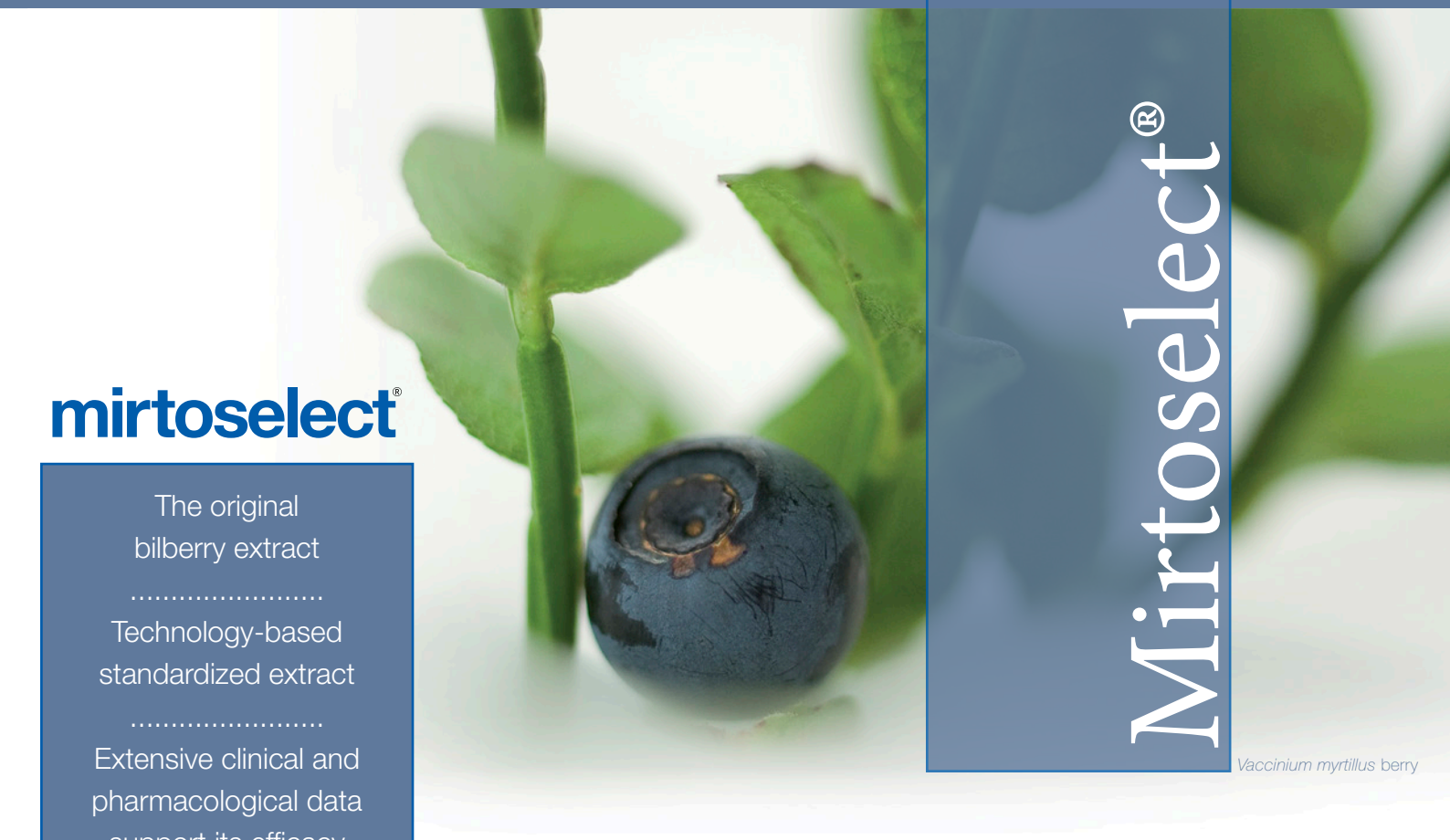
indena®



Mirtoselect®

Vaccinium myrtillus berry

mirtoselect®

The original bilberry extract

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Technology-based standardized extract

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Extensive clinical and pharmacological data support its efficacy

Vaccinium myrtillus **L.** is a small deciduous shrub growing on hilly heaths and underbrush throughout Central and Northern Europe.[1-5] The origin of the name *Vaccinium* is uncertain, and it could derive from the latin words *vacca* = cow, or *bacca* = berry. The name *myrtillus* derives instead from its similarity with the fruits and leaves of myrtle[3,4,6]. Among the **450 species**[7] belonging to genus *Vaccinium,* the traditional medicinal use of *Vaccinium myrtillus* is documented since the Middle Ages, when its fruits were recommended to promote menstruation, and from the 16th century the plant has been systematically mentioned in all major herbal treatises. Several compounds belonging to different chemical classes have been isolated from the berries of *Vaccinium myrtillus*, particularly **anthocyanins (also called anthocyanosides)** have been extensively documented in the scientific literature. Anthocyanins are found naturally in a number of foods. They can be found in red wine, certain varieties of cereals, and certain leafy and root vegetables (aubergines, cabbage, beans, onions, radishes), but are most abundant in colored fruits like bilberries.[8] Despite the difficulties in calculating the exact daily exposure, several attempts to estimate anthocyanidins intake in European,[9-13] US,[14] Australian[15] and Japanese populations[16] have been done. Total anthocyanidin mean intake ranged from 19.83 to 64.88 (se 1.86) mg/day in the most recent European study,[9] while much lower values have been instead reported in the US, Australian and Japanese population, where anthocyanidin intakes of 3.1 mg/day in the USA,[14] 2.9 mg/day in Australia[15] and 11.3 mg/day in Japan[16] have been calculated. In the early Seventies, Indena developed a standardized bilberry extract whose efficacy has been extensively clinically evaluated in vascular health, with over 50 positive studies, including at least 25 controlled or double-blind studies.[17]

Please note that the physiological activity of the ingredient described herein is supported by the referenced clinical trial reports. Marketers of finished products containing the ingredient described herein are responsible for determining whether the claims made for such products are lawful and in compliance with the laws of the country in which they will market the products.

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Bilberry: innovation meets tradition

The original titre "Bilberry 25%" referring to the anthocyanidin content by UV analysis, became a globally recognized reference for bilberry extracts. Over the past decade, the specification "Bilberry 25%" has been applied to products that do not conform to the quality of Indena's bilberry extract.[18-20] For this very reason, Indena has developed a specific and indisputable analytical method for the identification and quantification of bilberry anthocyanins and anthocyanidins. The method, originally used for the release of Indena's first registered product in Italy, has been ultimately released to the market.[18] This HPLC-based method defines the anthocyanins content of the standardized bilberry extract as **36% anthocyanins** (the glycosilated compounds) and this titer corresponds to the "old" 25% specification by UV analysis, that was based on anthocyanidins (the aglycones).

This method, more suitable to quantify accurately the anthocyanosidic content and profile of bilberry, has now become a standard reference for most Pharmacopoeias of the Western countries.[21-24]

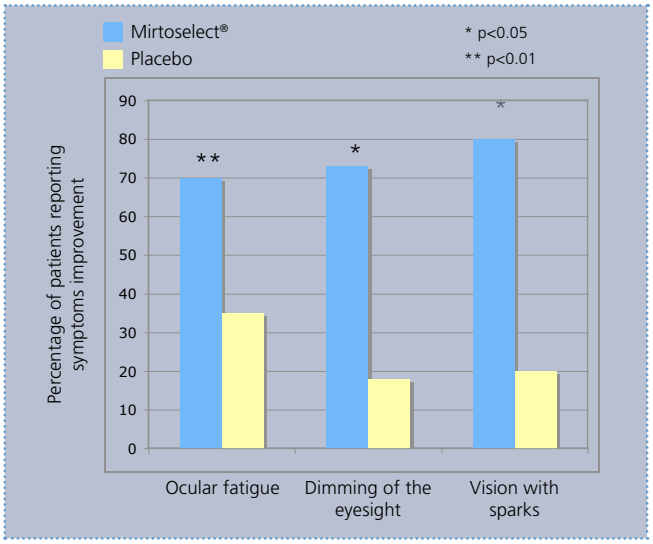
Main Clinical Use

Studies show that bilberry extract, reach in anthocyanins, positive influences on a variety of health conditions. Probably most known activity to the average person is related to a traditional story that during World War II the ingestion of bilberry jam (made from *Vaccinium myrtillus* berries) improved the sight of Royal Air Force pilots on night flights.
Although the vericity of this story has been questioned, the effect of anthocyanins in improving vision has been validated by instrumental techniques, like computerized perimetry, suggesting that a standardized bilberry extract containing 36% anthocyanins (Mirtoselect®) can play an important role in improving retinal sensitivity.[25,26]
Other activities, somehow explaining the activity at the eye level, have been deeply studied. Primarily many pharmacological trials have confirmed the efficacy of 36% anthocyanin bilberry extract on microvascular health as well as in phlebology and its efficacy in the treatment of symptoms associated with venous health has been demonstrated in randomized, double-blind, placebo-controlled clinical trails carried out on hundreds of patients.[27-33]
Furthermore anthocyanins of bilberry are emerging as an alternative dietary strategy to support healthy blood sugar levels and its complications associated to inflammation and oxidative stress.[34]

Clinical studies on Mirtoselect® in ophthalmology

Mirtoselect® and eyesight fatigue

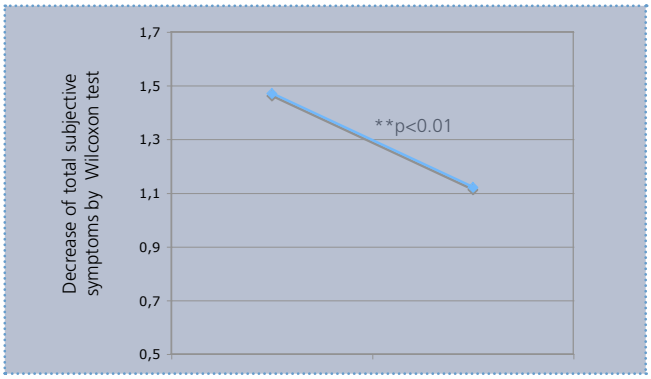
Mirtoselect® has been shown to help support healthy visual function due to eye fatigue. In a crossover, double-blind, placebo-controlled study on 20 patients,[35] four weeks of daily treatment with 250 mg of Mirtoselect®, showed an improvement in subjective symptoms like the occurrence of vision sparks (80% of subjects), eyesight dimming (73% of subjects) and ocular fatigue (70% of subjects) in computer operators. Other improved symptoms were lacrimation and heavy headedness.
Flicker values improved significantly following the administration of bilberry anthocyanins, and an overall improvement of eye fatigue could be established.



Effect of Mirtoselect® on the improvement of symptoms associated with eyesight fatigue when compared to a placebo group.

Mirtoselect® and healthy eyesight

Prolonged intake of Mirtoselect® has been associated with significant changes in visual acuity. An 8-weeks trial[36] with a daily dosage of 150 mg of Mirtoselect® was carried out on 63 school children. This suggests that Mirtoselect® could be a powerful tool in the support of ocular health related to increased eye accommodation associated with prolonged reading and computer work, activities that are typical of school education.
The anthocyanins in Mirtoselect® have an affinity for small blood vessels and have been shown to improve the blood flow in the eye bulb tissues, activating the nutrition supply.



Effect of Mirtoselect® on eyesight recovery in school children affected by pseudomyopia.

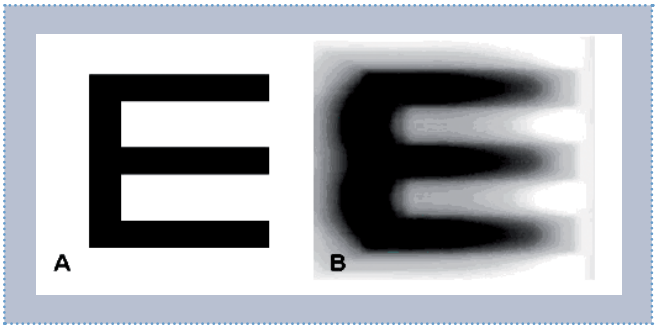
Anthocyanins have been reported to help maintain healthy synthesis of retinal rhodopsin and attenuate free radical impacts associated with accommodation and its muscular burden.[37]

Mirtoselect® in supporting healthy visual function

Several clinical investigations have been carried out with Indena's bilberry extract.[38-41] In particular, in a multicentric study,[38] daily use of 510 mg (three 170 mg capsules/die) of Mirtoselect® over a period of one year on 88 patients was associated with remarkable improvement of contrast sensitivity and stabilization of visual acuity leading to improved visual quality.[38]

Additionally prolonged administration (6 to 53months) of Mirtoselect® (120mg/day divided in two capsules of 60mg) in 132 patients,[42] resulted in an amelioration of the best-corrected visual acuity (measured as logMAR) and of the Visual Field (Humphrey Visual Field test) compared to the initial conditions.

Furthermore the amelioration of the best-corrected visual acuity was statistical significant also compared the control (97 patients) and *Ginkgo biloba* (103 patients) traded group, while the visual field increase could not reach statistical significance amelioration when compared to the *Gingko biloba* treated group.



Comparison of image with different contrast sensitivity.
A: image with high contrast sensitivity; B: image with low contrast sensitivity.

Bilberry extracts and night vision

Bilberry extracts were extensively investigated in the Sixties for different conditions related to visual function.

The extracts, when administered alone or in association with beta-carotene and vitamin E to healthy patients, induced a significant **improvement in night vision**, a **quicker adaption to darkness**, and a faster restoration of visual acuity following exposure to a flash light.[43-47]

Trials performed on air traffic controllers, air pilots, and car and truck drivers, showed that a bilberry anthocyanins-containing extract was able to improve night vision and the adjustment to darkness.[48-51]

Although a critical review of the available clinical studies under reduced light conditions (1964-2001) has recently been published,[52] its negative results are confounded by several factors: different products having different phytochemical compositions were used in the trials analyzed; the amount of anthocyanins administered varied considerably within the trials, and the negative outcomes were generally associated with the lowest dosages. These considerations highlight the relevance of **standardizing bilberry extracts** and using them at **clinically effective dosages**.

Pharmacokinetics

After oral administration of a single dose of 400 mg/kg in rats,[53] Indena's 36% anthocyanin bilberry extract was rapidly absorbed from the gastrointestinal tract, reaching a C_{max} value of 2.5 µg/mL anthocyanins in plasma within 15 minutes. Anthocyanins disappeared from systemic circulation within 2 hours, and underwent a rapid distribution in highly vascularized tissues due to the specific affinity to endothelial membranes, a property that has great relevance for the vaso-protective activity of anthocyanins. The elimination of bilberry anthocyanins occurs in 24 hours, mainly through the bile.

Similar results have been observed also in a human pharmacokinetic study with anthocyanins found in portal blood 5 hours after ingestion and under the detection level after 8 hours,[54] while the stomach has been reported the predominant site of Mirtoselect® anthocyanins absorption in humans[55] After a single intraperitoneal dose of 36% anthocyanin bilberry extract (200 mg/kg), anthocyanins were detected in rats kidneys, skin, liver and in the heart respectively,[56] while in another study, modelling human familial adenomatous polyposis in mice, anthocyanins were detected in intestinal mucosa at a 8.1 ng/mL concentration after oral administration of Mirtoselect®.[57]

Chemical profile

Mirtoselect® is a standardized bilberry extract containing 36% anthocyanins, and is characterized by a very **specific and consistent HPLC profile** that represents the "**fingerprint**" of the extract. Mirtoselect® is obtained exclusively from bilberry (*Vaccinium myrtillus* L.) fresh fruits harvested when ripe, between July and September.

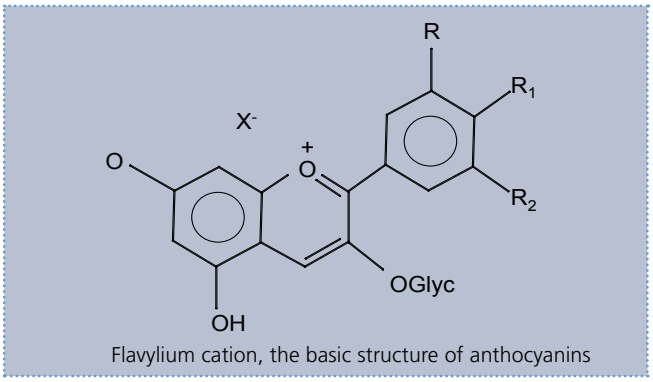
Anthocyanins and anthocyanidins

Anthocyanins (**anthocyanosides**),[58] the water-souluble pigments responisible for the deep blue color of the berries, represent the main active fraction of the numerous **biological properties** of Mirtoselect®.

Anthocyanins occur in nature as **glycosides** and their aglycones, the anthocyanidins, are derived from the 2-phenylbenzopyrylium cation, more commonly referred to as **flavylium cation**. This name emphasizes the close relationship with **flavonoids**, a class of natural products to which also anthocyanins belong.

Bilberry **anthocyanins** are **3-O glucosides**, galactosides and arabinosides of five anthocyanidins (cyanidin, delphinidin, malvidin, peonidin and petunidin).

Anthocyanidins, anthocyanins without the sugar moiety, are trace components of Mirtoselect® (≤1%) and should be considered as anthocyanins degradation products. Anthocyanidins are diagnostic of an incorrect manufacturing and/or storage of the extract.



Flavylium cation, the basic structure of anthocyanins

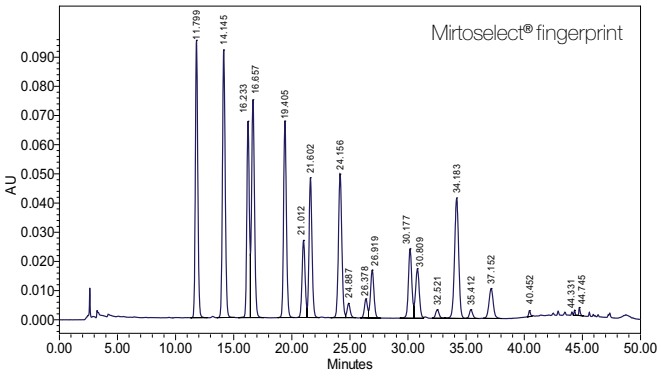
Main *V. myrtillus* anthocyanins			
Anthocyanins	R	R_1	R_2
Cyanidin 3-O-glycoside	OH	OH	H
Delphinidin 3-O-glycoside	OH	OH	OH
Malvidin 3-O-glycoside	OCH_3	OH	OCH_3
Peonidin 3-O-glycoside	OCH_3	OH	H
Petunidin 3-O-glycoside	OH	OH	OCH_3

The analytical method

A new **high-performance liquid chromatography method** was developed and validate the identification and quantification of both anthocyanins and anthocyanidins present in bilberry extract and products.[18]

The quantification procedure employs cyanidin-3-glucoside as external standard and the content of each individual anthocyanin is evaluated by means of a weight-correction factor.

Mirtoselect® specifications	
HPLC content of total anthocyanins (anthocyanosides) as such	≥ 36.0%
Spectrophotometric content of anthocyanosides as anthocyanidins	≥ 25.0%
HPLC content of free anthocyanidins	≤ 1.0%



The method is highly reproducible and, due to its high specificity, is suitable to the univocal identification of raw materials, as well as the evaluation of the phytochemical pattern of bilberry extracts, securing a high degree of **product consistency** and **quality**.

The reliability of this innovative HPLC-based method is such that it has become the official method for analyzing bilberry's identification and chemical composition in the European, Italian and US Pharmacopoeias.[22-24]

Pharmacology

The most characteristic compounds of bilberry fruits are colorful polyphenols belonging to the anthocyanin- and proanthocyanidin-classes. The pharmacological properties of these compounds are well established, and mainly, but not exclusively, related to their strong antioxidant activity. This property is at the basis, or at least contributes significantly, to vasoactive activity reported for these compounds. Most human clinical studies have focused on potential applications such as supporting vascular health, eye health and the health of the digestive tract, confirming the results obtained with cellular- and animal-models.

Antioxidant protection

Many studies have reported that bilberry anthocyanins are **potent scavengers of free radicals** such as superoxide anion[59,60] and other ROS.[61] Animal studies[62] have also shown that Mirtoselect® can support healthy kidney function. $KBrO_3$ is an environmental pollutant formed as a by-product during the ozone-based purification of drinking water. $KBrO_3$ can form free radicals that challenge the kidney, and the protective properties of Mirtoselect® result from its capacity to **improve the antioxidant capacity of renal tissues.**
By scavenging free radicals and preventing lipid peroxidation, Mirtoselect® has also been able to address liver challenge induced by oxidative stress in mice.[63]
Mirtoselect® seems effective in eye health challenges in mice[64] and has been shown to reduce levels of nitric oxide and malondialdehyde in eyes and to elevate ORAC, glutathione, vitamin C, superoxide dismutase, glutathione peroxidase activity in eyes. Moreover, the increased expression of copper/zinc superoxide dismutase, manganese superoxide dismutase, and glutathione peroxidase mRNA, indicates that administration of Mirtoselect® could support eye health by increasing levels of antioxidants.

Vasoprotection

The vasoprotective activity of bilberry anthocyanins is related to their ability to **reduce capillary permeability** and increase capillary resistance via several mechanisms, including **stimulation of mucopolysaccharides biosynthesis,**[65] inhibition of proteolytic enzymes involved in the degradation of the extravascular matrix components of the blood vessels,[66] and the interaction with collagen metabolism.[67] The stimulation of polysaccharides production is considered critical for vasoprotective activity, since mucopolysaccharides play crucial role in the physiology of perivascular tissues.

Effect on arteriolar vasomotion

Arteriolar vasomotion, the rhythmic variation of arteriolar diameter in the microvascular network, modulates the mechanism underlying the formation of interstitial fluid. Indena's standardized 36% anthocyanin bilberry extract was proven to induce arteriolar vasomotion and increase vasomotion frequency,[68] indicating that bilberry extract may prevent or control the formation of interstitial fluid, with an overall improvement of blood flow redistribution into microvascular network.

Inflammation response function

A recent study[69] on microarray-based gene expression, has shown that, in an inflammatory response function model, Mirtoselect® anthocyanins can attenuate expression levels of numerous relevant genes, while supporting other relevant genes expression levels. These observations provide a rationale for support of a healthy inflammatory response function of bilberry anthocyanins.

Concluding remarks

Mirtoselect® 36% anthocyanin bilberry extract has demonstrated its efficacy in:

- **increasing capillary resistance**
- **reducing vascular permeability**
- **exerting antioxidant activity at vascular level**
- **improving arteriolar vasomotion**
- **exerting healthy inflammatory response function activity**

The major applications investigated so far for Mirtoselect® are in the realms of vascular health and ophthalmology (eye protection at the retina level), but animal models and pilot clinical studies suggest a broader clinical profile of anthocyanins encompassing memory improvement,[70] cardiovascular health,[71,72] metabolic syndrome and overweight.[73] Mirtoselect® is used worldwide as a functional ingredient and has also been authorized as a functional food with a specific claim in Korea.[74]

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DPR0199 - 02/2012*07/2014

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