

The original bilberry extract

.....
Technology-based
standardized extract

.....
Extensive clinical and
pharmacological data
support its efficacy

.....
A safe product, devoid of
side effects

■ *Vaccinium myrtillus* L. is a deciduous small shrub growing on hilly heaths and underbrush throughout Central and Northern Europe¹⁻⁵.

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}. The fruits of *V. myrtillus* were considered a staple food for their high nutritive value, while today they represent mainly a precious delicacy. The genus *Vaccinium* includes, worldwide, **450 species**⁷.

The medicinal use of *V. 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.

Bilberry monographs, to which Indena has actively contributed, are currently present in the European, Italian and US Pharmacopoeias⁸⁻¹⁰.

Several compounds belonging to different chemical classes have been isolated from the berries of *V. myrtillus*, and the pharmacological and clinical activity of **anthocyanins (also called anthocyanosides)**, their major constituents, has been well documented in the scientific literature. **Mirtoselect®** is obtained **exclusively from the fresh fruits of *Vaccinium myrtillus* L.** harvested when ripe, and its production does not involve any chemical treatment.

Bilberry: a long-lasting story

In the early Seventies, Indena developed a standardized bilberry extract named "Bilberry 25% dry extract"¹¹. This specification was so popular to become a globally recognized reference for bilberry extracts. The standardized bilberry extract by Indena has been extensively clinically evaluated for its efficacy in vascular protection, with over 50 positive studies, including at least 25 controlled or double-blind studies.

Over the past decade, it became clear that the specification "bilberry 25%" was often applied to products that did not comply with the quality of the bilberry extract by Indena¹²⁻¹⁴.

For this reason Indena has developed an improved analytical method, originally used for the release of Indena's first registered pharmaceutical product in Italy¹⁵, and next released to the market¹². 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 countries⁸⁻¹⁰. This HPLC-based method defines the anthocyanins content of the standardized bilberry extract as **36% anthocyanins** (the glycosilated compounds). This titer corresponds to the "old" 25% specification by UV analysis, that was based on anthocyanidins (the aglycones).

Clinical Use

The traditional tale 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 led to a general interest for bilberry in ophthalmology. Although the veracity of this tale 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 in myopic patients^{16,17}.

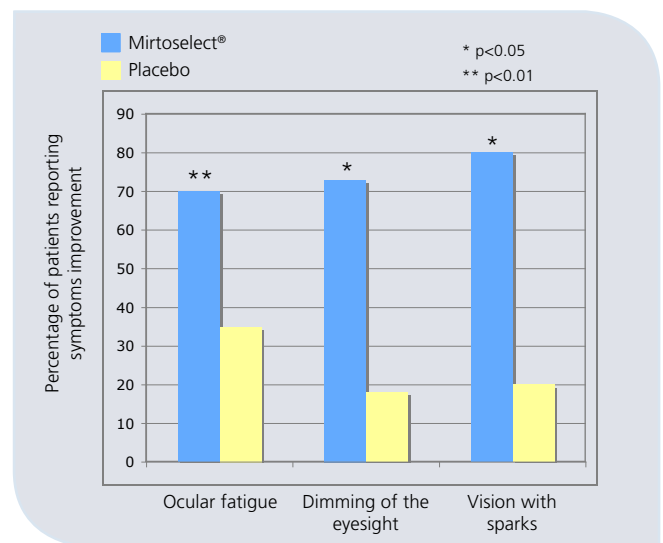
Furthermore, many pharmacological trials have confirmed the efficacy of 36% anthocyanin bilberry extract on microvascular disorders as well as in phlebology. Its efficacy in the treatment of symptoms associated with venous insufficiency has been demonstrated in randomized, double-blind, placebo-controlled clinical trials carried out on hundreds of patients¹⁸⁻²⁴.

Clinical studies on Mirtoselect® in ophthalmology

Mirtoselect® and eyesight fatigue²⁵

The administration of Mirtoselect® could help to recover the visual function in eyesight due to eye fatigue. In a cross-over, double-blind, placebo-controlled study on 20 patients treated with 250 mg of bilberry extract for 28 days, an improvement in subjective symptoms like the occurrence of vision sparks, eyesight dimming and ocular fatigue was observed in computer operators. The chart shows the percentage of patients reporting improvements in symptoms associated with eyesight fatigue: 70% reported ocular fatigue reduction, 73% an improvement of eyesight dimming and 80% a reduction of visual sparks. Other improved symptoms were lacrimation, soar eyes, headache or heavy headedness.

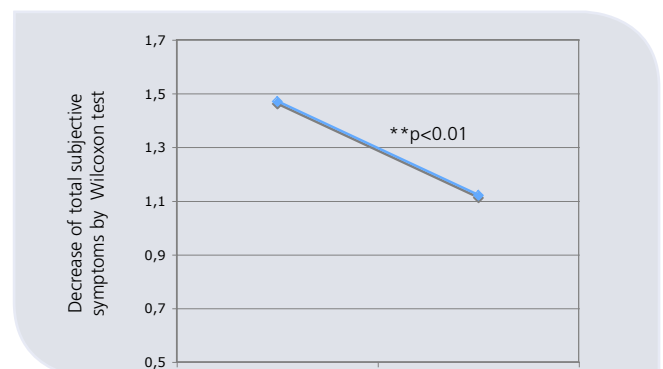
Flicker values improved significantly following the administration of bilberry anthocyanins, and an overall improvement of asthenopia could be established.



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

Mirtoselect® and eyesight recovery²⁶

In addition, a trial on 63 school children affected by pseudomyopia was carried out with a dosage of 150 mg/die of Mirtoselect® for 8 weeks. This suggests that the prolonged intake of Mirtoselect® could be useful in preventing the ocular problems related to increased eye accommodation associated to the burden of reading and computer work, activities that are typical of school education. The 36% anthocyanins bilberry extract could improve the bloodstream into the eye bulb tissues at the initial stage of myopia, activating the nutrition supply and preventing the transition from accommodative to axial myopia.



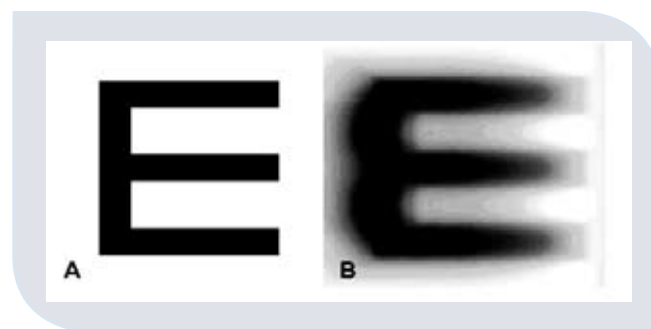
Effect of Mirtoselect® on eyesight recovery in school children affected by pseudomyopia.

Anthocyanins have been reported to accelerate the re-synthesis of retinal rhodopsin and attenuate free radical damage associated to accommodation and its muscular burden²⁷.



■ Mirtoselect® in diabetic retinopathy²⁸

Diabetic retinopathy is one of the main causes of blindness, and its incidence is rapidly increasing as diabetic patients get older. Various clinical investigations have been carried out with Indena's bilberry extract²⁹⁻³¹, in particular, in a multi-centric study, Mirtoselect® was administered to 88 patients at a dosage of 510 mg/die (three 170 mg capsules/die) over a period of one year, with a remarkable improvement of contrast sensitivity; additionally, visual acuity and macular edema were stabilized. Treatment with Mirtoselect® led therefore to an improvement of visual quality and satisfaction in nonproliferative diabetic patients.



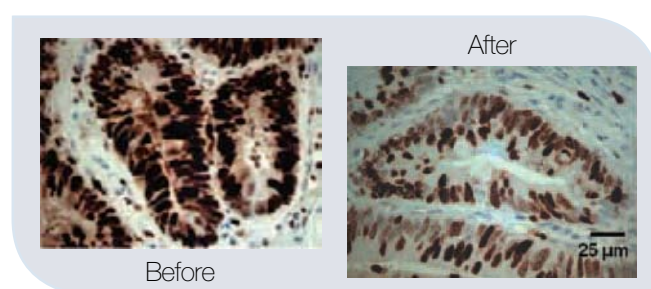
Comparison of image with different contrast sensitivity. A: image with high contrast sensitivity; B: image with low contrast sensitivity.

Clinical studies on Mirtoselect® in chemoprevention

■ Mirtoselect® in chemoprevention³²

Bilberry anthocyanins show colorectal cancer chemopreventive properties in rodent models³³. Based on these data, a clinical pilot study on Mirtoselect® for colorectal cancer chemoprevention was carried out in 25 colorectal cancer patients scheduled to undergo resection of primary tumor or liver metastases. The patients received 1.4, 2.4 or 5.6 grams of Mirtoselect® daily for 7 days before surgery. In tumor tissues, proliferation decreased by 7% compared to pre-intervention values.

Urine, blood and target tissue levels of anthocyanins were also measured, and results are consistent to the levels detected in rodent models³⁴.



Immuno-histographs of colorectal tumor tissue from a representative patient after staining for Ki-67 before and after consumption of 1.4 grams of 36% anthocyanin bilberry extract.

Bilberry extracts and night vision

Bilberry extracts were extensively investigated in the Sixties for different conditions related to an impaired visual function. The extracts, when administered alone or in association with beta-carotene and vitamin E to healthy patients with visual disorders, induced a significant **improvement in night vision**, a **quicker adaption to darkness**, and a faster restoration of visual acuity following exposure to a flash light³⁵⁻³⁹.

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 darkness⁴⁰⁻⁴².

Although a critical review of the available clinical studies under reduced light conditions (1964-2001) has recently been published⁴³, 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 rats⁴⁴, the 36% anthocyanin bilberry extract was rapidly absorbed from the gastrointestinal tract, reaching a C_{max} value of 2.5 mcg/mL anthocyanins in plasma within 15 minutes. Anthocyanins disappeared from blood 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

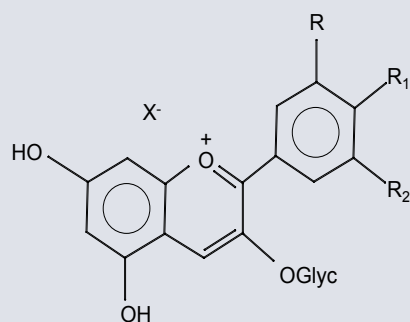
pharmacokinetic study with anthocyanins found 5 hours after ingestion in the portal blood and under the detection level after 8 hours³².

After a single intraperitoneal dose of 36% anthocyanin bilberry extract (200 mg/kg), anthocyanins were detected in rats in kidneys, skin, liver and in the heart respectively⁴⁵, while in another study in mice, modelling human familial adenomatous polyposis, after oral administration of Mirtoselect® anthocyanins were detected in intestinal mucosa at a 8.1 ng/mL concentration³³.

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



Flavylium cation, the basic structure of anthocyanins

The main actives accounting for the various **biological properties** of Mirtoselect® are **anthocyanins** (anthocyanosides).

The term anthocyanin, originally coined to designate the substance responsible for the color of cornflower (from the greek *anthos*, flower, and *kuanos*, blue) refers to a class of water-soluble pigments responsible for red, pink, mauve, purple, blue and violet color of most flowers and fruits⁴⁶.

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

Main <i>V. myrtillus</i> 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

Mirtoselect® specifications	
HPLC content of total anthocyanins (anthocyanosides) as such	$\geq 36.0\%$
Spectrophotometric content of anthocyanosides as anthocyanidins	$\geq 25.0\%$
HPLC content of free anthocyanidins	$\leq 1.0\%$

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 products¹².

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.

The method is endowed with a **good reproducibility** and, due to its high specificity, is suitable to the univocal identification of the botanical raw materials used for manufacturing, and for the evaluation of the phytochemical pattern of bilberry extracts, securing a high degree of **product consistency** and **quality**.

The reliability of this innovative method of analysis is such that it has become the official method for bilberry both in the European and Italian Pharmacopoeias as well as in the USP⁸⁻¹⁰.

Pharmacology

The most characteristic compounds of bilberry's fruits are colorful polyphenols belonging to the anthocyanin- and proanthocyanidin-classes. The pharmacological properties of these compounds are nowadays 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 the anti-inflammatory, vasoactive, hypolipidemic, hypoglycemic, chemopreventive activity reported for these compounds. Most human clinical studies have focused on only few potential applications (vasculopathies of different nature, retinal diseases and ulcerations 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** like superoxide anion^{47,48} and other ROS⁴⁹. Recent animal studies⁵⁰ have also shown that Mirtoselect[®] can protect kidneys from the damage induced by potassium bromate. KBrO₃ is an environmental pollutant formed as a by-product during the ozone-based purification of drinking water. KBrO₃ can form free radicals that trigger harmful degenerative processes in the kidney tissue, and the protective properties of Mirtoselect[®] are the result of an **improved antioxidant capacity of renal tissues**.

By scavenging free radicals and preventing lipid peroxidation, Mirtoselect[®] has also been able to alleviate **liver damage** induced by oxidative stress in mice⁵¹.

In a recent study in mice Endotoxin-induced **uveitis** (EIU)⁵², Mirtoselect[®] 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, Mirtoselect[®] increased expression of copper/zinc superoxide dismutase, manganese superoxide dismutase, and glutathione peroxidase mRNA, indicating that Mirtoselect[®] could attenuate inflammation-induced oxidative stress in EIU 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 by means of several mechanisms, includ-

ing **stimulation effect of the biosynthesis of mucopolysaccharides**⁵³, the inhibition of proteolytic enzymes⁵⁴, and the interaction with collagen metabolism⁵⁵. The stimulation of polysaccharides production is considered critical for this activity, since mucopolysaccharides play an important role in the physiology of perivascular tissues.

■ *Effect on arteriolar vasomotion*

Arteriolar vasomotion is a rhythmic variation of the arterioles diameter in the microvascular network that modulates the mechanism underlying the formation of interstitial fluid. Colantuoni *et al*⁵⁶ studied the effect of a standardized 36% anthocyanin bilberry extract on arteriolar vasomotion in two different experimental models, namely the induction of vasomotion in cheek pouch arterioles, and the increasing of vasomotion frequency in the skeletal muscle arteriolar network. These findings indicate that bilberry extract may prevent or control the formation of interstitial fluid, with an overall contribution to blood flow redistribution into microvascular network.

■ *Chemoprevention*

Recent investigations³³ on the chemopreventive properties of bilberry anthocyanins have shown that Mirtoselect[®] can reduce, in a dose-dependent way, the development of intestinal adenoma in rodents. The activity was related to a high concentration of anthocyanins in the target organs, sharply contrasting with very low systemic concentrations detected in plasma. A possible mechanism of action has been recently proposed⁵⁷ based on the interaction of anthocyanins with several tyrosine kinases believed to play a crucial role in carcinogenesis and tumor progression. Mirtoselect[®] showed a broad spectrum tyrosine kinase inhibitory activity, suggesting potential chemopreventive activity.

■ *Inflammation*

A very recent study⁵⁸ on microarray-based gene expression has shown that, in an inflammatory model, Mirtoselect[®] anthocyanins can attenuate the expression level of numerous pro-inflammatory genes, restoring at the same time that of anti-inflammatory genes. These observations provide a rationale for the anti-inflammatory activity of bilberry anthocyanins.

Concluding remarks

Numerous studies have been conducted to evaluate the pharmacological activities of bilberry anthocyanins, proving the efficacy of the 36% anthocyanin bilberry extract Mirtoselect[®] to:

- **increase capillary resistance**
- **reduce abnormal vascular permeability**
- **exert antioxidant activity at vascular level**
- **improve arteriolar vasomotion**
- **exert chemopreventive activity**
- **exert anti-inflammatory activity**

The major applications investigated so far for Mirtoselect[®]

are in the realms of vascular pathologies (chronic venous insufficiency) and ophthalmology (eye protection at the retina level), but animal models and pilot clinical studies suggest a broader clinical profile of anthocyanins, that encompasses memory improvement⁵⁹, cardiovascular health⁶⁰⁻⁶¹, metabolic syndrome and obesity⁶².

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