Mirtoselect®
THE ORIGINAL BILBERRY EXTRACT
(FROM Vaccinium myrtillus L.)

The only bilberry extract with proven efficacy

High technology in the extractive process

Wide pharmacological and clinical documentation

science is our nature™
Vaccinium myrtillus L. is a deciduous small shrublet belonging to the Ericaceae family, which grows on hilly and mountainous regions of Europe, Asia and North America. The genus Vaccinium comprises nearly 200 species, but it is beyond doubt Vaccinium myrtillus has been written about since the Middle Ages due to its many and varied therapeutic applications in traditional medicine. Several compounds belonging to different chemical classes have been isolated from Vaccinium myrtillus berries and particularly the pharmacological and clinical activities of anthocyanosides have been deeply and well documented in scientific literature.

**HIGH TECHNOLOGY MEANING EFFICACY**

Mirtoselect® is obtained exclusively from Vaccinium myrtillus and flavonoids, specifically anthocyanosides, constitute the bilberry’s active fraction. Mirtoselect® is standardized to contain 36% anthocyanosides (equivalent to 25% anthocyanidins) and it is characterized by a very specific and reproducible HPLC profile that may be defined as the “fingerprint” of the extract (Fig. 1). Additional investigations, such as a multivariate analysis comparing mathematically several parameters and recently the Near Infrared Spectroscopic analysis, enable the precise identification of the Mirtoselect® extract among its controtypes. Indena’s Mirtoselect® is the only standardized bilberry extract whose pharmacological, pharmacokinetics and clinical activities(1) have been the subject of scientific research/investigation.

**PHARMACOKINETIC DATA**

Mirtoselect® is well absorbed by the oral route, giving plasma levels sufficiently elevated to guarantee the biological effects(1,2). In fact, after oral administration of a single dose of 400 mg/kg in rats, Mirtoselect® is rapidly absorbed from the gastrointestinal tract, raising plasma peek levels of anthocyanosides (2.5 mcg/ml) within 15 min (Fig. 2). Anthocyanosides disappear from the systemic circulation in about 2 hours and undergo a rapid distribution to the high vascularized tissues thanks to its particular affinity with the microvessels wall (selective binding with phospholipidic constituents of endotelial membranes; Fig. 3). This property is typical of anthocyanosides and has great relevance in exerting their biological activities on microvessels(3). The elimination of anthocyanosides occurs mainly through the bile after 24 hours.

**PHARMACOLOGICAL ACTIVITIES**

The pharmacological effects of anthocyanosides are mainly evident on microcirculation where different activities have been reported:

**vasoprotective action**

This activity is related to the ability of the anthocyanosides both to reduce capillary permeability and to increase capillary resistance, working through several different mechanisms of action:

- stimulation of the biosynthesis of mucopolysaccharides, constituents of perivascular tissues, where are recognised as playing an important role in maintaining the integrity of microvessels(6);
- inhibition of proteolytic enzymes, such as elastase, which are involved in the degradation of collagen and other components of the extravascular matrix of the smallest blood vessels(5);
- antioxidant activity that gives protection to the integrity of microvessels against free radicals damages, particularly after ischemia - reperfusion injury in the microvascular network(6).

These effects prevent the formation and promote the regression of hard exudates (index of altered permeability of capillaries) and microhaemorrhages (index of altered resistance of capillaries) in some tissues (such as the retina) where the microvascular network is significantly compromised during very common pathologies (diabetes, arterial hypertension). The vasoprotective action of the anthocyanosides has been shown using a large number of experimental models and in different parts of the body, including the Central Nervous System and the eye(5). This interesting ophthalmic property has been demonstrated in an experimental study where anthocyanosides were able to reduce the abnormal permeability of the vessels of the rabbit eye ciliary body (Fig. 4).
activation of arteriolar vasomotion
Anthocyanoside extract is reported to increase arteriolar vasomotion, the rhythmic variation in arteriolar diameter in the microvascular network (Fig. 5). The stimulation of arteriolar vasomotion may improve microvascular blood flow, promoting the redistribution of blood flow and decreasing the formation of interstitial fluid. These findings also indicate that Mirtoselect® may be beneficial in increasing the supply of nutrients to the tissues with a very active metabolism (such as the retina, involved in a continuous regeneration of rhodopsin) and reducing the effects of increased vascular permeability, including localized oedema.

stimulation of regeneration rate of rhodopsin
Experimental studies have shown that anthocyanosides are able to improve the visual function, probably by increasing the regeneration rate of rhodopsin present on the retina. In fact, excessive stimulus of light over long hours (i.e. heavy exposure to computer or TV screens) can accelerate the decomposition of rhodopsin, resulting in the shortage of this pivotal substance for vision, giving rise to a decline in visual function.

CLINICAL EFFICACY
The results of pharmacological tests on anthocyanosides have suggested further clinical studies to evaluate the efficacy of Mirtoselect® in the treatment of microvascular disorders in ophthalmology and phlebology. In addition, the potential ability of anthocyanosides in sight improvement has been investigated in adults and children suffering from ocular fatigue due to overuse of eyes.

Mirtoselect® in diabetic and hypertensive retinopathy
Diabetes and hypertension are known as clinical conditions that lead to heavy structural abnormalities in the microvascular network of the retina. An increase of vascular permeability, the formation of localized oedema, along with retinal microhaemorrhages have been shown to be a significant part of the retinopathy. The pivotal clinical goal is to control the progression of retinopathy, since this is currently considered to constitute a major cause of blindness in industrialised countries. Several randomized, double-blind, placebo-controlled clinical trials, have been carried out in patients with either diabetic or hypertensive vascular retinopathy. Patients received a branded drug containing Mirtoselect® (Tegena) generally at doses of 160 mg os twice daily over a 3-6 month period.

Ophthalmoscopic examinations, including fundus fluorescein angiography performed both before and after the study, showed a significant reduction of retinal microhaemorrhages and a regression of retinal localised oedema following treatment with bilberry extract. These findings confirm the vasoprotective properties of anthocyanosides from Vaccinium myrtillus by clinical investigations.

Mirtoselect® and visual acuity
During the Second World War, the empirical observation that ingestion of bilberry jam (made from Vaccinium myrtillus berries) improved the sight of RAF pilots on night flights led to an interest in their ophthalmologic properties. Subsequently, the effect of anthocyanosides in improving vision has been evaluated by instrumental techniques, such as computerised perimetry, showing that Mirtoselect® really can improve the retinal sensitivity in myopic patients. More recently, some investigators reported that the administration of Mirtoselect® could help to recover reduced visual function in eyesight due to overuse of the eyes. These studies reported an improvement in subjective symptoms such as vision with sparks, dimming of the eyesight, ocular fatigue in computer operators, office workers and students. In addition, a significant visual acuity recovery has been shown in school children with pseudomyopia, suggesting that a long-term intake of bilberry extract can be useful in preventing an advancement to axial myopia.

Mirtoselect® in chronic venous insufficiency of the lower limbs
Patients suffering from chronic venous insufficiency of the lower limbs complain of symptoms due to altered capillary permeability and fragility. The vasoprotective activity of anthocyanosides contained in Mirtoselect® leads to a rapid and significant improvement of symptoms such as limb oedema, heaviness, cramp-like pain (Fig. 7 and 8) and dysesthesic skin phenomena (superficial petechiae on the thigh). The efficacy of Mirtoselect® in the treatment of symptoms associated with venous insufficiency has been shown in different clinical trials, mainly randomized, double-blind and placebo-controlled, on hundreds of patients affected by this disease.


**SAFETY**

Preclinical studies in animals on acute and chronic toxicity have shown that Mirtoselect® has an excellent safety and tolerability profile. In dogs, a single oral dose of 3,000 mg/kg did not induce any sign of adverse effects as well as the oral administration of 80-320 mg/kg daily over a period of six months. In all the clinical trials, including long-term treatment extending up to six months in duration carried out with the oral administration of 480 mg os daily, no adverse effects were found in treated patients. A post-marketing surveillance study in more than 2000 patients has been carried out to assess the tolerability profile over several months of treatment with a branded drug containing Mirtoselect®. The result analysis has shown the total absence of clinically relevant adverse effects. Confirming its excellent safety profile, Mirtoselect® has been studied and proposed for the treatment of symptoms associated with venous insufficiency during pregnancy.

**MIRTOSELECT® AND THERAPEUTICS**

The pharmacological and clinical findings suggest several clinical applications of Mirtoselect® in ophthalmology and phlebology:

- treatment of fragility and altered permeability in the microvascular network of the retina associated with diabetes and arterial hypertension. The vasoprotective activity promotes the regression or disappearance of retinal microhaemorrhages and exudates, counteracting the progress of retinopathy.
- treatment of ocular fatigue due to excessive stimulus of light over long hours for example by heavy PC or TV monitor screen viewing or in myopic patients with a decline in visual function due to overuse of the eyes. In fact, anthocyanosides from Vaccinium myrtillus restore vision in a rapid manner accelerating resynthesis of rhodopsin present on the retina, a chromoprotein with a pivotal function in recognizing the things visually. In addition, Mirtoselect® increases the blood supply to the retina, apporting in this way a big amount of nutrients for its functionality.
- treatment of symptoms associated with chronic venous insufficiency of the lower limbs. Mirtoselect® provides a rapid relief of limb oedema, feeling of heaviness, cramp-like pain, thanks to the reduction of capillary permeability and a vasoprotective action.

**COMPATIBILITY OF MIRTOSELECT® WITH OTHER ACTIVE AGENTS**

Mirtoselect®’s anthocyanosides can be used to produce multi-component formulations containing other active substances (i.e. vitamin E, vitamin C, β-carotene, flavonoids from other sources) for a synergic vasoprotective action on microcirculation. For restoring vision it may be interesting to associate anthocyanosides with agents that act synergically in accelerating the resynthesis of rhodopsin (i.e. β-carotene or vitamin A).

**CONCLUSION REMARKS**

Numerous studies have been conducted to identify the pharmacological activities of anthocyanosides from Vaccinium myrtillus berries and to assess their clinical efficacy. Most pivotal studies have been carried out with Mirtoselect®, a standardized bilberry fruit extract containing 36% anthocyanosides. Therefore, Mirtoselect® is the only bilberry extract with proven efficacy. Pharmacological studies have shown that Mirtoselect® is effective in increasing capillary resistance, reducing abnormal vascular permeability and performing antioxidant activity at vascular level. These pharmacological findings have suggested a clinical application in the treatment of vascular disorders of the retina due to diabetes and hypertension (retinopathy) and in the management of symptoms associated with chronic venous insufficiency. Several randomized, double-blind and placebo-controlled clinical trials have clearly shown the significant efficacy of Mirtoselect® in hundreds of patients treated. In addition, Mirtoselect® promotes the resynthesis of retinal pigments (rhodopsin) and there is clinical evidence that the intake of bilberry extract is useful for the recovery of visual acuity and relief of eye fatigue symptoms in case of eye overuse.

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**Fig. 8** Significant reduction in the severity of symptoms in the chronic venous insufficiency of the lower limbs after 30 day treatment with Mirtoselect®.

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**References**

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