Bilberry

Vaccinium myrtillus L.

[Fam. *Ericaceae*]

Overview

Bilberry is the name of a small European blueberry. Dietary supplements made from the standardized extract of bilberry have become popular in the U.S. over the past decade. Sales in the mainstream retail markets ranked 13th of all herbs in 2000. The standardized, concentrated extract of bilberry fruit is used by consumers primarily for ocular, microcirculatory and vascular-related disorders.

Primary Uses

- Retinopathy, hypertensive
- Retinopathy, diabetic
- Peripheral vascular disorders, blood purpuras
- Venous insufficiencies, varicose veins, capillary fragility, kidney capillary fragility
- Diarrhea (the bilberry fruits, not the standardized extracts)

Other Potential Uses

- Blindness, night and day
- Cataracts
- Macular degeneration
- Retinitis pigmentosa
- Retinopathy, hemorrhagic
- Dysmenorrhea
- Reduction of surgical bleeding

Pharmacological Actions

Astringent; antiplatelet aggregation; collagen-stabilizing activity; decreased vascular permeability associated with injury.

Dosage and Administration

Ranges from 160–480 mg daily depending on the conditions being treated. Therapeutic benefits appear to take effect in 4–8 weeks.

DRIED, RIPE FRUIT: 20–60 g daily (4–8 g with water, several times daily).

INFUSION/DECOCTION: 20–60 g daily.

COLD MACERATE: 20–60 g daily.

GARGLE: Mouthwash containing 10% decoction.

FLUID EXTRACT: 2–4 ml, 3 times daily [1:1 (*g/ml*)].

FOR DIARRHEA: Crude preparations (non-standardized) for no more than 3–4 days.

DRY STANDARDIZED EXTRACT: (25% anthocyanidins) 80–160 mg, 3 times daily.

Contraindications

None known.

PREGNANCY AND LACTATION: No known restrictions.

Adverse Effects

None known (at therapeutic dosages).

Drug Interactions

Pharmacological studies suggest that very high doses (>170 mg anthocyanins per day for 30–60 days) may interact with warfarin or other antiplatelet drugs. Bilberry (form unstated) reportedly may reduce insulin requirements; therefore, conventional antidiabetic therapy would need close monitoring or dosage adjustment.

Clinical Review

Fifteen clinical studies on bilberry that included a total of 694 participants were reviewed. All but one of the studies demonstrated positive effects for indications, including various ocular conditions (night/day vision and retinopathy), and vascular conditions, including venous insufficiencies and micro- and macroperipheral circulation. Two double-blind, placebo-controlled (DB, PC) studies focused on retinopathy and confirmed results of two earlier open studies. One DB, PC study on nighttime vision confirmed preliminary findings of five previous open studies. A recent DB, PC, crossover study failed to find that bilberry extract (25% anthocyanosides) had an effect on night vision or night contrast sensitivity. One DB, PC study conducted on peripheral vascular disorder concluded positive results for Raynaud's sufferers. Another DB, PC study on chronic dysmenorrhea was positive and further supports pharmacological findings. One single-blind (SB), PC study on venous insufficiencies in 60 participants further supported the findings of four similar studies, including two open studies and two using pregnant subjects. Bleeding was investigated in a SB, PC study finding bilberry reduced intra- and postoperative bleeding and prevented subsequent hemorrhaging. Another study focused on bleeding associated with intrauterine devices.

Bilberry

Vaccinium myrtillus L.
[Fam. *Ericaceae*]

Overview

Bilberry is the name of a small, European blueberry. The standardized, concentrated extract of bilberry fruit is used by consumers mainly for disorders of the eyes and circulatory system. Sales in the mainstream retail markets ranked 13th of all herbs in 2000. Some concentrated extracts of the berry are standardized for an exact amount of water-soluble substances called anthocyanidins.

Uses

Visual problems such as circulatory disorders of the retina; vein and circulatory disorders, including varicose veins, inadequate vein strength, and fragile capillaries.

Dosage

Ranges from 160–480 mg daily depending on the conditions being treated. Therapeutic benefits appear to take effect in 4–8 weeks.

FOR DIARRHEA: Non-standardized preparations for no more than 3–4 days.

DRIED, RIPE FRUIT: 20–60 g daily (4–8 g with water, several times daily).

INFUSION/DECOCTION: 20–60 g daily.

COLD MACERATE: 20–60 g daily.

GARGLE: Mouthwash containing 10% decoction.

FLUID EXTRACT: 2–4 ml, 3 times daily [1:1 (*g/ml*)].

DRY STANDARDIZED EXTRACT: 80–160 mg, 3 times daily [25% anthocyanidins].

Contraindications

None known.

PREGNANCY AND LACTATION: None known.

Adverse Effects

Bilberry is not known to cause adverse effects in normally recommended therapeutic doses.

Drug Interactions

There are no known drug interactions in therapeutic doses. However, very high doses (more than 170 mg anthocyanins daily for 30–60 days) may interact with anticoagulating drugs such as warfarin (Coumadin, Sofarin). Bilberry reportedly may reduce daily insulin requirements. Patients who are simultaneously taking antidiabetic medications and bilberry may need to be monitored or have the dosage of their antidiabetic drugs adjusted.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

AMERICAN BOTANICAL COUNCIL

Bilberry

Vaccinium myrtillus L.

[Fam. *Ericaceae*]

Overview

Bilberry is the name of a small European blueberry. Dietary supplements made from the standardized extract of bilberry have become popular in the United States over the past decade. Sales in the mainstream retail markets ranked 13th of all herbs in 2000 (Blumenthal, 2001). The standardized, concentrated extract of bilberry is used by consumers to help treat or prevent ocular, microcirculatory, and vascular-related disorders. Bilberry *leaf* extract (not the fruit that is covered in this monograph) was used as a treatment for diabetes before the availability of insulin. It was found effective in adult onset diabetes as a method of reducing glycosuria and postprandial hyperglycemia (Allen, 1927). For that reason, the *leaf* extract is contraindicated for diabetes patients taking insulin (Bailey and Day, 1989).

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Description

Bilberry preparations consist of the whole, dried, ripe, black or bluish-black fruit of *Vaccinium myrtillus* L. [Fam. *Ericaceae*]. Some concentrated extracts are standardized to anthocyanosides, calculated as 25% anthocyanidins, but may actually contain about 37% by weight (Pizzorno and Murray, 1999).

Primary Uses

Gastrointestinal

- Diarrhea: The German Commission E approved crude (i.e. non-concentrated) fruit preparations for acute diarrhea (Blumenthal *et al.*, 1998), particularly in children (Blumenthal *et al.,* 1998; Ofek *et al.,* 1996)

Ophthalmic

- Retinopathy, hypertensive (Repossi *et al.,* 1987), and diabetic (Ghiringhelli *et al.,* 1978; Treviso *et al.,* 1979; Scharrer *et al.,* 1981; Grismondi *et al.,* 1981; Orsucci *et al.,* 1983; Perossini *et al.,* 1987; Repossi *et al.,* 1987)

Vascular

- Peripheral vascular disorders and blood purpuras (Allegra *et al.,* 1982)
- Venous insufficiencies (Gatta *et al.,* 1988; Teglio *et al.,* 1987), varicose veins (Ghiringhelli *et al.,* 1978), capillary fragility (Coget and Merlen, 1980; Grismondi *et al.,* 1980; Mian *et al.,* 1977; Neumann, 1973; Treviso *et al.,* 1979), and kidney capillary fragility (Pennarola *et al.,* 1980)

Other Potential Uses

- Blindness, night and day (Jayle *et al.,* 1965; Gloria and Peria, 1966; Sala *et al.,* 1979; Caselli, 1985; Vannini *et al.,* 1986; Zavarise *et al.,* 1987)
- Cataracts (Bravetti *et al.,* 1989)
- Gargle for inflamed oral and pharyngeal mucous membranes (Blumenthal *et al.*, 1998)
- Macular degeneration, retinitis pigmentosa, hemorrhagic retinopathy (Scharrer and Ober, 1981)
- Dysmenorrhea (Colombo and Vescovini, 1985)
- Reduction of intra- and post-operative bleeding (Gentile *et al.,* 1987; Cerutti *et al.,* 1984)

Dosage

Crude Preparations

DRIED, RIPE FRUIT: 20–60 g daily (4–8 g with water, several times daily) (Braun *et al.*, 1993; Meyer-Buchtela, 1999; Wichtl and Bisset, 1994).

INFUSION/DECOCTION: 20–60 g daily. The berries are prepared by placing 5–10 g crushed, dried fruit in 150 ml cold water. This mixture is boiled for approximately 10 minutes; then strained while hot. The preparation is drunk cold several times daily until the diarrhea subsides (Braun *et al.*, 1993; Meyer-Buchtela, 1999; Wichtl and Bisset, 1994).

COLD MACERATE: 20–60 g daily. The berries are prepared by soaking 5–10 g crushed dried fruit in 150 ml cold water for 2 hours, allowing the fruit to swell. The preparation is drunk cold several times daily (Braun *et al.*, 1993; Meyer-Buchtela, 1999; Wichtl and Bisset, 1994).

GARGLE: Mouthwash containing 10% decoction (prepared as described above) for local application in the treatment of mild inflammation of oral and pharyngeal mucous membranes (Blumenthal *et al.*, 2000).

FLUID EXTRACT: 1:1 (*g/ml*), 2–4 ml, 3 times daily (Anderhuber, 1991; Cunio, 1993).

Standardized Preparations

DRY STANDARDIZED EXTRACT: (25% anthocyanidins) 80–160 mg, 3 times daily (Pizzorno and Murray, 1999).

NOTE: Doses may range from 160–480 mg daily depending on the conditions being treated (see the following table, "Clinical

Studies on Bilberry"). Therapeutic benefits appear to take effect in 4–8 weeks.

Duration of Administration

Crude Preparations

DIARRHEA: Not more than 3–4 days.

Standardized Preparations

VASCULAR AND OCULAR-RELATED DISORDERS: 2–6 months depending on the condition.

Chemistry

Dried bilberries contain 5–10% catechins (tannins), ca. 30% invertose (invert sugar) (Schulz *et al.,* 2001), and flavonoids. Bilberry contains a small amount of anthocyanosides (0.1–0.25% in fresh fruit) consisting of 3-O-glycosides of cyanidin, delphinidin, malvidin, peonidin, and petunidin (Baj *et al.*, 1983), and proanthocyanidins B1-B4 (Bruneton, 1999).

Pharmacological Actions

Crude Preparations

Astringent (Blumenthal *et. al.*, 2000).

Standardized Preparations

Human

Anti-platelet aggregation (Pulliero *et al.*, 1989) (*ex vivo*); collagen-stabilizing activity (Mian *et al.*, 1977); decreased vascular permeability associated with injury (Mian *et al.*, 1977).

Animal

Antiplatelet aggregation (Morazzoni and Magistretti, 1990; Zaragoza *et al.*, 1985; Bottecchia *et al.*, 1987); anti-ulcer (Cristoni and Magistretti, 1987); decreased capillary fragility (anti-inflammatory activity) (Detre *et al.*, 1986; Lietti *et al.,* 1976); collagen-stabilizing (Detre *et al.*, 1986); vascular smooth muscle relaxant (Bettini *et al.*, 1984a; Bettini *et al.*, 1984b); vascular permeability regulator (Detre *et al.*, 1986; Lietti and Forni, 1976); increased regeneration of rhodopsin (a light-sensitive pigment found in rods and retina) (Alfieri *et al.*, 1966; Cluzel *et al.*, 1969).

In vitro

Antioxidant (Meunier *et al.*, 1989); free radical scavenger (Pietta *et al.*, 1998; Martin-Aragon *et al.*, 1998); inhibits cAMP phosphodiesterases (Ferretti *et al.*, 1988); chemopreventative (Bomser *et al.*, 1996); inhibits lipid peroxidation (Meunier *et al.*, 1989).

NOTE: The pharmacological actions — antioxidant, anti-inflammatory, decreases in capillary permeability, and stabilization of collagen — are further supported by research conducted on flavonoids in general (Gabor, 1972; Kuhnau, 1976; Havsteen, 1983; Monboisse *et al.,* 1983).

Mechanism of Action

- Inhibits enzymatic cleavage of collagen by enzymes secreted by leukocytes during inflammation (Mian *et al.*, 1977)
- Increases the endothelium barrier effect through stabilizing the membrane phospholipids and increasing the biosynthesis of the acid mucopolysaccharides of the connective ground substance, thus restoring the altered mucopolysaccharide pericapillary sheath (Mian *et al.*, 1977)
- Decreases basement membrane collagen hydrolysis by significantly reducing permeability of the blood-brain barrier (BBB), and increases recovery rate of the BBB caused by permeability-increasing agents (Robert *et al.*, 1977)
- Prevents the liberation of lactate dehydrogenase in heart, plasma, and cardiac isoenzymes (Marcollet *et al.,* 1970)
- May result in retinal protection due to the inhibition of retinal phosphoglucomutase and glucose-6-phosphatase (Cluzel *et al.*, 1969)
- Reduces microvascular impairments due to ischemia reperfusion injury, with preservation of endothelium, attenuation of leukocyte adhesion, and improvement of capillary perfusion (Bertuglia *et al.*, 1995)
- Produces dose-dependent inhibition of platelet aggregation and clot retraction (Bottecchia, 1987)

Contraindications

None known.

PREGNANCY AND LACTATION: No known restrictions.

Adverse Effects

None known (at therapeutic doses).

Drug Interactions

None known. It has been inferred, based on pharmacological studies, that very high doses (>170 mg anthocyanins per day for 30–60 days) may interact with warfarin or other antiplatelet drugs (Bone and Morgan, 1997). *Leaf only*: There have also been claims that bilberry *leaf*, as mentioned in the overview, may reduce insulin requirements. Therefore, conventional antidiabetic therapy would require close monitoring or adjustment (De Smet *et al.,* 1993; Bailey and Day, 1989).

American Herbal Products Association (AHPA) Safety Rating

CLASS 1: Can be safely consumed when used appropriately (McGuffin *et al.*, 1997).

Regulatory Status

AUSTRIA: Dried fruit official in the 1990 *Austrian Pharmacopoeia*, 1991 Addendum II (Meyer-Buchtela, 1999; ÖAB, 1991; Wichtl and Bisset, 1994).

CANADA: Multiple-ingredient Traditional Herbal Medicines (THMs) containing bilberry, in tea infusion form, and homeopathic mono-preparations of bilberry are scheduled OTC drugs requiring premarket registration and assignment of a drug identification number (DIN) (Health Canada, 2001).

FRANCE: Fresh or dried fruits are permitted for oral or topical use (Bruneton, 1999).

GERMANY: Dried fruit, for tea infusions and other equivalent galenical dosage forms, is an approved nonprescription drug of the German Commission E monographs (Blumenthal *et al.*, 1998). Dried fruit is official in the *German Drug Codex* supplement to the *German Pharmacopoeia* (DAC, 1998). Bilberry dried-fruit tea is an approved nonprescription drug listed in the *German Standard License* (St. Zul.) monographs (Braun *et al.*, 1993). The fresh, ripe fruit for preparation of hydro-alcoholic mother tincture and liquid dilutions is an official drug of the *German Homeopathic Pharmacopoeia* (GHP, 1993).

ITALY: Dried hydro-alcoholic extract is listed in the *Italian Pharmacopoeia* (Morazzoni and Bombardelli, 1996).

SWEDEN: Classified as foodstuff (De Smet *et al.*, 1993). As of January 2001, no bilberry products are listed in the Medical Products Agency (MPA) "Authorised Natural Remedies" (MPA, 2001).

SWITZERLAND: Dried fruit is official in the *Swiss Pharmacopoeia* (Meyer-Buchtela, 1999; Ph.Helv.VII, 1987–1997; Wichtl and Bisset, 1994). A semipurified extract (Myrtaven®), standardized to 58 mg anthocyanosides per capsule, is a Category C nonprescription drug with sale limited to pharmacies (Morant and Ruppanner, 2001).

U.K.: Not listed in *General Sale List* (GSL). No monograph in the *British Pharmacopoeia*.

U.S.: Dietary Supplement (USC, 1994). Tincture of the ripe berries is a Class D over-the-counter drug of the *Homeopathic Pharmacopoeia of the United States* (HPUS, 1993).

Clinical Review

Fifteen studies are outlined in the following table, "Clinical Studies on Bilberry," including a total of 694 participants. All but one of the studies (Muth *et al.*, 2000) demonstrate positive effects for indications, including various ocular conditions (night/day vision and retinopathy), and vascular conditions, including venous insufficiencies and micro- and macroperipheral circulation. Two double-blind, placebo-controlled (DB, PC) studies (Perossini *et al.*, 1987; Repossi *et al.*, 1987) focused on retinopathy and confirmed results of two earlier open studies (Orsucci *et al.*, 1983; Scharrer and Ober, 1981). One DB, PC study (Vannini *et al.*, 1986) on nighttime vision confirmed preliminary findings of five previous open studies (Jayle and Auber, 1964; Jayle *et al.*, 1965; Gloria and Peria, 1966; Sala *et al.*, 1979; Terrasse *et al.*, 1966). A recent DB, PC, crossover study (Muth *et al.*, 2000) failed to find an effect of a bilberry extract (25% anthocyanosides) on night vision or night contrast sensitivity. One DB, PC study conducted on peripheral vascular disorder (Allegra *et al.*, 1982) concluded positive results for Raynaud's sufferers. Another DB, PC study (Colombo and Vescovini, 1985) on chronic dysmenorrhea was positive and further supports pharmacological findings (Bettini *et al.*, 1984a, Bettini *et al.*, 1984b). One single-blind, PC study on venous insufficiencies in 60 participants (Gatta *et al.*, 1988) further supported the findings of four similar studies, including two open studies (Ghiringhelli *et al.*, 1977; Mian *et al.*, 1977), and two using pregnant subjects (Teglio *et al.*, 1987; Grismondi *et al.*, 1980). Bleeding was investigated in a SB, PC study (Gentile *et al.*, 1987), finding bilberry reduced intra- and postoperative bleeding and prevented subsequent hemorrhaging. Another study (Cerutti *et al.*, 1984) focused on bleeding associated with intrauterine devices. The most comprehensive review of research and clinical information on bilberry was compiled by Morazzoni and Bombardelli (1996).

Branded Products*

Difrarel 100™: Laboratoires Chibret / c/o Societe Anonyme Corporation / 200 Boulevard Etienne-Clementel Clermont-Ferrand / Puy-de-Dome / France. No product information available; no longer manufactured.

Myrtocyan®: Indena S.p.A. / Viale Ortles 12 / 20139 Milano / Italy / Tel: +39-02-57-4961 / Fax: +39-02-57-4046-20 / Email: indenami@tin.it. Extract standardized to 25% anthocyanidins containing 36% anthocyanosides.

Tegens™: Synthelabo-Pharma SA of France / 11 Rue de Veyrot, 1217 Meyrin / France / Tel: +33-02-29-89-0147 / Fax: +33-02-29-89-0188. The product is standardized to 25% anthocyanidins containing 36% anthocyanosides by the extract Myrtocyan®.

American equivalents, if any, are found in the Product Table beginning on page 398.

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Clinical Studies on Bilberry *(Vaccinium myrtillus)*

Ocular (night/day vision, retinopathy, etc.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Muth *et al.*, 2000	Night vision and contrast sensitivity	DB, PC n=15 males, all except 2 with good vision (ages 25–47 years)	90 days	160 mg, 3x/day (25% anthocyanosides)	Not specified	Study failed to find an effect of bilberry on night visual acuity (VA) ($p>0.15$) or night contrast sensitivity (CS) ($p>0.35$) for a high dose of bilberry taken for a significant duration. Hence, this study casts doubt on the proposition that bilberry supplementation, in forms currently available and in doses recommended, improves night VA or night CS.
Perossini *et al.,* 1987	Retinopathy (patients with diabetic retinopathy, n=35; hypertensive vascular retinopathy n=5) (stage IV excluded)	DB, PC n=40	30 days	160 mg 2x/day	Tegens™ 160 mg capsule	Improved opthalmoscopic and angiographic patterns were demonstrated in 77–90% of the patients. Concluded to be an effective and safe treatment of diabetic and hypertensive retinopathy. (No statistics reported.)
Repossi *et al.,* 1987	Early diabetic or hypertensive retinopathy	DB, PC n=40	1 year	160 mg 2x/day	Tegens™ 160 mg capsule	Improvements were observed in 50% (vs. 20% in control group). Patients with exudate deposits improved in 15% of the cases (vs. 10% control group). A lower percentage of patients (10% vs.15%) with hard exudates worsened.
Vannini *et al.,* 1986	Nighttime vision in healthy subjects	DB, PC n=40 (mean age 25.5 years)	2 hours	240 mg/single dose	Myrtocyan®	Improved pupillary photomotor response, most evident 2 hours after administration; decreased total pulpillary contraction time ($p<0.05$); increased pupillary contraction ($p<0.05$).
Orsucci *et al.,* 1983	Diabetic retinopathy in Type II diabetes mellitus	O n=10	6 months	80 mg 3x/day	Tegens™ 80 mg capsule	Improvement in retinal picture; reduction or disappearance of hemorrhages.
Scharrer and Ober, 1981	Diabetic retinopathy	O n=31: 2 with hemorrhages due to anticoagulants, 4 with arterial sclerosis with hemorrhages of the retina, 20 with diabetic retinopathy (Keith Wagner Stages II and III)	4 weeks	Two, 80 mg capsules 3x/day	Difrarel 100™ capsule	Reduced vascular permeability during treatment. Mitigated changes of retinal vessels and prevented alterations in the visual field. (No statistics reported.)

KEY: C – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on Bilberry *(Vaccinium myrtillus)* (cont.)

Vascular (micro and peripheral circulation, venous disorders/insufficiencies, etc.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Gatta *et al.*, 1988	Venous insufficiency (various causes)	SB, PC n=60 (mean age 44 years)	30 days	160 mg 3x/day	Tegens™ 160	Decreased severity of edema, sensations of pressure, paresthesia, and cramp-like pain were observed in the bilberry group ($p<0.01$ for all outcomes).
Gentile *et al.*, 1987, unpublished	Preventive bleeding due to otorhinolaryngological surgery	SB, PC n=181 (ages 3–76 years)	10 days prior to surgery	160–320 mg/day dosed according to clinical symptoms	Myrtocyan®	Reduced intra- and postoperative bleeding and prevented subsequent hemorrhaging when treated with bilberry before surgery. (No statistics reported.)
Teglio, 1987	Venous insufficiency symptoms in pregnant women	n=51 (mean period of pregnancy 27 weeks) (mean age 30 years)	3 months	160, 240, 360 mg/day dosed according to symptom severity	Tegens™	Reduction in symptoms of pruritus (94.6%), paresthesia (87.5%), cramps (80.1%), pain (78.5%), exhaustion and heaviness (60%), and hemorrhoidal symptoms (75.5–83%).
Allegra *et al.*, 1982	Peripheral vascular disorder	DB, PC n=47	30 days	480 mg/day	Myrtocyan®	Decreased edema, paresthesia, and pain while increasing joint mobility in patients with Raynaud's disease.
Grismondi *et al.*, 1981	Phlebopathies induced by pregnancy	n=54 (ages 24–37 years)	60–90 days	320 mg/day started in 6th month of pregnancy	Myrtocyan®	Improvements in burning and itching ($p<0.001$), heaviness ($p<0.001$), and pain ($p<0.001$) were observed in bilberry users, as well as in diurnal and nocturnal cramps ($p<0.01$), and a reduction in edema and in capillary fragility ($p<0.001$).
Ghiringhelli *et al.*, 1977	Varicose veins of lower limbs	O n=47 (mean age 45 years)	30 days	480 mg/day	Myrtocyan®	Bilberry significantly improved symptoms such as limb edema and dyschromic skin phenomena as well as heaviness, paresthesia, and pain.
Mian *et al.*, 1977	Ulcerative dermatitis due to post thrombophlebitis	O n=15	10 days	240 mg/day	Myrtocyan®	Bilberry reduced the protein content of the exudate produced by venous occlusion and stasis, a symptom of post-thrombotic and varicose veins stasis. (No statistics reported.)

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Colombo, 1985	Chronic dysmenorrhea	DB, PC n=30	3 days prior to and during the cycle	320 mg/day	Myrtocyan® capsule	Bilberry significantly reduced dysmenorrhea symptoms including headache, heaviness of lower limbs, mammary tension, sickness and emesis, and pelvic and lumbosacral pain by the second month.
Cerutti *et al.*, 1984	Side effects of copper IUD's	n=48	6 months	Two, 160 mg capsules 2x/day	Myrtocyan®	Decreased incidents of spotting and hyperpoly-menorrhea were observed in bilberry users.

KEY: C – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.