Bilberry

Species (Family)

Vaccinium myrtillus L. (Ericaceae)

Synonym(s)

Blueberry, bogberry, huckleberry, *Myrtilus niger* Gilib., *Vaccinium angulosum* Dulac, *Vaccinium montanum* Salisb., whortleberry

Part(s) Used

Fruit (berries), leaves

Pharmacopoeial and Other Monographs

Complete German Commission E[G3]
Martindale 32nd edition (Myrtillus)[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]

Legal Category (Licensed Products)

Bilberry is not included in the GSL.

Constituents[G2,G55]

Berries

Flavonoid glycosides Anthocyanins (particularly glycosides of delphinidin, cyanidin, petunidin, peonidin, malvidin),[1,2] quercetin-3-glucuronide and hyperoside.[3]

Polyphenols Catechin, epicatechin and tannins.

Other constituents Pectins[1] and vitamin C.

Leaves

Flavonoids Quercetin and its glycosides (hyperoquercitrin).[1]

Phenolic acids Caffeic, *p*-coumaric, *p*-hydroxybenzoic, protocatechuic and melilotic.[4]

Other constituents Tannins and iridoids.[1]

Food Use

Bilberries are used in foods.[1] Bilberry is listed by the Council of Europe as a natural source of food flavouring (category N1). This category indicates that there are no restrictions on the use of bilberry in foods.[G16]

Herbal Use[G64]

Bilberry is stated to possess astringent, tonic and antiseptic properties and has traditionally been used in the treatment of diarrhoea, dysentry, haemorrhoids, gastrointestinal inflammations, mouth infections, scurvy and urinary complaints.[1] It has also been used in diabetes, gout and rheumatism and applied locally in eye inflammation, burns and skin infections.[1]

Dosage

Dried fruit 20–60 g daily as a decoction for the treatment of diarrhoea.[G2]

Pharmacological Actions

Several pharmacological activities have been documented for bilberry, including ophthalmic activity and anti-inflammatory, wound-healing, anti-ulcer, anti-atherosclerotic and vasoprotective properties. The biochemical, biological, pharmacological and clinical effects of bilberry have been reviewed.[1]

In vitro and animal studies

An anthocyanidin extract of *V. myrtillus* has been reported to act as a superoxide anion scavenger[1,5] and as an inhibitor of lipid peroxidation in rat liver microsomes[1,5,6] and in mouse liver tissue *in vivo*,[5] and to inhibit potassium ion loss induced by free radicals in human erythrocytes.[1] *V. myrtillus* extract is stated to have a potent protective antioxidant action on human low-density lipoproteins (LDLs) *in vitro* during copper-mediated oxidation.[7] Oxidative activity is recognised as a major process in tissue damage in a variety of pathological conditions, such as atherosclerosis and carcinogenesis. In addition, oxidative stress is thought to be involved in brain ageing and age-related neurodegenerative disease. A study in rats reported that, compared with rats fed a control diet, dietary

supplementation of blueberry (bilberry) extract for eight weeks reversed age-related deficits in several neuronal and behavioural parameters, such as enhancement of dopamine release from striatal slices and a water maze performance test.[8]

V. myrtillus anthocyanins have been reported to inhibit aggregation of human platelets *in vitro* in a dose-dependent manner[9] and, in rats, *V. myrtillus* anthocyanins administered orally at doses ranging from 5 to 400 mg/kg have been shown to prolong bleeding time markedly.[10] Inhibition of platelet aggregation has also been reported in humans treated with *V. myrtillus* anthocyanins (*see* Clinical studies).[11]

In vitro inhibition of elastase, a proteolytic enzyme involved with elastic fibre and connective tissue degeneration and with some pathological vascular conditions, has been demonstrated in studies using anthocyanins extracted from *V. myrtillus*.[12]

The hypolipidaemic activity of oral administration of extracts of *V. myrtillus* leaves has been demonstrated in rats.[13,14] In genetically hyperlipidaemic rats, plasma triglyceride and cholesterol concentrations, but not free fatty acids, decreased significantly.[13] In streptozotocin-induced diabetic rats, plasma glucose concentrations as well as plasma triglyceride concentrations decreased significantly compared with values in control rats.[14] In further experiments using blueberry and clofibrate, both preparations reduced plasma triglyceride concentrations in a dose-dependent manner in rats fed a hyperlipidaemic diet and in ethanol-treated normolipidaemic rats.[14] Blueberry, however, did not prevent fructose-elicited increases in plasma triglyceride concentrations. Other studies in glucose-loaded mice failed to demonstrate hypoglycaemic activity following oral administration of blueberry leaf extract.[15]

Several *in vitro* studies have demonstrated the relaxing effects of *V. myrtillus* anthocyanins on isolated vascular smooth muscle preparations, including the thoracic vein and splenic and coronary arteries.[16–18] There is evidence that the mechanism for this smooth muscle relaxant effect is via stimulation of prostaglandin release within vessel walls.[19]

Effects of *V. myrtillus* anthocyanins on enhancing arterial vasomotion (rhythmic variation of arteriole diameter in the microvasular network which influences microvascular blood flow and the formation of interstitial fluid) have been shown in experimental models, including the cheek pouch microcirculation of hamsters.[20] This model has also been used to investigate the effects of *V. myrtillus* anthocyanins on ischaemia–reperfusion injury.[21] Oral administration for two and four weeks of Myrtocyan, a commercially available product comprising bilberry anthocyanin complex, reduced the increase in capillary permeability, decreased leukocyte adhesion and improved capillary perfusion compared with controls. In rats, oral administration of *V. myrtillus* anthocyanins for 12 days before the induction of hypertension (by ligature of the abdominal aorta) limited the increase in vascular permeability and maintained a normal blood–brain barrier permeability.[22]

Components of bilberry have been reported to exhibit potential anticarcinogenic activity *in vitro* as demonstrated by inhibition of the induction of ornithine decarboxylase (ODC) by the tumour promoter phorbol 12-myristate 13-acetate (TPA).[23]

Myrtocyan and one of its anthocyanin constituents have been shown to have anti-ulcer activity in various experimental models of acute gastric ulcer and in chronic ulcer induced by acetic acid.[24] The mechanism for this may be by potentiation of the defensive barriers of the gastrointestinal mucosa, such as the secretion of gastric mucus or stimulation of cellular regeneration.[24]

Extracts of *V. myrtillus* leaves have demonstrated antibacterial activity against several species, including *Staphylococcus aureus* and *Escherichia coli*, as determined by the hole-plate diffusion method and the microdilution broth method.[25] *V. myrtillus* fruit extracts were less active.

The pharmacokinetics of *V. myrtillus* anthocyanins have been studied in rats.[26] Following a single oral administration, plasma anthocyanin concentrations peaked after 15 minutes and declined rapidly within 2 hours. No hepatic first-pass effect was observed; elimination occurred mostly through the urine and bile.

Clinical studies

Clinical studies with extracts of *V. myrtillus* fruits (berries) have focused mainly on its therapeutic applications in certain ophthalmological conditions and in altered microcirculation and peripheral venous insufficiency. The clinical efficacy of *V. myrtillus* fruits has been reviewed.[1]

A study involving 30 healthy subjects with normal platelet aggregation investigated the effects of administration of *V. myrtillus* anthocyanins (Myrtocyan) (480 mg) daily, ascorbic acid 3 g daily and *V. myrtillus* anthocyanins plus ascorbic acid on collagen- and ADP-induced platelet aggregation.[11] Platelet aggregation in blood samples taken from participants after 30 and 60 days' treatment was clearly reduced in all subjects compared with baseline values. The reduction in platelet aggregation was greater in subjects who received *V. myrtillus* anthocyanins alone than in those who received ascorbic acid alone and was most

marked in subjects who received both preparations. Platelet aggregation returned to baseline values when tested 120 days after discontinuation of treatment.[11]

Early studies involving healthy subjects and patients with visual disorders who received *V. myrtillus* extracts alone or in combination with β-carotene and vitamin E reported improvements in night vision and faster adjustment to darkness and restoration of visual acuity following exposure to a bright flash of light.[1] Other studies reported improvements in retinal sensitivity and the visual field in patients with myopia or glaucoma following short- or long-term (six months) treatment with *V. myrtillus* anthocyanins.[1] However, all these studies appear to have been uncontrolled. Other uncontrolled studies in small numbers of patients with retinal pathologies have reported improvements in retinal function, compared with pretreatment values (e.g. ref. 27).

In a randomised, double-blind, placebo-controlled trial, 40 patients with diabetic and/or hypertensive retinopathy received Myrtocyan (160 mg) twice daily or placebo for one month.[28] At the end of the study, the placebo group received Myrtocyan for one month. It was reported that 77–90% of treated patients experienced improvement compared with the pretreatment period, as determined by ophthalmoscopy and fluorescein fundus angiography.[28] However, there does not appear to have been a statistical comparison between the treatment and placebo groups. A similar placebo-controlled trial involving 40 patients with early-phase diabetic retinopathy who received Myrtocyan for 12 months also reported improvements in Myrtocyan-treated patients.[29]

In a randomised, double-blind trial involving 51 patients with mild senile cortical cataract who received *V. myrtillus* anthocyanins plus vitamin E twice daily for four months, treated patients showed significant improvements in lens opacity compared with placebo recipients.[30]

Studies involving patients with peripheral vascular disorders of various origins are stated to have demonstrated clinical benefits with *V. myrtillus* extracts.[1] Other studies in patients with ulcerative dermatitis secondary to post-thrombotic or venous varicose stasis, capillary fragility secondary to liver disorders and other conditions, or chronic venous insufficiency have been reported to have shown improvements in clinical signs and symptoms.[1] However, several of these studies appear to have been uncontrolled (e.g. refs 31–33) and/or included only small numbers of patients (e.g. refs 31 and 32). A double-blind, placebo-controlled study involving 47 patients with peripheral vascular disorders reported reductions in subjective symptoms, such as paraesthesia, pain and heaviness and improved oedema in patients treated with Myrtocyan (480 mg/day) for 30 days.[1] A single-blind study involving 60 patients with venous insufficiency who received Myrtocyan (480 mg/day) or placebo for 30 days reported significant improvements in oedema, paraesthesia, cramp-like pain and pressure sensation in Myrtocyan-treated patients compared with pretreatment values in these patients.[1]

V. myrtillus anthocyanins have been investigated in a variety of other disorders.

A randomised, double-blind, placebo-controlled trial of *V. myrtillus* anthocyanins (320 mg/day) taken for three days before menstruation was conducted involving 30 patients with chronic primary dysmenorrhoea.[34] Significant differences between the active treatment and placebo groups were reported for several symptoms investigated, including nausea and vomiting and breast tenderness; there was no effect on headache.

A trial involving 60 patients who had undergone haemorrhoidectomy who were randomised to receive *V. myrtillus* anthocyanins (320–480 mg/day) postoperatively in addition to usual medical care or to no additional treatment reported reductions in itch and oedema, but no effect on other symptoms, in bilberry recipients.[35]

Other studies, all of which were uncontrolled, have reported beneficial effects following administration of *V. myrtillus* extracts in patients with fibrocystic mastopathy[36] and type II diabetes mellitus,[37] in infantile dyspepsia[38] and in pregnant women with lower limb venous insufficiency and acute-phase haemorrhoids.[39]

Side-effects, Toxicity

A review of clinical trials of *V. myrtillus* extracts stated that no adverse effects had been observed, even following prolonged treatment.[1] However, most trials involved relatively small numbers of patients and, therefore, would only be able to detect very common acute adverse effects.

The same review summarised the results of an unpublished postmarketing surveillance study which had involved 2295 subjects who had taken Myrtocyan, usually 160 mg twice daily for 1–2 months, for lower limb venous insufficiency, capillary fragility, functional changes in retinal microcirculation or haemorrhoids. Ninety-four subjects reported side-effects, mainly relating to the skin and gastrointestinal and nervous systems.[1]

Long-term consumption of bilberry leaves may lead to toxicity. Chronic administration of doses of

1.5 g/kg per day or more to animals has been reported to be fatal.[G2]

Unpublished animal toxicity data for Myrtocyan have also been summarised.[1] In mice and rats, the LD_{50} for Myrtocyan is over 2000 mg/kg and, in dogs, single doses of 3000 mg/kg produced no adverse effects other than marked darkening of urine and faeces (demonstrating absorption). Oral daily doses to rats and dogs of 125–500 and 80–320 mg/kg, respectively, for six months did not induce mortality or toxic effects.[1] Pharmacokinetic studies of *V. myrtillus* anthocyanins in rats demonstrated that anthocyanins are removed rapidly from the systemic circulation within 2 hours of oral administration.[26]

Contra-indications, Warnings

In view of the inhibitory effects of *V. myrtillus* anthocyanins on platelet aggregation, the use of bilberry concurrently with other antiplatelet agents and anticoagulants may enhance the risk of bleeding.

Pregnancy and lactation In an uncontrolled study, *V. myrtillus* anthocyanin extract (Tegens) (80 or 160 mg) twice or three times daily for three months was administered to pregnant women with lower limb venous insufficiency and acute-phase haemorrhoids with no apparent adverse effects.[39] However, the safety of bilberry has not been established and, in view of the lack of toxicity data, the use of bilberry during pregnancy and lactation should be avoided.

Pharmaceutical Comment

The chemistry of bilberry is well documented and there is good evidence that the anthocyanin constituents are responsible for the pharmacological effects of bilberry.

Documented scientific evidence from *in vitro* and animal studies provides supportive evidence for some of the uses of bilberry. There have been several clinical studies investigating the effects of bilberry in a range of conditions. However, many studies have been uncontrolled, involved only small numbers of patients and had other methodological flaws. Further, well-designed clinical trials are required to establish the efficacy of bilberry.

There are some limited toxicity and safety data for bilberry which together with data on adverse effects reported in clinical trials provide some support for the safety of bilberry when used at recommended doses in the short term. However, further data on the long-term safety of bilberry use are required and, therefore, excessive use of bilberry should be avoided.

Patients wishing to use bilberry for medicinal purposes should be advised to consult a pharmacist, doctor or other suitably trained health care professional for advice.

References

See also General References G2, G3, G31, G36, G43, G50 and G55.

1 Morazzoni P, Bombardelli E. *Vaccinium myrtillus* L. *Fitoterapia* 1996; 66: 3–29.

2 Di Pierro F, Morazzoni P. Reaping the benefits: the role of two edible plants (*Vaccinium myrtillus* and *Glycine max*). Proceedings of the Herbal Medicine in the New Millenium Conference, Lismore, NSW, Australia, 1999: 146–150.

3 Fraisse D *et al.* Composition polyphénolique de la feuille de myrtille. *Ann Pharm Fr* 1996; 54: 280–283.

4 Dombrowicz E *et al.* Phenolic acids in leaves of *Arctostaphylos uva ursi* L., *Vaccinium vitis idaea* L. and *Vaccinium myrtillus* L. *Pharmazie* 1991; 46: 680–681.

5 Martín-Aragon S *et al. In vitro* and *in vivo* antioxidant properties of *Vaccinium myrtillus*. *Pharm Biol* 1999; 37: 109–113.

6 Martín-Aragon S *et al.* Antioxidant action of *Vaccinium myrtillus* L. *Phytother Res* 1998; 12(Suppl.): S104–S106.

7 Laplaud PM *et al.* Antioxidant action of *Vaccinium myrtillus* extract on human low-density lipoproteins *in vitro*: initial observations. *Fund Clin Pharmacol* 1997; 11: 35–40.

8 Joseph JA *et al.* Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. *J Neurosci* 1999; 19: 8114–8121.

9 Bottecchia D *et al.* Preliminary report on the inhibitory effect of *Vaccinium myrtillus* anthocyanosides on platelet aggregation and clot retraction. *Fitoterapia* 1987; 58: 3–8.

10 Morazzoni P, Magistretti MJ. Activity of Myrtocyan, an anthocyanin complex from *Vaccinium myrtillus* (VMA), on platelet aggregation and adhesiveness. *Fitoterapia* 1990; 61: 13–21.

11 Pulliero G *et al. Ex vivo* study of the inhibitory effects of *Vaccinium myrtillus* anthocyanosides on human platelet aggregation. *Fitoterapia* 1989; 60: 69–75.

12 Jonadet M *et al.* Anthocyanosides extraits de *Vitis vinifera*, de *Vaccinium myrtillus* et de *Pinus maritimus*. *J Pharm Belg* 1983; 38: 41–46.

13 Cignarella A *et al.* Hypolipidaemic activity of *Vaccinium myrtillus* leaves on a new model of genetically hyperlipidaemic rat. *Planta Med* 1992; 58(Suppl.1): A581–A582.

14 Cignarella A *et al.* Novel lipid-lowering properties of *Vaccinium myrtillus* L. leaves, a traditional

antidiabetic treatment, in several models of rat dyslipidaemia: a comparison with clofibrate. *Thromb Res* 1996; 84: 311–322.

15 Neef H *et al.* Hypogylcaemic activity of selected European plants. *Phytother Res* 1995; 9: 45–48.

16 Bettini V *et al.* Effects of *Vaccinium myrtillus* anthocyanosides on vascular smooth muscle. *Fitoterapia* 1984; 55: 265–272.

17 Bettini V *et al.* Interactions between *Vaccinium myrtillus* anthocyanosides and serotonin on splenic artery smooth muscle. *Fitoterapia* 1984; 55: 201–208.

18 Bettini V *et al.* Mechanical responses of isolated coronary arteries to barium in the presence of *Vaccinium myrtillus* anthocyanosides. *Fitoterapia* 1985; 56: 3–10.

19 Morazzoni P, Magistretti MJ. Effects of *Vaccinium myrtillus* anthocyanosides on prostacyclin-like activity in rat arterial tissue. *Fitoterapia* 1986; 57: 11–14.

20 Colantuoni A *et al.* Effects of *Vaccinium myrtillus* anthocyanosides on arterial vasomotion. *Arzneimittelforschung* 1991; 41: 905–909.

21 Bertuglia S *et al.* Effect of *Vaccinium myrtillus* anthocyanosides on ischaemia reperfusion injury in hamster cheek pouch microcirculation. *Pharmacol Res* 1995; 31: 183–187.

22 Detre Z *et al.* Studies on vascular permeability in hypertension: action of anthocyanosides. *Clin Physiol Biochem* 1986; 4: 143–149.

23 Bomser J *et al. In vitro* anticancer activity of fruit extracts from *Vaccinium* species. *Planta Med* 1996; 62: 212–216.

24 Magistretti MJ *et al.* Antiulcer activity of an anthocyanidin from *Vaccinium myrtillus*. *Arzneimittelforschung* 1988; 38: 686–690.

25 Brantner A, Grein E. Antibacterial activity of plant extracts used externally in traditional medicine. *J Ethnopharmacol* 1994; 44: 35–40.

26 Morazzoni P *et al. Vaccinium myrtillus* anthocyanosides pharmacokinetics in rats. *Arzneimmittelforschung* 1991; 41: 128–131.

27 Forte R *et al.* Fitotherapy and ophthalmology: considerations on dynamized myrtillus retinal effects with low luminance visual acuity. *Ann Ottal Clin Ocul* 1996; 122: 325–333.

28 Perossini M *et al.* Diabetic and hypertensive retinopathy therapy with *Vaccinium myrtillus* anthocianosides (Tegens) double-blind placebo-controlled clinical trial. *Ann Ottal Clin Ocul* 1988; 113: 1173–1190.

29 Repossi P *et al.* The role of anthocyanosides on vascular permeability in diabetic retinopathy. *Ann Ottal Clin Ocul* 1987; 113: 357–361.

30 Bravetti GO *et al.* Preventive medical treatment of senile cataract with vitamin E and *Vaccinium myrtillus* anthocianosides: clinical evaluation. *Ann Ottal Clin Ocul* 1989; 115: 109–116.

31 Coget J, Merlen JF. Étude clinique d'un nouvel agent de protection vasculaire le difrarel 20, composé d'anthocyanosides extraits du *Vaccinum myrtillus*. *Phlebologie* 1968; 21: 221–228.

32 Piovella F *et al.* Impiego di antocianosidi da *Vaccinium myrtillus* al 25% come antocianidine nel trattamento della diatesi emorragica da deficit dell'emostasi primaria. *Gaz Med It* 1981; 140: 445–449.

33 Tori A, D'Errico F. Gli antocianosidi da *Vaccinium myrtillus* nella cura delle flebopatie da stasi degli arti inferiori. *Gaz Med It* 1980; 139: 217–224.

34 Colombo D, Vescovini R. Studio clinico controllato sull'efficacia degli antocianosidi del mirtillo cel trattamento della dismenorrea essenziale. *Giorn It Ost Gin* 1985; 7: 1033–1038.

35 Pezzangora V *et al.* La terapia medica con antocianosidi del mirtillo nei pazienti operati di emorroidectomia. *Gaz Med It* 1984; 143: 405–409.

36 Leonardi M. Il trattamento della mastopatia fibrosa con antocianosidi di mirtillo. *Minerva Ginecol* 1993; 45: 617–621.

37 Ionescu-Tirgoviste C *et al.* Efectul unui amestec pe plante asupra echilibrului metabolic la bolnavii cu diabet zaharat de tip 2. *Med Intern* 1989; 41: 185–192.

38 Tolan L *et al.* Utilizarea prafului de afine in dispepsiile sugarului. *Pediatria* 1969; 18: 375–379.

39 Teglio L *et al. Vaccinium myrtillus* anthocyanosides in the treatment of venous insufficiency of inferior limbs and acute piles in pregnancy. *Quaderni Clin Osterica Ginecol* 1987; 42: 221–231.