

# BILBERRY

## *Vaccinium myrtillus L.*

### Family

Ericaceae.

### Parts Used

Fruit.

### Description

Bilberry (*Vaccinium myrtillus*), of the Ericaceae family, is commonly known as European blueberry, huckleberry, whortleberry, or blueberry. It is a shrubby perennial plant 30 to 60 centimetres in height and can be found in the mountains, and forests, of Europe and the northern United States. Its branches contain alternating, elliptical, bright green leaves and its flowers, which appear from April to June, are reddish or pink and bell-shaped.<sup>1</sup>

### Traditional Use

Bilberry has been used as food for centuries due to its high nutritive value. Bilberry's history of medicinal use dates back to the Middle Ages but it did not become widely known to herbalists until the 16th century when its use was documented for treating bladder stones, biliary disorders, scurvy, coughs, and lung tuberculosis.<sup>2</sup> Bilberry's medicinal use was described by the 12th Century German herbalist Hildegard von Bingen (1098 to 1179), who purportedly recommended it for the induction of menses.

Mrs Grieves writes in A Modern Herbal, from 1931, that bilberry leaves can be used in the same way as those of *uva ursi* (Bearberry or *Arctostaphylos uva-ursi*). The fruits are astringent, and are especially valuable in diarrhoea and dysentery, in the form



of syrup. The ancients used them largely, and Dioscorides spoke highly of them. They are also used for discharges and as antigalactagogues. A decoction of the leaves, or bark of the root, may be used as a local application to ulcers and in ulceration of the mouth and throat. The fruit is helpful in scurvy and urinary complaints, and when bruised with the roots and steeped in gin has diuretic properties valuable in dropsy and gravel. A tea made of the leaves is also a remedy for diabetes if taken for a prolonged period.<sup>3</sup>

The dried fruit has remained popular for the symptomatic treatment of diarrhoea, for topical relief of minor mucus membrane inflammation and for a variety of eye disorders, including poor night vision, eyestrain and myopia. Bilberry is also commonly used to make jams, pies, cobblers, syrups and alcoholic/non-alcoholic beverages. Fruit extracts are also used as colouring agents in wines.

### Constituents

Several active constituents have been isolated from the berries and leaves of the bilberry plant, including anthocyanoside flavonoids (anthocyanins), vitamins, sugars and pectins, which are found in the berries, and quercetin, catechins, tannins, iridoids and acids, which are found in the leaves. The anthocyanosides are considered the most important of the pharmacologically active components. Anthocyanoside concentration in the fresh fruit is approximately 0.1 to 0.25%, while concentrated bilberry extracts are usually standardized to 25% anthocyanosides. The berry's anthocyanoside content increases as the fruit ripens, while the reverse is true of its leaf constituents.<sup>4</sup>

### Actions

Antioxidant, anti-inflammatory, astringent, hypoglycaemic, antiplatelet, vasoprotective, antiulcer, antidiarrhoeal, cytoprotective, apoptosis inducing.

### Pharmacokinetics

An early study found that oral administration of pure anthocyanosides in rats had moderate gastrointestinal absorption with a bioavailability of less than 2%.<sup>5</sup> Later studies however have

found that anthocyanin glycosides are rapidly and efficiently absorbed from the small intestine, and that they are quickly metabolized and excreted into the bile and urine as intact glycosides, as well as methylated forms and glucuronidated derivatives.<sup>6</sup>

In a study of the bioavailability of bilberry extract it was found that an extract containing 15 different anthocyanins had a bioavailability of about 1%. The plasma concentration of anthocyanins as a whole reached the maximum level of 1.2 microM at 15 minutes after oral administration of 400 mg/kg bilberry extract (153.2mg/kg as anthocyanins) and then decreased with time.<sup>7</sup>

Quercetin has also been shown to have very good bioavailability.<sup>8,9</sup> Plasma quercetin levels have been shown to increase by up to 50% in subjects consuming 100g/day of bilberries, black currants, and lingonberries as a part of their normal diets for two months.<sup>10</sup>

### Pharmacological Activity

Although bilberry constituents have multiple pharmacological actions, most of the research has focused on the activities of the anthocyanosides. Extracts containing anthocyanosides have been shown to possess strong antioxidant properties, stabilize collagen fibres and promote collagen biosynthesis, decrease capillary permeability and fragility, and inhibit platelet aggregation.<sup>11</sup>

### Cardiovascular Activity

Anthocyanin reduces inflammation, protects blood vessels<sup>12</sup> inhibits platelet aggregation and stimulation of vascular prostacyclin, scavenges free radicals and inhibits cAMP phosphodiesterase.<sup>13</sup> Bilberry has also been shown to improve micro-circulation by decreasing vascular permeability while improving vascular tone and blood flow<sup>14,15</sup> Reactive oxygen species (ROS) play a critical role in the impairment of nitric oxide-mediated vascular functions and overall pathogenesis associated with cardiovascular disease. The vasoactive and vasoprotective properties of bilberry were demonstrated in an *in vitro* study where an anthocyanin-rich extract was shown to cause endothelium-dependent relaxation in porcine coronary arteries. The bilberry extract was shown to

protect coronary arteries from ROS without altering vasorelaxation to endogenous or exogenous nitric oxide (NO).<sup>16</sup>

Another significant property of bilberry extracts is the capability to exert potent protective action on LDL particles during copper-mediated oxidation. This was accomplished using only trace amounts of bilberry extract (15 to 20mcg/mL), therefore the extract may be even more potent than ascorbic acid in protecting LDL from oxidative stress.<sup>17</sup>

In a human study of 30 subjects with normal platelet aggregation, 480mg of Myrtocyan® (*Vaccinium myrtillus* anthocyanins) daily, three grams of ascorbic acid daily, or both treatments all reduced platelet aggregation after 30 and 60 days. Bilberry anthocyanins reduced platelet aggregation more than ascorbic acid alone, but bilberry anthocyanins and ascorbic acid together were the most effective.<sup>18</sup>

Together these studies suggest that bilberry may be a potentially useful medicine in the prevention and treatment of hypertension and cardiovascular diseases and two early clinical studies found that bilberry extract improved microcirculation in patients suffering a variety of venous diseases.<sup>19,20</sup>

### **Cytoprotective Activity**

Potassium bromate is an oxidizing agent used as a food additive, which causes kidney damage via the generation of oxygen free radicals. Bilberry has been shown to protect kidney tissue in an experimental study of potassium bromated-induced kidney damage. Five-day oral administration of bilberry extract at 50, 100, and 200mg/kg resulted in a reversal in serum urea nitrogen and creatinine to normal levels and decreased kidney malondialdehyde, NO and xanthine oxidase levels. Also, bilberry extract improved oxygen radical absorbance capacity (ORAC) levels in kidney tissue, which showed that bilberry extract reduced the degree of oxidative stress and kidney damage induced by potassium bromide. The protective effect of bilberry extract is attributed to its free radical scavenging activity and lipid peroxidation inhibitory effect.<sup>21</sup>

Both the neurotransmitter dopamine and its neurotoxic metabolite, 6-hydroxy dopamine, can be oxidized to generate hydrogen peroxide and other reactive species (ROS). ROS promote

oxidative stress and have been implicated in dopaminergic neurodegeneration, e.g. Parkinson's disease. There is also evidence for a relation between catecholamine-mediated oxidative damage in dopaminergic neurons and the effects of these neurotransmitters on the redox state of cytochrome c. In neurons and other cells, oxidative stress may be enhanced by abnormal release of cytochrome c and other mitochondrial proteins into the cytoplasm. Cytochrome c release can result in apoptosis but sub-apoptogenic-threshold release can also occur, and may be highly damaging in the presence of dopamine metabolites. Loss of mitochondrial membrane integrity, which is seen in several aging-related neurodegenerative disorders, including Parkinson's disease and cancer, contributes to release of cytochrome c and the level of such release is known to be indicative of the extent of mitochondrial dysfunction. Anthocyanin-rich extracts of bilberry have been shown to effectively reduce cytochrome c enhanced, 6-hydroxy dopamine-induced oxidative stress. Interestingly the complex extract was more effective than pure anthocyanin. Vitamin C, even in 4-fold doses, did not result in significant inhibition.<sup>22</sup>

### **Ophthalmological Activity**

There is evidence to support the use of bilberry in various disorders of the eye, although the mechanisms of action behind the beneficial effect on the eye are not completely understood. They include the ability to improve oxygen and blood delivery to the eye and to scavenge free radicals that can disrupt collagen structures and contribute to conditions such as cataracts and macular degeneration. In addition, the anthocyanosides have an affinity for the pigmented epithelium (visual purple) area of the retina, the portion of the retina responsible for vision and adjustments to light and dark.<sup>23</sup> Anthocyanosides have been shown to exert direct effects on the retina, including the alteration of local enzymatic reactions and enhancement of the recovery of rhodopsin.<sup>24</sup>

### **Glaucoma**

Classic glaucoma treatment focuses on intraocular pressure (IOP) reduction. Better knowledge of the pathogenesis of the disease has opened up new therapeutic approaches. Whereas most of

these new avenues of treatment are still in the experimental phase, others such as magnesium, ginkgo, salt and fludrocortisone, are already used by some practitioners. Reduction of oxidative stress, especially at the level of mitochondria, also seems to be protective. This can be achieved by gingko, dark chocolate, polyphenolic flavonoids occurring in tea, coffee or red wine, anthocyanosides found in bilberries, as well as by ubiquinone and melatonin.<sup>25</sup>

#### Macular Degeneration and Cataracts

Cataracts and macular degeneration remain the major cause of blindness and acuity of vision deterioration in the elderly. Both pathologies have been attributed to damage by free radicals and there has therefore been a great deal of interest in antioxidants. Bilberry's flavonoids are known as potent antioxidants, scavenging free radicals and used for multiple age-related ocular disorders. A recent animal study found that a bilberry extract standardised to 25% anthocyanosides completely prevented impairments in the lenses and retina in an experimental model of cataract and macular degeneration, while 70% of the animals in the control group developed cataracts and macular degeneration.<sup>26</sup>

#### Connective Tissue Stabilizing Effects

Anthocyanosides have been shown *in vitro* to stabilise connective tissue by enhancing collagen synthesis, inhibiting collagen degradation and enhancing collagen cross linking.<sup>27</sup> However a later study found a significant decrease in connective tissue synthesis (collagen and glycoproteins) in gingival tissue samples of 12 adult diabetics treated with 600mg of anthocyanosides daily for two months.<sup>28</sup>

#### Gastrointestinal Activity

Bilberry contains tannins that have been used medicinally as astringents and to treat diarrhoea. The protozoan parasites *Giardia duodenalis* and *Cryptosporidium parvum* are common causes of diarrhoea worldwide and water soluble extracts of bilberry have been shown to kill *G. duodenalis* trophozoites and modify the morphology of *G. duodenalis* and *C. parvum*.<sup>29</sup>

#### Anti-inflammatory Activity

Bilberry extracts have demonstrated anti-inflammatory properties in animals, and thus may

be useful in the treatment of conditions such as rheumatoid arthritis.

#### Diabetes Mellitus

A decoction of bilberry leaf is a traditional remedy for diabetes. In normal and depancreatized dogs, oral administration of bilberry leaves has been shown to reduce hyperglycemia, even when the glucose was concurrently injected intravenously.<sup>30</sup> Additionally, bilberry anthocyanosides have been shown to enhance collagen integrity, stabilize capillary permeability, and inhibit sorbitol accumulation, thus providing protection against vascular and neurological sequelae of diabetes.<sup>31</sup>

#### Antiulcer Activity

The antiulcer activity of one of bilberry's anthocyanosides (IdB 1027) has been demonstrated in various experimental models. IdB 1027 has been shown to decrease the incidence and severity of numerous forms of experimentally induced ulcers in rats.<sup>32</sup> Bilberry extract has been shown to significantly ( $p < 0.05$ ) inhibit *H. pylori*, compared with controls, and also increase susceptibility of *H. pylori* to clarithromycin *in vitro*.<sup>33</sup>

#### Anticancer Activity

Berries, including bilberry, are thought to have anticancer and chemopreventive properties.<sup>34,35,36</sup> An extract of bilberry has been shown to inhibit human leukemia cells and human colon carcinoma cells growth through the induction of apoptosis.<sup>37</sup> Bilberry has also been shown to protect against myelotoxicity induced by the chemotherapy. The toxicities associated with 5-fluorouracil (5-FU), a potent broad-spectrum chemotherapeutic agent, can not only affect the morbidity and the efficacy of chemotherapy but also limit its clinical use. A single injection of 5-fluorouracil at 200mg/kg induced severe peripheral erythrocytopenia, thrombocytopenia and leucopenia as well as hypocellularity of the spleen and bone marrow in mice. Oral administration of 500mg/kg of anthocyanin-rich extract from bilberry for 10 days significantly increased the number of red blood cells, neutrophils and monocytes in peripheral blood to 1.2-fold, 9-fold and 6-fold, respectively, compared with those seen after treatment with 5-fluorouracil alone ( $p < 0.05-0.001$ ). Furthermore, the bilberry

extract did not interfere with, but rather enhanced, the chemotherapeutic efficacy of 5-FU *in vitro*.<sup>38</sup>

## Clinical studies

### Glaucoma

In one study, eight patients with glaucoma were given a single oral dose of 200mg bilberry anthocyanosides and demonstrated improvement based on electroretinography. A collagen-stabilizing effect on the trabecular meshwork, facilitating aqueous outflow, may provide a potential mechanism.<sup>39</sup>

### Cataract and Macular Degeneration

In a clinical case study, bilberry extract standardised to 25% anthocyanosides (180mg twice daily) combined with vitamin E, reduced cataract formation in 48 of 50 patients with early stage cataracts.<sup>40</sup>

### Retinopathy (Diabetic, Vascular)

In Europe, bilberry anthocyanoside extracts are recognized as highly effective in preventing diabetic retinopathy, with several clinical studies supporting its use. Clinical trials in the European literature, mostly from Italy, have reported effects on parameters of retinopathy and microangiopathy in humans. In a double-blind study, 14 patients with diabetic and/or hypertensive retinopathy were supplemented with bilberry extract equivalent to 115mg anthocyanosides daily (or placebo) for one month. Significant improvements were observed in the ophthalmoscopic parameters of 11 subjects receiving bilberry, and 12 patients showed improvement in angiographic parameters.<sup>41</sup>

A double-blind, placebo controlled study was conducted in 40 patients with vascular retinopathy (diabetic or hypertensive). A bilberry extract was administered at a dose of 160mg twice daily for one month. Placebo patients were then given bilberry for one month (although bilberry patients were not crossed over to placebo). Moderate mean improvements in ophthalmoscopic and fluoroangiographic findings were found following bilberry treatment, as measured by a multi-item clinician questionnaire. According to the authors, a 77 to 90% improvement was seen in bilberry-

treated patients. The clinical validity of these results is limited by the lack of adequate description of blinding or randomization and by the lack of crossover of the placebo group (preventing true between-group comparisons).<sup>42</sup>

In a case series of 30 subjects (10 with diabetic retinopathy, 10 with non-diabetic retinopathy, and 10 normal "controls") treatment with procyanidolic anthocyanosides produced a statistically significant improvement in microangiopathic measures in patients with retinopathy, although details of measurement instrument and method of analysis were not reported.<sup>43</sup>

### Vision Improvement

A meta-analysis of studies on vision improvement casts doubts on the usefulness of bilberry extract in improving night vision in healthy people. The review identified 30 trials with outcome measures relevant to vision in reduced light. Of these, 12 were placebo-controlled. The four most recent trials were all randomized controlled trials (RCTs) and were negative in outcome. A fifth RCT and seven non-randomized controlled trials reported positive effects on outcome measures relevant to night vision. Negative outcome was associated with more rigorous methodology but also with lower dose level and extracts from geographically distinct sources that may differ in anthocyanoside composition. Healthy subjects with normal or above average eyesight were tested in 11 of the 12 trials. The hypothesis that bilberry anthocyanosides improves normal night vision is not supported by evidence from rigorous clinical studies. There is a lack of research into the effects of the extract on subjects suffering impaired night vision due to pathological eye conditions, however evidence from animal studies, trials of synthetic anthocyanosides, and a recent randomized controlled trial of *Ribes nigrum* (black currant) anthocyanosides suggest that bilberry anthocyanosides could be beneficial in subjects with impaired night vision.<sup>44</sup>

### Chronic Venous Insufficiency

Chronic venous insufficiency (CVI) is a syndrome that is characterized by lower extremity oedema, varicosities, pain, pruritus, atrophic skin changes and ulcerations. A review of uncontrolled trials from 1979 to 1985 on a total of 568 patients with

venous insufficiency of the lower limbs showed bilberry extract was effective in rapidly decreasing symptomatology and improving both venous microcirculation and lymph drainage.<sup>45</sup> Subjective improvements in oedema, pain and bruising were reported, with no statistical analysis.

A single-blind placebo controlled study in 60 patients with CVI showed a significant reduction in symptom severity after 30 days of bilberry therapy. Subjects were given bilberry extract equivalent to 173mg of anthocyanins daily or placebo. Reporting of blinding technique and randomization was limited, thus weakening the conclusions of this trial.<sup>46</sup>

### **Fibrocystic Breast Disease**

A total of 257 women selected on the basis of absence of malignant disease and presence of clinical, echographic or mammographic symptoms of fibrocystic mastopathy and presenting with mastodynia were treated with bilberry extract for three months. The results were encouraging. There was a marked improvement in 75 patients, equivalent to 3%, symptoms were reduced in 61 women (27%) and disappeared in 14 (6%), whereas treatment had no effect in 72 cases (32%).<sup>47</sup>

### **Dysmenorrhoea**

Additionally, women with dysmenorrhoea were given bilberry extract (115mg anthocyanosides per day) for three days before and during menstruation. A significant improvement in pelvic/lumbosacral pain, mammary tension, nausea and lower-limb heaviness was noted.<sup>48</sup>

### **Indications**

- Chronic venous insufficiency, haemorrhoids, varicose veins, peripheral vascular disorders (such as Raynaud's syndrome) and capillary fragility
- Impaired night vision, retinopathy (diabetic and vascular), glaucoma, cataract and macular degeneration
- Fibrocystic breast disorder, dysmenorrhoea
- Cancer prevention, adjunct to chemotherapy
- Prevention and treatment of cardiovascular disorders
- Diarrhoea, ulcerative colitis

- Inflammatory disorders
- Externally for inflammation of the mouth and mucous membranes

### **Energetics**

Cold, dry.

### **Use in Pregnancy**

Likely to be safe when consumed in dietary amounts.

### **Contraindications**

A theoretical risk exists that high doses (>170 mg anthocyanidins) may increase bleeding risk, however this remains uncertain as there is inadequate clinical evidence. Use with caution in people with haemorrhagic disorders.

### **Drug Interactions**

Monitor with antidiabetic drugs. Avoid use with topoisomerase chemotherapy drugs until safety can be established. Reduced absorption of iron is theoretically possible if taken at the same time because of the tannin content of the herb. Separate doses by two hours.

### **Administration and Dosage**

Liquid Extract: 1:2

Alcohol: 50%

Weekly Dosage: 20 to 80mL

**For diarrhoea:** 4 to 8g of dried fruit taken orally with water twice daily, decoction of dried fruit three times daily (made by boiling 5 to 10g of crushed dried fruit in 150mL of water for 10 minutes and straining while hot) or a cold macerate of dried fruit three times daily (made by soaking dried crushed fruit in 150mL water for several hours). Only preparations of dried bilberry should be used for diarrhoea, as the fresh fruit may actually have a laxative effect.

**Fresh berries:** 55 to 115g three times daily.

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