***Vaccinium myrtillus* L.** **Ericaceae**
SCN: bilberry
OCN: European blueberry; huckleberry; whortleberry
Part: fruit

Quick Reference Summary
Safety Class: 1
Interaction Class: A

Contraindications
None known.

Other Precautions
None known.

Drug and Supplement Interactions
None known.

Standard Dose
A dose of 20 - 60 g dried berries (European Scientific Cooperative on Phytotherapy 2003; Wichtl 2000) or 160 - 540 mg standardized dry extract (drug extract ratio 153-76:1; containing 36% anthocyanins, or 25% anthocyanidins) (European Medicines Agency 2015) is recommended daily. A dose of 55 - 115 g fresh berries three times daily is recommended in adults (Ulbricht et al. 2009).

Editors' Note
This entry was revised November 2020.

Bilberry fruit is traditionally consumed as a food (Ulbricht et al. 2009; Upton 2001).

Adverse Events and Side Effects

Four recent clinical trials and one systematic review of clinical trials showed no adverse events associated with bilberry (Arevström et al. 2019; Gizzi et al. 2016; Ozawa et al. 2015; Hoggard et al. 2013; Canter and Ernst 2004). However, mild to moderate flatulence and mild heartburn was reported in a pilot study including 13 ulcerative colitis patients who were taking a standardized anthocyanin-rich bilberry preparation (160 g) daily for six weeks (Biedermann et al. 2013). Gastrointestinal complaints were also noted in the patients of herbalists through an anonymous questionnaire (Cicero et al. 2004). A postmarketing survey of persons taking bilberry fruit extract indicated that respondents reported adverse events involving the gastrointestinal tract, skin, or nervous system, although no causal association between bilberry and any of the symptoms could be established (Eandi 1987).

Pharmacological Considerations

A cohort study including 9,732 adults showed increased systolic and diastolic blood pressure levels in bilberry users but the relationship was considered non-causal by the researchers (McCarty et al. 2013). A study on the use of bilberry fruit extract prior to surgery showed reduced bleeding during surgery (Gentile 1987). One ex vivo human study, one animal study, and two in vitro studies indicated that bilberry fruit may reduce blood coagulation (Gomez-Serranillos et al. 1983; Morazzoni and Magistretti 1990; Pulliero et al. 1989; Zaragoza et al. 1985).

Pregnancy and Lactation

A limited number of human studies of bilberry fruit extract used during pregnancy have not shown any adverse effects on mother or fetus (Ulbricht et al. 2009; Eandi 1987; Grismondi 1980; Pourrat et al. 1967; Zaragoza et al. 1985). No information was identified on the safety of bilberry fruit or leaf during lactation, although traditional consumption as a food suggests that no adverse effects are expected from bilberry fruit (Drugs and Lactation Database 2018; Ulbricht et al. 2009; Upton 2001).

Review Details

I. Drug and Supplement Interactions

Clinical trials of drug or supplement interactions

No clinical trials of drug or supplement interactions were identified.

Case reports of suspected drug or supplement interactions

No case reports of suspected drug or supplement interactions were identified.

Animal trials of drug or supplement interactions

To assess the effect of bilberry on select drug metabolizing enzymes and their nuclear receptors, rats were orally administered powdered dried ripe fruit bilberry extract with water for four and eight weeks. The low dose (0.15 g/L) was determined from the approximate minimum human consumption of anthocyanins from either fresh or dried bilberry fruit. The high dose (1.5 g/L) reflected the previously determined no observed adverse effect level for cranberry (*Vaccinium macrocarpon*) juice in rats. Although CYP2E1 activity significantly increased after 4 weeks,

several plasma markers led the authors to conclude that bilberry did not actually increase oxidative stress. Overall, the moderate bilberry-induced modulation of CYPs and mild changes in select biochemical parameters were determined to have no physiological or clinical significance. Bilberry had no effect on hematological, oxidative stress, or antioxidant markers (Prokop et al. 2019).

II. Adverse Events

Adverse events reported in clinical trials

~~A systematic review identified cachexia, anemia, and icterus as possible adverse events from bilberry overdose based on prior studies (Ige and Liu 2020).~~ A systematic review of placebo-controlled studies on the anthocyanins from bilberry fruit indicated that no adverse effects were reported in any of the clinical trials on bilberry extracts (Canter and Ernst 2004).

In a prospective, open-label, randomized, controlled clinical trial, 50 patients (42 male) with a history of acute myocardial infarction were allocated to receive standard medical therapy with a 40 g dose of freeze-dried bilberry powder or standard medical therapy alone for eight weeks. No adverse events were reported in the bilberry group (Arevström et al. 2019).

In an open-label study, 140 individuals with different types of retinopathy were enrolled in the following groups: standard management; standard management with 160 mg bilberry extract (standardized in 36% anthocyanins with the full-range of non-anthocyanin components); standard management with 160 mg generic bilberry extract (standardized in 36% anthocyanin with highly purified anthocyanins diluted with maltodextrin). At the conclusion of the six-month study, no side effects, safety issues, or tolerability concerns were reported. No clinically relevant changes in blood and physiological parameters were observed (Gizzi et al. 2016).

In a prospective, double-blind, placebo-controlled study of eye fatigue, 88 video display terminal office workers were randomized to receive either bilberry extract (480 mg) or placebo capsule daily for eight weeks. Of the 80 participants that completed the study, five (11.6%) subjects in the bilberry group and five (13.5%) in the placebo group reported minor adverse events, the most common being headache (bilberry, n = 1; placebo, n = 3) and malaise (both, n = 2). Gastritis, gastric distress, tinnitus, throat pain, and nausea were also reported in both groups. No statistically significant differences between the groups were noted, and the authors concluded that none of the presenting symptoms were related to the intervention (Ozawa et al. 2015).

In an open-label, prospective, non-blinded, non-controlled pilot study, 13 patients with mild to moderate ulcerative colitis were given a standardized anthocyanin-rich bilberry preparation (160 g daily) for six weeks. The main components of the preparation were 59.63% dried bilberries and 25.90% concentrated bilberry juice and the daily dose equates to approximately 600 g fresh fruit according to the authors. One-third of patients reported mild to moderate flatulence and one patient reported mild heartburn. No serious adverse events nor changes in electrolytes, inflammatory markers, or renal and liver function were observed (Biedermann et al. 2013; Rahman et al. 2017).

In a randomized, double-blind crossover study, eight male volunteers with type 2 diabetes were given a single oral capsule of 0.47 g standardized hydroalcoholic extract of bilberry fruit (36% w/w anthocyanins) or placebo followed by a two-week washout period. No side effects were reported, and no changes in gut, pancreatic, and anti-inflammatory peptides or antioxidant responses were observed (Hoggard et al. 2013; Yatoo et al. 2018).

Case reports of adverse events

In an anonymous questionnaire completed by 685 Italian herbalists, gastrointestinal complaints were sometimes reported in diabetic patients following bilberry consumption (Cicero et al. 2004). In a postmarketing survey of persons taking bilberry fruit extract, 94 of the 2,295 survey respondents noted side effects, mostly related to the gastrointestinal and nervous systems or skin. Due to the nature of the survey, a causal association between bilberry and the symptoms could not be established (Eandi 1987).

III. Pharmacology and Pharmacokinetics

Human pharmacological studies

A cohort study to assess the potential association of different dietary supplements and blood pressure evaluated dietary intake and blood pressure data from 9,732 Midwestern adults. A significant increase in systolic and diastolic blood pressures was observed for bilberry in the cohort. Both mean systolic (126.3 bilberry users; 118.6 non-users) and diastolic blood pressure (74.7 bilberry users; 71.9 non-users) was significantly higher in a subset of subjects with no hypertension-related diagnoses. These findings should not be interpreted as causal, however, due to the limitations of the study, including a lack of characterization regarding bilberry dose(s) and preparation(s) (McCarty et al. 2013).

After oral administration of bilberry fruit extract (173 mg daily) to healthy volunteers, platelet aggregation was inhibited in blood samples tested ex vivo after 30 days of bilberry administration and was further inhibited after 60 days of consumption (Ulbricht et al. 2009 Pulliero et al. 1989). In contrast, preoperative treatment with bilberry fruit standardized extract (160 – 320 mg daily) in patients undergoing ear, nose, or throat surgery significantly reduced the incidence and severity of intraoperative and postoperative bleeding and hemorrhagic complications (Gentile 1987). One older study reported that bilberry anthocyanins had a tendency to reduce hemorrhagic retinopathy due to anticoagulant therapy (Scharrer and Ober 1981).

Animal pharmacological studies

~~purified~~ Bilberry anthocyanins ~~extract~~ were orally administered to 4- and 12-month old female rats (10, 20, and 40 mg/kg) daily for 10 weeks in a study of intestinal function. The doses used were 5, 10, and 20 times the bilberry anthocyanin recommended daily intake in humans. While the growth of some beneficial intestinal bacteria was not negatively impacted, the growth of other beneficial bacteria was inhibited at the high dose. Overall, the authors concluded the gut

microbiota was not altered in a significant manner. Activity of select digestive enzymes significantly decreased in the cecum in the groups receiving bilberry (Li 2019).

A bilberry fruit extract high in anthocyanins administered to rats in single oral doses from 2.5 to 400 mg/kg significantly increased bleeding time at doses of 5 mg/kg or more (Morazzoni and Magistretti 1990).

In vitro pharmacological studies

An anthocyanin-rich bilberry extract showed an antagonistic effect with the cytostatic properties of erlotinin, a chemotherapeutic drug, in human epithelial cells. The antagonistic interaction was also seen in bilberry's major anthocyanin (delphinidin-3-O-glucoside) and corresponding anthocyanidin (delphinidin) but not in its two degradation products, gallic acid and phloroglucinol aldehyde (Aichinger et al. 2016).

Encapsulated commercial bilberry fruit did not inhibit drug metabolizing uridine diphosphate-glucuronosyltransferase (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) enzymes in human liver microsomes exposed to different pharmaceutical drugs (nilotinib, hecogenin, 1-naphthol, niflumic acid, and efavirenz) at a 3.0% concentration. Bilberry's low solubility in the study solvent was a limitation of the study since higher concentrations of organic solvent are associated with stronger UGT inhibitory activity (Choi et al. 2014).

A water-ethanol bilberry fruit extract significantly inhibited uptake of estrone-3-sulfate, an organic anion-transporting polypeptide B (OATP-B) substrate, by human embryonic kidney cells by 75.5%. Therefore, co-administration of bilberry may decrease absorption of drugs or estrogens transported by OATP-B in the intestine and the mechanism may be primarily attributable to its flavonoid content (Fuchikami et al. 2006)

Two in vitro studies of bilberry fruit anthocyanins indicated that inhibition of platelet aggregation by bilberry was greater than that of aspirin (Gomez-Serranillos et al. 1983; Zaragoza et al. 1985).

IV. Pregnancy and Lactation

No treatment-related adverse events were reported in a study of pregnant women taking a standardized bilberry fruit extract (320 mg anthocyanins daily) for 60 to 90 days, starting in the sixth month of pregnancy (Grismondi 1980), nor in pregnant women taking a standardized bilberry fruit extract (160 – 320 mg daily) for 90 days (Teglio et al. 1987).

A standardized bilberry fruit extract demonstrated no adverse effects on fertility in rats (Eandi 1987). Administration of anthocyanins or standardized bilberry fruit extracts did not produce any teratogenic activity in a single generation of rats or in three generations of rats and rabbits (Eandi 1987; Pourrat et al. 1967).

No information on the safety of bilberry fruit during lactation was identified. Based on the traditional safe consumption of bilberry fruit as a food, no adverse effects are expected (Drugs and Lactation Database 2018; Upton 2001).

V. Toxicity Studies

Acute toxicity

The LD_{50} of intraperitoneally administered standardized bilberry fruit extract in rats is 2.4 g/kg, and 0.24 g/kg for intravenously administered extract. No lethal dose could be determined for orally administered standardized extract at doses up to 20 g/kg in rats (Pourrat et al. 1967). In mice, the LD_{50} of intraperitoneally administered standardized bilberry fruit extract is 4.1 g/kg, and 0.84 g/kg for intravenously administered extract. No lethal dose could be determined for an orally administered standardized extract at doses up to 25 g/kg in mice (Pourrat et al. 1967). Other acute toxicity studies indicated that no signs of toxicity were observed for orally administered bilberry fruit extract at doses over 2 g/kg in mice and rats and over 3 g/kg in dogs. A darkening of urine and feces was noted in the animals (Eandi 1987).

Short-term toxicity

No toxic effects were observed in guinea pigs administered bilberry fruit extract at doses up to 43 mg/kg daily for 2 weeks, nor in rats fed the same dose for 6 weeks (Pourrat et al. 1967).

Similarly, no toxic effects were observed in rats administered up to 36 mg/kg bilberry fruit extract intravenously every day for 4 weeks or in dogs administered 12 mg/kg bilberry extract intravenously every day for 13 weeks, although dark blue pigmentation of urine, skin, eyes, and sometimes liver, kidneys, and ovaries was observed in the rats and dogs (Eandi 1987).

Chronic toxicity

No changes in urinary, hematological, gross, or microscopic parameters were observed after oral administration of standardized bilberry fruit extract in rats at doses of 125 to 500 mg/kg daily nor in dogs administered 80 to 320 mg/kg daily for 6 months (Eandi 1987).

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