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SHORT REVIEW

Vaccinium myrtillus: Unveiling the Pharmacognostic Secrets of a Superfruit

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Abstract

The bilberry (*Vaccinum myrtillus* L.) is one of the most plentiful sources of reddish-blue phenolic substances known as anthocyanins. These substances are considered to be the predominant bioactive responsible for the many health benefits connected with bilberries. Bilberries have higher anthocyanin outputs than many other berries because the skin and flesh of the berry both contain anthocyanins. It is also believed that berries have a distinct and delicious scent. It blooms from April to June and bears spheroidal, blue-black fruits with many seeds that mature from July to September. Notwithstanding assertions that bilberries have anti-oxidant, anti-inflammatory, antibacterial, lipid-lowering, cancer-preventive, and neuroprotective potential. It's great sources of functional food because not any adverse responses have been reported. This overview explains the characteristics and profile of bilberries as well as the evidence that confirms up their health.

Major Findings: It is a great source of functional food, as no adverse effects have been reported.

Keywords: Anthocyanins, Bilberry, Health Benefits, Phytoconstituents

1. Introduction

One of the most valuable wild berries for European economy is the Bilberry, a dwarf shrub of the genus *Vaccinium*, occasionally referred to as the European blue-berry (*V. myrtillus* L.). A perennial shrub that reaches a height of 35 to 60 cm, Bilberries are a member of the *Ericaceae* family and may be grown in coniferous woods, moors, America, and meadows in Northern Europe. They can also be found in Asia. It can also be referred to as Huckleberry or Whortleberry. Flowering from April to June, it bears many-seeded, blue- or black-coloured fruits that develop from July to September. The Danish term "*Bollebar*", which means "dark berry," is the origin of the fruit's name, which originates from its striking colour. Although bilberries are rich in substances that promote health and have several biological qualities, they have been referred to as "superfoods". Berries are a prominent fruit that are with lots of vitamins, minerals, and polyphenols, besides other nutrients and non-nutritive ingredients. Bilberries are mostly consumed and sold commercially as dried, frozen, and fresh berries. They are also occasionally used to make syrups, pies, drinks, and tarts, as well as industrial goods that includes concentrates, juices, and jams that are canned. In fact, the leaves are mostly utilized in the making of infusions. The bilberry is an extremely concentrated natural source of anthocyanins. Approximately 90% of the phenolic chemicals in bilberries are formed up of anthocyanins. The element of anthocyanins is an anthocyanidin aglycon linked to one or more sugar moieties. The anthocyanidin aglycons that are frequently found are cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petudinin. Seldom can pelargonidins be identified in Vaccinium berries. Five aglycons 3-O-glucosides, 3-O-galactosides, or 3-O-arabinosides are one of the 15 primary anthocyanidin glycosides that are frequently found in bilberries. Alongside with a number of active ingredients including resveratrol, flavonols (quercetin,

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catechins), ellagitannins, phenolic acids, and iridoids, these are the main components that have been extracted and identified from berries (which make up to 0.1-0.25% of the fresh fruits) and leaves. Whilst this range varies with cultivar, growing circumstances, and berry maturity, the total anthocyanin concentration of bilberries is typically in the range of 300-700 mg/100 g fresh fruits. 100 g of fresh bilberries provide little quantities of vitamin C, quercetin, and catechin in addition to anthocyanins. Further, there is a wide range in recommended daily doses (20-60 g of dried berries and 160-480 mg of powdered extract, for instance). Whereas the amounts of commercial bilberry products might vary widely, it is often standardized with a 25% anthocyanidin content, that's comparable to 36% anthocyanins. Anthocyanins are discovered in plants to serve various purposes, one of which is to shelter them from harm triggered by radiation, such as UV rays from the sun. Natural plant-based items consumed by humans may also defend against radiation harm. In addition, using cellular resources from growth and reproduction to apply chemical elicitors to generate defense responses is a very worthwhile technique for plants to defend against herbivores. Humans as well as animals must consume anthocyanins because of their vital function in maintaining health. It may be helpful when treating or preventing diseases linked to reducing oxidative stress, inflammation, cancer, microbial growth suppression, cardiac support, dipped glucose levels, neuroprotective, ophthalmic, and cosmetic applications. Consuming fruits on a regular basis may slow down the aging process and lower the chance of getting a number of diseases, includes cancer, heart disease, rheumatoid arthritis, eyesight problems, dementia, and Alzheimer's or Parkinson's. Juices from black currant and bilberry plants reveal strong antibacterial and antiadhesive properties against *Asaia*-related food-spoiled bacteria. In particular, bilberry juice stands out for having an elevated level of polyphenols, such as A-type proanthocyanidin, which possesses potent antibacterial qualities. Due to their high concentration of recognized health-promoting bioactive components, they are a beneficial addition to consumer beverages and a good substitute for artificial additives in drinks that must retain their antibacterial stability. About 18% of Americans consumed the recommended minimum of two cups of fruit daily. Youngsters between the ages of two and five ingested the greatest amount of fruit overall, with only 4% being berries and nearly half having juice, greatly lowering the antioxidant activity[1-3].

2. Profile of Phenolic Constituents in Bilberry

The bilberry business is focusing its research primarily on anthocyanins. This is because bilberry fruits, one of the most effective sources of anthocyanins, contain substantial concentrations of those substances in both the skin and the flesh. Anthocyanins, along with terpenoids (which include triterpenoids, tetraterpenes, and iridoids), flavonols (like quercetin and myricetin), tannins and flavanols (like epicatechin and catechin), coumarins, phenolic acids, and resveratrol, account for almost all of phenolic compounds in bilberries, approximately 90% (Figure 1)[4,5].

Berries and leaves have a range of bioactive elements, including flavonols (quercetin, catechins), ellagitannins, phenolic acids, and iridoids in along with resveratrol. The primary ingredients taken from berries that can be detected in up to 0.1-0.25% of fresh fruits are termed anthocyanins. One of the constituents of anthocyanins is an aglycon called anthocyanidin, which forms a connection with one or more sugar moieties. The anthocyanins identified in bilberries that are most concentrated are cyanidin and delphinidin; the least concentrated are malvidin, petunidin, and peonidin.

Three-o-glucosides, three-o-galactosides, and three-o-arabinosides of 5 different aglycons are the 15 primary anthocyanidin glycosides that are usually believed to be found in bilberries[6]. When compared to those from southern latitudes, the phenolic content of bilberry fruits that are grown in Northern latitudes is considered to be greater. A small number of anthocyanidins have been identified in bilberry, practically all of which are glycosides. Sugars, vitamins, pectin, and phenolics are all observed to be present in bilberries when utilized[7-9].

3. Health Benefits of Bilberry

3.1 Anti-oxidant Activity

Anthocyanins are renowned for their powerful antioxidant effects, which make it possible to bind to metal

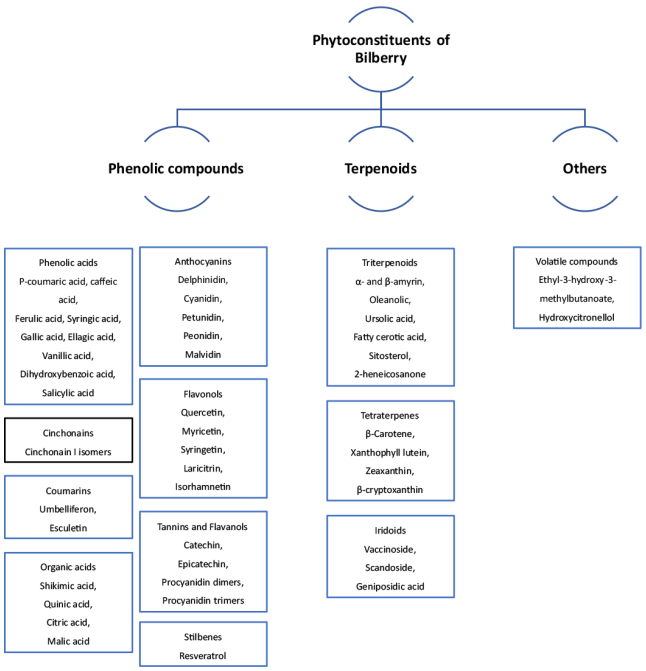


Figure 1. Bioactive phytoconstituents of Bilberry.

ions to effectively neutralize free radicals. Researcher indicates that bilberries and bilberry anthocyanin-rich extract are highly successful at protecting rat liver microsomes from oxidative harm and apolipoprotein B from UV-induced oxidative fragmentation[10]. Moreover, bilberry revealed exceptional scavenging action against hydroxyl and superoxide radicals in mouse stomach tissue homogenates, which results in an important decrease in lipid peroxide levels. With an IC50 value of 3.99 ± 0.14 µg/ml, Bilberry possessed the highest capacity to neutralize the 1,1-Diphenyl 2-Picrylhydrazyl radical (DPPH) in a separate research evaluation. With a value of 2359 µmol TE/100g, bilberry juice has the highest Oxygen Radical Absorbance Capacity (ORAC)[11]. Furthermore, Bilberry revealed a dose-dependent rapid elimination of the superoxide radical, with an activity of 108 ± 7.2 units of SOD per milligram of extract[12]. The findings of antioxidant studies on animals are contradictory. During 14 days, rats received an anthocyanin-enriched bilberry extract; nevertheless, this had no effect on the levels of the oxidative stress marker 8-Hydroxy-2-deoxyguanosine (8-OHdG) in their urine. Upon several efforts, the brains of OXYS rats fed BE-containing chow showed a significant reduction in malondialdehyde levels-a biomarker of lipid peroxidation[13]. Still, Wistar rats did not exhibit this phenomenon, indicating that the extract's effects are limited to situations in which high levels of MDA are present[14]. The study demonstrated that rats administered 1% w/w bilberry extract in their diet over a period of time showed increased levels of Glutathione (GSH) in their heart muscle cells and less amount of blood lipid peroxides[15]. Although promising results from studies on animals, bilberry use has not been shown to have any noticeable effect on lipid peroxidation in human volunteers[16]. The phenolic substances found in bilberries, such as anthocyanins, ellagitannins, and proanthocyanidins, exhibit various levels of antioxidant capacity. Also, the properties of the matrix in which they reside have a significant impact on their attributes[17].

3.2 Anti-inflammatory Activity

The anti-inflammatory abilities of bilberry have been shown by measuring the reduction in the manufacturing of excess nitric acid in RAW 264.7 cells when given Lipopolysaccharide (LPS). The amounts used for the bilberry therapy were 800 and 1000 µg/ml, accordingly. In LPS-induced RAW 264.7 cells, cytokines such as TNF-α and IL-6 from bilberries were seen, indicating that bilberries could serve as an effective alternative therapy for inflammatory diseases[18].

An experiment was conducted to evaluate the impact of *V. myrtillus* L. extract on the viability of RAW264.7 murine macrophages. The most effective experimental configurations, utilizing increasing quantities of H_2O_2 and extract for varied incubation times, were investigated prior to evaluating the viability of the cells. A 200 µM concentration of H_2O_2 was employed, which may inhibit PPARγ expression and boost the synthesis of COX2, IL1β, NFE2L2, NFκB1, NFκB2, NOS2, and TNFα on mRNA. It was shown that the extract down-regulates COX2, IL1β, NFκB1, NFκB2, TNFα, and NOS2 expression while up-regulating NFE2L2[19].

In one investigation, mice with edema from Carrageenan (450 mg/paw) were utilized to examine the anti-inflammatory effects of *V. myrtillus* L. extract. The paw volume was assessed 30, 90, 180, and 300 minutes after the injection of Carrageenan or Phosphate Buffered Saline (PBS). The results of the research demonstrated that paw edema reduced by 28.8% at extract concentrations of 50 and 200 mg/kg.

Carrageenan-injected neutrophils go to the swollen paw and provide Myeloperoxidase (MPO) and other enzymes. These findings indicate that in inflammatory tissues causes neutrophil counts to rise, perhaps increasing the inflammatory response. By diminishing MPO generation and lipid peroxidation byproducts, the *V. myrtillus* L. extract appeared to affect the inflammatory event through many pathways. Acute inflammation has been lowered by the extract due to its capacity to inhibit Reactive Oxygen Species (ROS) activity[20].

3.3 Anti-microbial Activity

Several phenolic compounds, especially tannins, lignans, phenolic acids, and flavonoids, are well recognized to have antibacterial effects[21]. It seems that the flavonoid portion, namely the anthocyanins, is responsible for the bilberry's effect. The bilberry and other modified berry polyphenolic extracts indicated antibacterial properties against *Salmonella* and *Staphylococcus aureus*, two human pathogenic bacteria. Bilberry also proved to be beneficial for inhibiting the growth of different gram-positive bacteria of *H. pylori*, *Clostridium*, and *Bacillus*. Simultaneously, it was demonstrated that the degree of hydroxylation of phenolic compounds is closely related to their ability to exclusively inhibit gram-negative bacteria, such as *Salmonella* species and *Escherichia coli*[22]. It concludes that all fruits or phytocomplexes have a greater antibacterial impact than the purified components.

3.4 Cardio-protective Effects

Although bilberry is most often used to improve eyesight, it has also been shown to reduce hyperglycemia, have calming and lipid-lowering effects, increase cell fortress resistance, and lower body weight[23]. Based to this hypothesis, bilberry has the potential to be an effective therapy or antidote for disorders linked to dyslipidemia, enlarged oxygen-expending weight, Cardiovascular Disease (CVD), improvement, diabetes, and picked age-related issues[24].

Additionally, reports on bilberry's antibacterial activity are shown in the middle of this part. The layout of bilberry and its many sections and qualities is also explored, along with an exhibit showing the berry's preferences for wellness. Anthocyanins found in berries act as a surprise cardioprotectant by maintaining vascular porosity, reducing inflammatory reactions and thrombocyte aggregation, and providing preferable vascular security when compared to other cardioprotective medications[25]. Vascular disease, sclerosis, and vein sclerosis reduce the blood vessel walls capacity to adapt, which exacerbates poor circulation and plaque development. The rogue fabric exhibited symptoms of loosening up and endothelial cells producing nitrous oxide when exposed to food additive-driven high bushberry separation in a test tube, examining inconsistently, treating rodents with *V. myrtillus*, a resveratrol derivative, for 12 weeks prior to the diagnosis of cardiovascular disease, completes the blood-cerebrum barrier porosity standard and limits the increase in vascular porosity within the skin and the channel divider. When compared to untreated controls, rodents administered an oral measured quantity (10 mg for every 10 g person amount) of a business product containing 36 bilberry anthocyanosides for 2 or 4 weeks showed diminished emerging leukocytes inside the vessels and higher capillary intromission[26].

3.5 Neuro-protective Effects

There has been suggestion that the neuron-protective qualities of food and dietary components, particularly those high in antioxidants, can help reduce neurodegeneration. Degenerative diseases associated with aging that impair cognitive function are an increasing and persistent occurrence. One of the primary causes of death and disability is stroke, which is usually brought on by thrombosis or hypertension. Bilberry's anti-inflammatory and vasodilatory qualities reduce the incidence of thrombotic and haemorrhagic strokes, which may have a significant effect on cognition and neuromotor function.

Numerous neurological diseases, including as Parkinson's disease, Huntington's disease, amyotrophic lateral induration, and Alzheimer's disease, have been linked to the development of aerophilic pressure, which is mainly caused by excessive ROS formation in cells[27,28]. Studies into animal behaviour have shown that consuming blackberries, bilberries, or strawberries can lessen the effects of brain aging. Growing research indicates that these plant extracts, together with their association with fruits, are good for human health and lower the risk of disorders, especially Type 2 polygenic disorder[29,30]. Commercial bilberry extract has been

found to raise triiodothyronine transport to different brain regions in rats. Bilberry has also been shown for improving short-term memory, vision, and the control of sensory input in animals[31-34].

3.6 Hypoglycemic Effects

Bilberry's capacity to inhibit insulin synthesis, glucose transport, and α-glucosidase activity accounts for its hypoglycaemic function. The major anthocyanins found in bilberries, cyanidins and delphinidins, have been demonstrated to have the greatest effect on the formation of insulin from cultured rat pancreatic B cells[35,36].

Bilberry juice or extract can lower blood sugar levels by at least 50% of the maximum values, as shown by several animal trials[37]. While there has been little human research on the hypoglycaemic effects of berries (such chokeberries and cranberries), there is a dearth of meaningful evidence from human experiments[38]. Actually, only three trials including people with Type II diabetes are now available on government's clinical trials website and only 1 of them has produced results. In patients with Type 2 Diabetes, this investigation showed that standardized bilberry extract was effective in lowering insulin levels and postprandial glycemia[39].

4. Interactions with Supplements

Numerous polyphenols have been shown to be able to lessen the cytostatic effects of erlotinib *in vitro*. Erlotinib is a chemotherapeutic medication approved for use in the management of non-small cell lung cancer and pancreatic cancer. Blocking the receptor tyrosine kinase known as the Epidermal Growth Factor Receptor (EGFR) is its main mode of action. Tyrosine kinases, including EGFR, have been demonstrated to be inhibited by some anthocyanins and anthocyanin-rich preparations, such as bilberry extract. An 80-year-old patient who had bilberry juice (200 ml/day) plus warfarin (27.5 mg/week for 1.5 years) was reported to have seen an INR drop to 1.6 (onset time 4 days). After that, the co-treatment was stopped, the warfarin dosage was raised to 32.5 mg/w, and the person had completely recovered. Bilberry anthocyanins, which have antiplatelet properties, ought to raise the risk of bleeding when coupled with treatment with anticoagulants, which is why warfarin's less effective action is surprising. It's unknown what mechanism drives this reciprocal relationship. At the indicated dosage of bilberry formulations, it was unable to prove a true interaction with anticoagulants and antiplatelet medications, despite anecdotal evidence[40,41]. Bilberry, a popular herbal supplement, has been found to be unable to inhibit uridine diphospho-glucuronosy ltransferase in a recent study of the *in vitro* and *in vivo* potential of several berries. Consequently, by this mechanism, it does not seem to produce herb-drug interactions that are clinically important[42].

5. Conclusion

The bilberry, with its many health benefits, is the best plant in the world for maintaining physical well-being. Bilberries have been utilized for edible and medicinal purposes since prehistoric times. These are some of the best sources of the colours known as anthocyanins. Bilberries contain a lot of anthocyanins, especially cyanidins and delphinidins. It has been found to offer several health advantages, including anti-inflammatory, antibacterial, hypoglycaemic, cardio-protective, and neuro-protective properties. It is believed that the high concentration of antioxidants in bilberry fruits has a significant role in the brain dysfunctions linked to diabetes. Their ability to control the release of neurotransmitters mitigates the deleterious effects of free radicals on cognitive function, which is primarily reason. The effects of anthocyanins include enhancing neuronal cognitive brain function, upregulating tumor suppressor genes, killing cancer cells, and repairing and maintaining genomic DNA integrity through the decrease of age-related oxidative stress. Anthocyanin consumption is associated with a lower risk of hypertension and cardiovascular disease.

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7. Author Contribution

Conceptualization: Divya Kanojiya and Ghanshyam Parmar; methodology: Divya Kanojiya and Sapana

Patil; Validation: Ghanshyam Parmar, Sweta B Besh and Maitri Mahant; formal analysis: Divya Kanojiya; writing – original draft preparation: Divya Kanojiya; writing – review and editing: Ghanshyam Parmar; visualization: Divya Kanojiya. All authors have read and agreed to the published version of the manuscript.

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