Vaccinium in Diabetes and Microvascular Complications

Subjects: Urology & Nephrology

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Vaccinium L. (Ericaceae) is a genus of plants enriched with polyphenolic compounds in their leaves and fruits. *Vaccinium* and its extracts have demonstrated good bioactivity in reducing blood glucose, oxidative stress, and inflammation, making them excellent candidates for the management of diabetes and diabetic vascular complications.

diabetes mellitus | diabetic kidney disease | diabetic retinopathy

1. Vaccinium

1.1. General

The *Vaccinium* L. (Ericaceae) genus, consisting of approximately 450 species, contains a range of terrestrial or epiphytic shrubs and dwarf shrubs that mainly grow in cooler areas across Europe, Southeast and Central Africa, North and Central America, and Asia [1][2]. Most *Vaccinium* fruits are edible, and some have a long history of human consumption. *V. corymbosum* (blueberry), *V. oxycoccos* (cranberry), *V. macrocarpon* (American cranberry), *V. myrtillus* (bilberry), *V. Arctostaphylos* (bearberry), and *V. vitis idaea* (lingonberry) are the species of *Vaccinium* most investigated [3]. Arevka illustrated the differences between four common species: bilberry, blueberry, lingonberry, and cranberry [1].

Leaves and fruits have been widely used in traditional medicine for the treatment of stomatitis; diabetes; renal stones; and intestinal, liver, and urinary tract disorders, as early as the 18th century [4]. Some *Vaccinium* species were domesticated in the 20th century and are now cultured on a large scale in several regions worldwide as economic fruits.

1.2. Chemical Profile

The chemical components of *Vaccinium* have been extensively investigated in several studies. Polyphenolic components, including ANT (cyanidin, malvidin, and delphinidin), flavonoids (quercetin, isoquercetin, kaempferol, apigenin, and myricetin), phenolic acids (gallic, *p*-coumaric, cinnamic, syringic, ferulic, and caffeic acids), and ellagitannins, are considered the main bioactive compounds of *Vaccinium* [5].

ANT is the primary phytochemical characteristic of *Vaccinium*. To date, more than 35 anthocyanin glycosides have been identified in *Vaccinium*, with the principal anthocyanins varying among species. In addition, more than 50 other flavonoids, mainly flavanols and pro-anthocyanidins, have been identified in *Vaccinium*, and their profiles vary between species [2].

1.3. Bioactivity

Phytochemicals from several *Vaccinium* species exhibit good activity in multiple biofunctions. The enrichment of polyphenolic compounds leads to a strong antioxidant effect, which is the most acknowledged bioactivity of these berries [6]. Similarly, high concentrations of ANT and flavonoids contribute to the anti-inflammatory effects of *Vaccinium*. As many types of tissue damage are closely associated with oxidative stress and inflammation, *Vaccinium* demonstrates therapeutic potential under multiple pathological conditions, such as diabetes and diabetic vascular damage [7][8].

Moreover, *Vaccinium* has antimicrobial, anticarcinogenic, cardiovascular protective, vision improvement, and anti-neurodegenerative effects, which have been described in detail elsewhere [4][9][10][11][12]. Berries have the potential to reduce metabolic and cardiovascular risk [12][13]. Similarly, the intake of blueberries has been associated with a reduced risk of cardiovascular disease, death, and type 2 diabetes (T2D), as well as improved weight maintenance and neuroprotection in some epidemiological studies [14][15]. In addition, cranberries have special effect against urinary tract inflammation, tooth decay, periodontitis, and *Helicobacter pylori* infection of the stomach [16].

2. Clinical Evidence for the Effect of *Vaccinium* on Diabetes and Diabetic Microvascular Complications

Owing to the powerful antioxidant effects of *Vaccinium*, the therapeutic potential of these fruits and their extracts has been evaluated for several chronic diseases, including diabetes mellitus, cancer, and neurodegenerative and cardiovascular diseases. Researchers focus on *Vaccinium* extracts for the treatment of diabetes and diabetic microvascular complications (DR and DKD).

2.1. Effect of Vaccinium on Type 2 Diabetes Mellitus Treatment

There are many clinical studies on the treatment of diabetes with *Vaccinium*, which can lower blood glucose levels. Whole blueberry and soluble fiber supplementation prevents gestational weight gain, improves inflammation, and controls blood glucose levels in obese women [17]. In addition, in adults, pancreatic polypeptide (PP) concentrations were remarkably higher when 140 g of whole blueberries were administered [18]. The consumption of 22 g of freeze-dried blueberries for 8 weeks was beneficial to the hearts of men with T2D [19]. In addition to blueberries, bilberries, cranberries, and whortleberries have a similar effect on blood sugar control, and some studies have recommended the use of bilberries to regulate blood glucose levels in patients with T2D or metabolic syndrome [20][21][22]. In addition, one study showed that bilberries lower postprandial blood glucose and insulin levels [22]. One study showed that cranberries could improve postprandial glucose management [23]. In addition,

dried cranberries [24] and cranberry juice [25][26][27] have similar effects and that whortleberry extract considerably decreases HbA1c, fasting glucose, and 2 h postprandial glucose levels [28]. ANT are chemicals found in *Vaccinium* species. Purified ANT favorably affects glycemic control and the lipid profile [29][30].

A recent meta-analysis showed that consumption of blueberries and cranberries remarkably reduced fasting blood glucose and glycated hemoglobin levels in patients with diabetes is highly credible. In individuals with diabetes, the consumption of cranberries or blueberries considerably reduced fasting blood glucose [MD: −17.72 mg/dL; 95% CI: −29.62, −5.82; p = 0.03; I2 = 57%] and glycated hemoglobin [MD: −0.32; 95% CI: −0.57, −0.07; p = 0.15; I2 = 39%]; however, there was no effect on insulin resistance [8]. Similarly, another meta-analysis, including seven randomized controlled trials, involved 270 adult patients with T2D, who consumed cranberry juice (240 mL) daily for 12 weeks and were supplemented with powder or blueberry extract (9.1–9.8 mg of ANT) for 8 to 12 weeks to control blood glucose in patients with T2D, despite the heterogeneity in the form of dose, administration (natural, extract, dried, preparation-juice), duration of intervention, and type of population studied involving these two berries [7]. Grohmann et al. [11] showed that interventions with lingonberry and blackcurrant extracts resulted in a mean reduction in HbA1c and fasting glucose levels of 4.7% and 3%, respectively, and that lingonberry and blackcurrant extracts were beneficial for glucose metabolism, although the current evidence is supported by only a few studies in Chinese subjects with T2DM.

In clinical trials using *Vaccinium* specifically, oral administration of the fruit and its extracts has shown mixed results. Owing to the high amount of sugar present in *Vaccinium*, extracts without sugar tend to show better anti-diabetic effects than the whole fruit or juice because of the higher content of bioactive substances [9]. A study in which patients consumed 400 g of fresh bilberries for eight weeks showed a negative correlation between the dietary intake of lingonberries and fasting plasma glucose levels; however, insulin sensitivity remained unchanged [31].

However, other clinical studies have shown no significant differences in fasting glucose levels between treatment and control groups after 12 [32] or 24 weeks [33] of dietary anthocyanin supplementation, or 2 months of daily intake of 400 g of fresh lingonberries [34]. Even in the latest clinical study in Chinese patients with T2DM, using 1.4 g of bilberry extract daily for 6 weeks, HbA1c decreased by 0.31 ± 0.58% while taking the supplement; however, this change was not considerably different compared to placebo, and there was also no considerable difference between lingonberry extract and placebo in antioxidant status, oxidative stress and inflammatory status treatment [35].

2.2. Research for the Treatment of DR and DKD

There are few clinical studies on *Vaccinium* and its extracts in the treatment of DR. In the first open-label placebo-controlled study of bilberry extract in DR, a combination of 200 mg bilberry extract and 10 mg carotene administered thrice a day reduced vascular permeability and improved retinal vascularity [36]. In another study, in patients with diabetic and hypertensive retinopathy, 160 mg of bilberry extract containing 25% ANT taken twice daily showed a 77–90% improvement in fundus examination and fluoroscopic angiographic abnormalities

compared with placebo [37]. One study tested the effect of bilberry fruit extract on patients with diabetic retinopathy at a dose of 510 mg/day for one year, with gradual improvement in contrast sensitivity, but other measured parameters (corrected visual acuity, microaneurysms, hard exudates, and leaking points) remained unchanged for the entire duration of the study [38]. In a randomized, double-blind, monocentric, prospective study, supplementation with Macuprev (containing bilberries 36% and anthocyanosides 90 mg) increased the function of macular preganglional components, which helped to decrease inflammation in DR lesions [39]. Bilberries are also used to treat diabetes and microvascular complications [40]. However, high HDL levels are also associated with diabetic retinopathy [41]. Therefore, more basic experiments are needed to understand the mechanisms by which HDL affects DR. Further clinical trials are required.

Although there are few clinical studies on *Vaccinium* in the treatment of DKD, *Vaccinium* and its active components have shown promising results in the clinical intervention of CKD. *Vaccinium* is an important component of local diets in many countries. It is popular because of its pleasant taste and is often processed into alcoholic beverages, preservatives, jams, pies, and juices. Plant-based diets may help manage and prevent some of the symptoms and metabolic complications of CKD [42]. In a meta-analysis of cohort studies on CKD, seven studies including 15,285 participants showed that a plant-based diet reduced the risk of CKD [43]. There is growing evidence that an entire plant-based diet may slow the progression of CKD, reduce the incidence of cardiovascular disease, and lower the rates of obesity and diabetes, which, in turn, may delay the onset of kidney failure and dialysis [44][45][46].

In addition, some clinical studies have demonstrated the vascular protective effects of *Vaccinium*, indicating its potential application in the prevention of diabetic microvascular complications. One study showed the first sustained improvements in lipid status, vascular function, and underlying NO bioactivity following consumption of one cup of blueberries per day [47]. These findings suggest that blueberries exert immunomodulatory effects and reduce oxidative stress and inflammation in patients with metabolic syndrome [48]. Among the *Vaccinium* species, blueberry, cranberry, and bilberry have this vascular protective function. Cranberries decrease atherosclerotic cholesterol profiles, including total and LDL-C levels, and the total-to-HDL cholesterol ratio [49]. These findings suggest that daily consumption of cranberry beverages for 8 weeks may help reduce lipid status and alter certain biomarkers of oxidative stress in individuals with obesity and a pro-inflammatory state [50].

Despite progress in studies on the hypolipidemic and hypoglycemic effects of *Vaccinium* and improvement in DR, further studies with larger cohorts, longer follow-up periods, and more reliable endpoints (for example, proteinuria, glomerular filtration rate, and disease progression) are required to evaluate the use of lingonberry extract as an add-on therapy for T2D, diabetic retinal disease, and glycogenic kidneys.

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