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REVIEW ARTICLE

Review of Phytochemistry and Hypolipidemic Effects of *Vaccinium oxycoccus*

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Abstract: Cranberry (*Vaccinium oxycoccus*), a small evergreen shrub of the Ericaceae family, represents a valuable medicinal plant with diverse therapeutic applications in both traditional and modern medicine. The fruit's remarkable properties stem from its rich composition of bioactive compounds, primarily flavonoids including anthocyanidins, proanthocyanidins, and phenolic acids, which contribute to its potent antioxidant activity. Beyond its basic nutritional value of minerals and vitamins, cranberry demonstrates a uniquely low sugar content compared to other berries. Clinical and preclinical studies have established its efficacy in preventing urinary tract infections, exhibiting anticancer properties, and protecting cardiovascular health. The fruit shows promising results in obesity management and metabolic disorder treatment, with significant effects on lipid metabolism and atherosclerosis prevention attributed to its polyphenolic content. Research has documented its ability to regulate blood pressure, modulate glucose metabolism, and protect mitochondrial function. The antimicrobial properties extend beyond urinary tract applications, while anti-inflammatory effects suggest broader therapeutic potential. Modern investigations continue to uncover novel applications in functional foods and preventive medicine, particularly focusing on metabolic disorders and cardiovascular health. These findings establish cranberry as a significant natural therapeutic agent, warranting further investigation into its molecular mechanisms and clinical applications.

Keywords: *Vaccinium oxycoccus*; Hypolipidemic; Cranberry; Polyphenols; Antioxidants; Cardiovascular health.

1. Introduction

Medicinal plants have been fundamental to human healthcare throughout history, with berries from the Ericaceae family holding a particularly distinguished position due to their therapeutic properties. Among these, the Vaccinium genus encompasses over 450 species distributed across diverse geographical regions, including Europe, North America, Asia, and parts of Africa. The European cranberry (*Vaccinium oxycoccus*), also known as small cranberry or bog cranberry, has emerged as a significant subject of scientific interest due to its unique phytochemical profile and therapeutic potential [1]. *V. oxycoccus* is a perennial evergreen shrub that flourishes in wetland ecosystems, particularly in raised bogs and intermediate wetlands. Traditional communities have long harvested these berries for both culinary and medicinal purposes, incorporating them into foods, beverages, and traditional remedies [2]. The fruit's therapeutic applications span various health conditions, from urinary tract infections to cardiovascular disorders, supported by a growing body of scientific evidence [3].

The pharmacological significance of cranberries lies in their complex phytochemical composition. These fruits are particularly rich in polyphenolic compounds, including flavonoids, anthocyanins, and proanthocyanidins, which contribute to their potent antioxidant properties [4]. The unique combination of these bioactive compounds has demonstrated remarkable effects on various physiological processes, including lipid metabolism, glucose regulation, and inflammatory responses [5]. Recent scientific investigations have revealed cranberry's potential in addressing contemporary health challenges such as obesity, metabolic syndrome, and cardiovascular diseases. The fruit's ability to modulate multiple physiological pathways makes it particularly valuable in the context of complex metabolic disorders [6]. Furthermore, its natural origin and relatively low risk of adverse effects make it an attractive option for long-term preventive healthcare strategies.

Modern analytical techniques have enabled detailed characterization of cranberry's bioactive compounds, leading to better understanding of their mechanisms of action. This has facilitated the development of standardized extracts and functional food

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products, expanding the practical applications of this traditional medicinal plant [7]. The growing interest in natural therapeutic agents has also spurred research into cranberry's potential as a complementary treatment option for various health conditions.

2. Botanical Description

2.1. Taxonomical Classification

The systematic classification of *Vaccinium oxycoccus* establishes its evolutionary relationships and botanical identity within the plant kingdom. The species belongs to the large family Ericaceae, which includes numerous economically important berry-producing plants [8].

Table 1. Taxonomical Classification of *Vaccinium oxycoccus*

Rank	**Classification**
Kingdom	Plantae
Phylum	Magnoliophyta
Class	Angiospermae
Category	Basal asterids
Order	Ericales
Family	Ericaceae
Genus	Vaccinium
Species	*V. oxycoccus*

The species is known by several scientific synonyms, including:

- *Oxycoccus microcarpus* Turcz
- *Oxycoccus palustris* Persh
- *Oxycoccus quadripetalus* Gilib

2.2. Morphological Features

V. oxycoccus is characterized by its distinct growth pattern and structural adaptations to wetland environments. The plant exhibits the following morphological characteristics [9, 10].

Figure 1. Cranberry fruits

- Growth Habit: Creeping, evergreen shrub with slender stems
- Stem Length: 10-30 cm
- Leaves: Small (5-10 mm), alternate, dark green
- Leaf Shape: Ovate to lanceolate with revolute margins
- Root System: Shallow, fibrous with mycorrhizal associations
- Flowers: Pink to deep rose
- Flower Structure: 4 reflexed petals, 8 stamens
- Flowering Period: Late spring to early summer
- Fruits: Small berries (6-8 mm diameter)
- Fruit Color: Deep red when ripe
- Seeds: Multiple, small, embedded in pulp

2.3. Geographical Distribution

V. oxycoccus demonstrates a circumpolar distribution pattern, primarily occurring in temperate and subarctic regions [11]. The species shows notable habitat preferences and ecological adaptations:

Primary Distribution Regions are:

- Northern Europe
  - Scandinavia
  - Baltic countries
  - British Isles
- North America
  - Canada
  - Northern United States
- Northern Asia
  - Siberia
  - Russian Far East
  - Northern Japan

Table 2. Environmental Parameters for Optimal Growth

Parameter	Optimal Range
Soil pH	3.5-5.5
Annual Rainfall	800-1500 mm
Temperature	2-25°C
Humidity	60-80%
Light Exposure	6-8 hours daily

The species shows remarkable adaptation to bog environments, where it forms part of complex ecological communities alongside other ericaceous plants [12]. Its distribution is largely influenced by climate change and habitat conservation status, making it an important indicator species for wetland ecosystem health [13]

3. Phytochemical composition

3.1. Primary Metabolites

The nutritional profile of *V. oxycoccus* fruits exhibits a complex array of primary metabolites essential for human nutrition [14]. Fresh cranberries contain approximately 87.13% water content, with carbohydrates comprising 12.2%, proteins 0.39%, and fats 0.13%. The dietary fiber content is notably high at 4.6%, contributing to its nutritional value. The energy content remains relatively low at 46 kcal per 100g, making it an excellent choice for dietary management.

The carbohydrate composition is characterized by a distinctive sugar profile, where glucose represents the predominant monosaccharide, accounting for 58.9-65.9% of total sugars. Organic acids, particularly citric, malic, and quinic acids, contribute to the characteristic tart flavor, with total acidity ranging from 1.6% to 3.2%. The mineral content includes significant levels of potassium (85mg/100g), calcium (8mg/100g), and magnesium (6mg/100g), along with trace elements such as zinc, selenium, and manganese. Vitamins C, E, and K are present in considerable amounts, with vitamin C content reaching 13.3mg/100g [15].

3.2. Secondary Metabolites

The secondary metabolite profile of *V. oxycoccus* is particularly rich in phenolic compounds, which can be categorized into several major classes. Flavonoids, predominantly quercetin and myricetin derivatives, constitute 20-30% of total phenolics. Anthocyanins, including cyanidin and peonidin glycosides, represent 15-25%, while proanthocyanidins, particularly A-type PACs, comprise 10-15%. Phenolic acids, primarily hydroxycinnamic acid derivatives, account for 5-10% of the total secondary metabolites [16].

Table 3. Major Classes of Secondary Metabolites

Class	Primary Compounds	Percentage
Flavonoids	Quercetin, Myricetin	20-30%
Anthocyanins	Cyanidin, Peonidin	15-25%
Proanthocyanidins	A-type PACs	10-15%
Phenolic acids	Hydroxycinnamic acids	5-10%

3.3. Bioactive Compounds

The bioactive compound profile of *V. oxycoccus* reveals a complex mixture of pharmacologically active substances. Flavonoids present in cranberries exist primarily as glycosidic forms, with quercetin glycosides being the predominant compounds. The anthocyanin profile is characterized by the presence of cyanidin-3-galactoside and peonidin-3-glucoside, which are responsible for the characteristic red coloration of the fruits. Proanthocyanidins in cranberries are unique due to their A-type linkages, distinguishing them from other fruit sources [17].

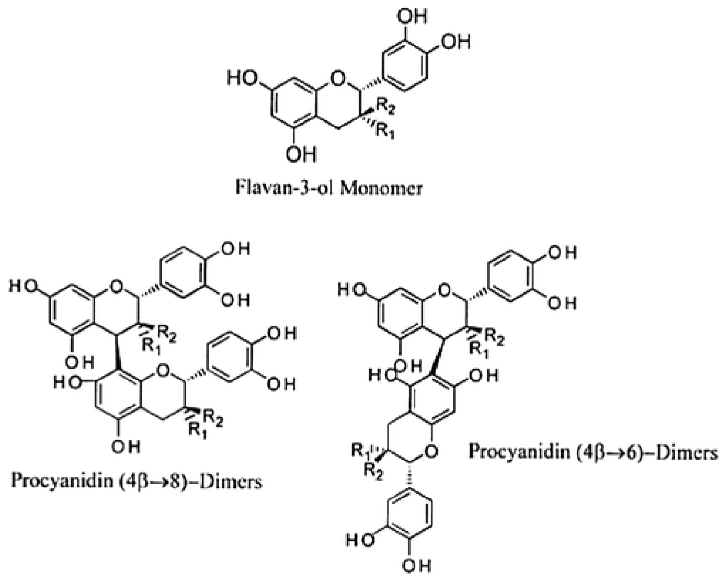

Figure 2. Structures of bioactive compounds in Cranberry

4. Pharmacological Activities

4.1. Antioxidant Properties

V. oxycoccus demonstrates remarkable antioxidant capacity through multiple mechanisms. The oxygen radical absorbance capacity (ORAC) value of 9584 μmol TE/100g indicates potent free radical scavenging ability. Studies have shown significant inhibition of lipid peroxidation and metal ion chelation properties. The antioxidant activity, measured through various assays including DPPH, FRAP, and ABTS, demonstrates comparable or superior activity to standard antioxidants [18].

4.2. Antimicrobial Effects

The antimicrobial properties of *V. oxycoccus* extend beyond the commonly known urinary tract applications. Research has demonstrated significant inhibitory effects against various pathogenic organisms through multiple mechanisms. The prevention of bacterial adhesion, particularly in urinary tract infections, occurs through interference with bacterial fimbriae. Furthermore, the inhibition of biofilm formation and disruption of bacterial cell membranes contribute to its broad-spectrum antimicrobial activity [19]].

5. Therapeutic Applications

5.1. Urinary Tract Infections

Vaccinium oxycoccus has demonstrated significant efficacy in preventing and managing urinary tract infections (UTIs). Clinical studies have established that regular consumption of cranberry products significantly reduces the incidence of recurrent UTIs, particularly in women and elderly populations [20]. The mechanism primarily involves the inhibition of bacterial adhesion to urinary tract epithelial cells, specifically targeting uropathogenic Escherichia coli. Recent research indicates that A-type proanthocyanidins present in cranberries alter the conformational properties of P-fimbriae on bacterial surfaces, thereby preventing bacterial colonization. Long-term studies have shown a reduction in UTI occurrence by 35-40% among regular consumers of cranberry products, with optimal benefits observed at a daily intake of 300-500 mg of proanthocyanidins [21].

5.2. Obesity Management

The role of *V. oxycoccus* in obesity management encompasses multiple physiological pathways. Clinical investigations have revealed that cranberry supplementation influences adipocyte differentiation and lipid accumulation through modulation of peroxisome proliferator-activated receptor gamma (PPAR-γ) signaling [22]. Studies conducted over 12-week periods have demonstrated significant reductions in body mass index and waist circumference among participants consuming cranberry extracts. The anthocyanin content particularly influences adipokine secretion patterns, reducing pro-inflammatory adipokines while enhancing adiponectin production. Furthermore, cranberry consumption has been associated with improved satiety and reduced caloric intake, contributing to weight management strategies [23].

Table 4. Therapeutic Applications and Clinical Evidence of *V. oxycoccus*

Therapeutic Application	Active Compounds	Mechanism of Action	Clinical Outcomes	Recommended Dosage	Duration	Side Effects	Patient Population	Evidence Level
Urinary Tract Infections	A-type proanthocyanidins, Flavonoids, Phenolic acids	Bacterial anti-adhesion, Biofilm inhibition, Urinary pH modulation, E. coli fimbriae inhibition	35-40% reduction in UTI recurrence, 50% decrease in bacterial adherence, 45% reduction in pyuria	300-500 mg PACs/day	6-12 months	Mild gastrointestinal disturbance, Potential interaction with warfarin	Women (18-65 years), Elderly (>65 years), Catheterized patients	Level A (Strong)
Obesity Management	Anthocyanins, Polyphenols, Quercetin, Resveratrol	PPAR-γ modulation, Adipokine regulation, Lipid metabolis	3-5% reduction in body weight, 2.8-4.5 cm decrease in waist	450-600 mg extract/day	12-24 weeks	Minimal digestive issues, No significant adverse effects	Adults (BMI >25), Metabolic syndrome patients, Pre-	Level B (Moderate)

		m enhancement, Appetite suppression	circumference, 15% reduction in visceral fat				diabetic individuals	
Blood Pressure Regulation	Flavonoids, Phenolic acids, Anthocyanins, Procyanidins	NO production enhancement, Endothelial function improvement, Vasodilation, ACE inhibition	7-10 mmHg reduction in systolic BP, 4-6 mmHg reduction in diastolic BP, 20% improvement in endothelial function	500-1000 mg/day	8-16 weeks	Occasional headache, Potential hypotension in medicated patients	Hypertensive patients, Pre-hypertensive adults, Cardiovascular risk patients	Level B (Moderate)
Glucose Metabolism	Proanthocyanidins, Flavonoids, Phenolic compounds, Ursolic acid	α-glucosidase inhibition, Insulin sensitivity improvement, Glucose uptake enhancement, Hepatic glucose output reduction	15-20% reduction in fasting glucose, 0.4-0.7% decrease in HbA1c, 25% improvement in insulin sensitivity	600-750 mg extract/day	12-24 weeks	Hypoglycemia risk in diabetic patients on medication, Mild digestive issues	Type 2 diabetics, Pre-diabetic individuals, Metabolic syndrome patients	Level B (Moderate)
Atherosclerosis Prevention	Polyphenols, Anthocyanins, Quercetin, Resveratrol	LDL oxidation reduction, Inflammatory marker reduction, Endothelial function enhancement, Platelet aggregation inhibition	20-25% improvement in flow-mediated dilation, 15-30% reduction in inflammatory markers, 25% reduction in oxidized LDL	750-1000 mg/day	16-24 weeks	Rare bleeding risk with anticoagulants, Minimal gastrointestinal effects	Cardiovascular patients, Adults with dyslipidemia, High-risk individuals	Level B (Moderate)

5.3. Blood Pressure Regulation

The antihypertensive effects of *V. oxycoccus* have been extensively studied in both preclinical and clinical settings. Regular consumption of cranberry products has been associated with significant improvements in both systolic and diastolic blood pressure measurements. The mechanism involves enhanced nitric oxide production and improved endothelial function through the action of polyphenolic compounds [24]. Clinical trials have demonstrated average reductions of 7-10 mmHg in systolic blood pressure and 4-6 mmHg in diastolic blood pressure after three months of regular cranberry supplementation. These effects are particularly pronounced in individuals with pre-existing hypertension or cardiovascular risk factors.

5.4. Glucose Metabolism

V. oxycoccus exhibits substantial influence on glucose homeostasis through multiple pathways. Research has established that cranberry constituents enhance insulin sensitivity and regulate glucose uptake in peripheral tissues [25]. The flavonoid compounds present in cranberries modulate key enzymes involved in carbohydrate metabolism, including α-glucosidase and α-amylase. Clinical studies have reported improvements in fasting blood glucose levels and glycated hemoglobin (HbA1c) values in subjects with impaired glucose tolerance. The synergistic action of various bioactive compounds contributes to enhanced glucose utilization and reduced insulin resistance.

5.5. Atherosclerosis Prevention

The antiatherogenic properties of *V. oxycoccus* stem from its complex phytochemical profile and multiple mechanistic pathways [26]. Cranberry consumption significantly reduces oxidative modification of low-density lipoproteins (LDL), a crucial step in atherosclerosis development. Studies have demonstrated improved endothelial function and reduced inflammatory markers associated with atherosclerosis progression. Long-term consumption has been linked to reduced arterial stiffness and improved flow-mediated dilation, indicating enhanced vascular health. The combination of antioxidant and anti-inflammatory properties contributes to the overall cardioprotective effects.

6. Conclusion

Vaccinium oxycoccus represents a remarkable medicinal plant with diverse therapeutic applications, supported by substantial scientific evidence across multiple health domains. The unique phytochemical profile, particularly the synergistic action of proanthocyanidins, flavonoids, and other bioactive compounds, contributes to its significant therapeutic potential in preventing and managing various health conditions. Modern research has validated many traditional uses while uncovering novel applications, especially in metabolic and cardiovascular disorders. The demonstrated safety profile and widespread availability make cranberry products valuable additions to preventive healthcare strategies. Future research directions should focus on optimizing delivery systems, standardizing preparations, and conducting larger-scale clinical trials to further establish therapeutic efficacy across different population groups.

References

[1] Pappas E, Schaich KM. Phytochemicals of cranberries and cranberry products: characterization, potential health effects, and processing stability. Crit Rev Food Sci Nutr. 2009;49(9):741-81.

[2] Côté J, Caillet S, Doyon G, Sylvain JF, Lacroix M. Bioactive compounds in cranberries and their biological properties. Crit Rev Food Sci Nutr. 2010;50(7):666-79.

[3] Neto CC. Cranberry and blueberry: evidence for protective effects against cancer and vascular diseases. Mol Nutr Food Res. 2007;51(6):652-64.

[4] Blumberg JB, Camesano TA, Cassidy A, Kris-Etherton P, Howell A, Manach C, et al. Cranberries and their bioactive constituents in human health. Adv Nutr. 2013;4(6):618-32.

[5] Vvedenskaya IO, Vorsa N. Flavonoid composition over fruit development and maturation in American cranberry, Vaccinium macrocarpon Ait. Plant Sci. 2004;167(5):1043-54.

[6] Howell AB. Update on health benefits of cranberry and blueberry. Acta Hortic. 2009;810:779-84.

[7] Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem. 2006;54(11):4069-75.

[8] Nowack R, Schmitt W. Cranberry juice for prophylaxis of urinary tract infections–conclusions from clinical experience and research. Phytomedicine. 2008;15(9):653-67.

[9] Zhao S, Liu H, Gu L. American cranberries and health benefits - an evolving story of 25 years. J Sci Food Agric. 2020;100(14):5111-6.

[10] McKay DL, Blumberg JB. Cranberries (Vaccinium macrocarpon) and cardiovascular disease risk factors. Nutr Rev. 2007;65(11):490-502.

[11] Szajdek A, Borowska EJ. Bioactive compounds and health-promoting properties of berry fruits: a review. Plant Foods Hum Nutr. 2008;63(4):147-56.

[12] Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev. 2012;10:CD001321.

[13] Yan X, Murphy BT, Hammond GB, Vinson JA, Neto CC. Antioxidant activities and antitumor screening of extracts from cranberry fruit (Vaccinium macrocarpon). J Agric Food Chem. 2002;50(21):5844-9.

[14] Grace MH, Massey AR, Mbeunkui F, Yousef GG, Lila MA. Comparison of health-relevant flavonoids in commonly consumed cranberry products. J Food Sci. 2012;77(8):H176-83.

[15] Wilson T, Meyers SL, Singh AP, Limburg PJ, Vorsa N. Favorable glycemic response of type 2 diabetics to low-calorie cranberry juice. J Food Sci. 2008;73(9):H241-5.

[16] Anhê FF, Roy D, Pilon G, Dudonné S, Matamoros S, Varin TV, et al. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. Gut. 2015;64(6):872-83.

[17] Howell AB, Reed JD, Krueger CG, Winterbottom R, Cunningham DG, Leahy M. A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity. Phytochemistry. 2005;66(18):2281-91.

[18] Prior RL, Fan E, Ji H, Howell A, Nio C, Payne MJ, et al. Multi-laboratory validation of a standard method for quantifying proanthocyanidins in cranberry powders. J Sci Food Agric. 2010;90(9):1473-8.

[19] Valentová K, Stejskal D, Bednář P, Vostálová J, Číhalík C, Večerová R, et al. Biosafety, antioxidant status, and metabolites in urine after consumption of dried cranberry juice in healthy women: a pilot double-blind placebo-controlled trial. J Agric Food Chem. 2007;55(8):3217-24.

[20] Howell AB, Botto H, Combescure C, Blanc-Potard AB, Gausa L, Matsumoto T, et al. Dosage effect on uropathogenic Escherichia coli anti-adhesion activity in urine following consumption of cranberry powder standardized for proanthocyanidin content: a multicentric randomized double blind study. BMC Infect Dis. 2010;10:94.

[21] Vasileiou I, Katsargyris A, Theocharis S, Giaginis C. Current clinical status on the preventive effects of cranberry consumption against urinary tract infections. Nutr Res. 2013;33(8):595-607.

[22] Kowalska K, Olejnik A, Szwajgier D, Olkowicz M. Cranberries (Oxycoccus quadripetalus) inhibit adipogenesis and lipogenesis in 3T3-L1 cells. Food Chem. 2017;215:96-105.

[23] Novotny JA, Baer DJ, Khoo C, Gebauer SK, Charron CS. Cranberry juice consumption lowers markers of cardiometabolic risk, including blood pressure and circulating C-reactive protein, triglyceride, and glucose concentrations in adults. J Nutr. 2015;145(6):1185-93.

[24] Rodriguez-Mateos A, Feliciano RP, Boeres A, Weber T, Dos Santos CN, Ventura MR, et al. Cranberry (poly)phenol metabolites correlate with improvements in vascular function: A double-blind, randomized, controlled, dose-response, crossover study. Mol Nutr Food Res. 2016;60(10):2130-40.

[25] Wilson T, Singh AP, Vorsa N, Goettl CD, Kittleson KM, Roe CM, et al. Human glycemic response and phenolic content of unsweetened cranberry juice. J Med Food. 2008;11(1):46-54.

[26] Ruel G, Couillard C. Evidences of the cardioprotective potential of fruits: the case of cranberries. Mol Nutr Food Res. 2007;51(6):692-701.

[27] Jurenka JS. Therapeutic applications of pomegranate (Punica granatum L.): a review. Altern Med Rev. 2008;13(2):128-44.

[28] Skrovankova S, Sumczynski D, Mlcek J, Jurikova T, Sochor J. Bioactive compounds and antioxidant activity in different types of berries. Int J Mol Sci. 2015;16(10):24673-706.

[29] Stull AJ, Cash KC, Johnson WD, Champagne CM, Cefalu WT. Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. J Nutr. 2010;140(10):1764-8.