Review article
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The impact of cranberry on lower urinary tract function: limitations due to gene expression and pharmacokinetic variability

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ABSTRACT

Cranberries are well known for their antioxidative, anti-inflammatory, antimicrobial, and anti-biofilm formation properties. Many studies indicate their potential for cancer prevention, blood sugar regulation, gastrointestinal and cardiovascular health, and antiviral properties. Such wide therapeutic potential for human health has made cranberries favourable for dietary formulations. Considering how prone patients are to accept treatment via nature's pharmacy instead of the conventional one, cranberries in the form of juice, tablets, capsules, or extracts are often prescribed alongside antibiotic therapy for urinary tract infection (UTI) treatment. This review paper aims to provide a better understanding of the limitations of the usage of berry dietary formulations for health improvement. The healing potential of cranberries is limited due to the bioaccessibility of their ingredients and their pharmacokinetic properties. Although rich with pharmacologically active substances, including anthocyanins, proanthocyanidins, vitamin C, vitamins (B1, B2, B3, B5, B6, B9), and organic acids, their potential is limited due to low absorption and distribution, extensive metabolism, and elimination. The variability in gene expression affecting the biosynthesis of anthocyanins and proanthocyanidins within the *Vaccinium* berries results in diminished concentrations of active ingredients within the plant material itself. Also, the results from the clinical trials are inconsistently standardized. This paper offers a comprehensive analysis of the available data and presents a clear direction for future research.

Keywords: proanthocyanidin, anthocyanins, cranberry, *Vaccinium* sp, urinary tract infection, *Escherichia coli*

INTRODUCTION

Cranberries have a long history of medicinal use, dating back to Native American tribes and early European settlers, who utilized them for wound dressing, urinary conditions, and dyeing fabrics (Thomas, Joseph D, 1990). They are particularly favoured by women for urinary tract infection (UTI) treatment. The European Medicines Agency (EMA) acknowledges the traditional use of *Vaccinium macrocarpon* Ait. for alleviating mild recurrent lower urinary tract infection symptoms in women, such as burning and frequent urination, after ruling out serious conditions.

Despite their richness in pharmacologically active ingredients, therapeutic efficacy is limited due to poor metabolism, elimination, and absorption (Nemzer et al., 2022). The most promising compounds are proanthocyanidins and anthocyanins. Cranberries possess a unique anthocyanin profile that consists of cyanidin-3-*O*-glucoside (C3Gl), cyanidin-3-*O*-galactoside (C3Ga), cyanidin-3-arabinoside (C3Ar), peonidin-3-*O*-galactoside (P3Ga), peonidin-3-*O*-glucoside (P3Gl), and smaller amounts of peonidin-3-*O*-arabinoside (P3Ar) (Brown and Shipley, 2011). Notably, cranberries are distinguished by their high levels of A-type proanthocyanidins (PAC), unlike

the B-type PACs prevalent in other fruits (Krueger et al., 2013; Xia et al., 2021). While numerous *in vitro* studies indicate cranberries' therapeutic potential for various health issues (Dong et al., 2022; Bennet et al., 2008; Webb et al., 2008; Chen et al., 2022; Kumar and Pandey, 2013), these findings do not always align with the effects observed in human consumers. The healing efficacy of cranberries is primarily constrained by two factors: the plant material itself and human metabolism. Specifically, the concentration of active ingredients in cranberries varies due to differences in gene expression related to phenylpropanoid and flavonoid pathways among species within the *Vaccinium* berries.

The second factor that limits the healing potential of cranberries is the pharmacological parameters of active ingredients. If the concentration is below the minimal therapeutic concentration, there will be no healing effect.

Structure of cranberry active ingredients

Anthocyanins are glycosides derived from anthocyanidins, which have a basic structure known as the flavylium cation (figure 1), that gives rise to different anthocyanidins by hydroxylation in different positions, primarily on carbon C3, C5, C6, C7, and C3', C4', and C5' (Rauf et al., 2019; Mattioli et al., 2020).

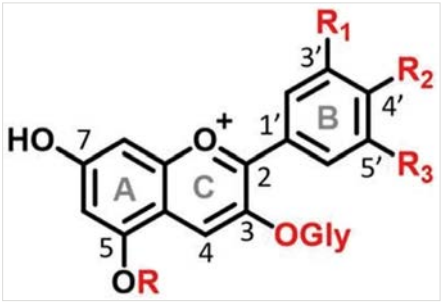

Figure 1. Basic structure of flavylium cation

Proanthocyanidins are plant flavonoids made of oligomers and polymers of catechin or epicatechin units and their gallic acid esters (Rauf et al., 2019).

Catechin (name origin: catechu, which is the tannic juice or boiled extract of *Mimosa catechu* L.f.) is a polyphenolic benzopyran compound. It is a typical flavan-3-ol, consisting of two benzene rings (A and B) and the dihydropyran heterocycle (the C ring) with the hydroxyl group on position C3 (figure 2).

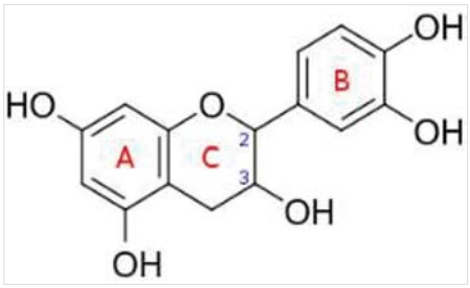

Figure 2. Basic structure of catechin

Due to their saturation, carbons C2 and C3 do not have the properties of flavylium cations. C2 and C3 are chiral centres as well. Four diastereoisomers exist for catechin; two of these isomers are *trans* (catechin), while the other two are *cis* (epicatechin). PACs can be categorized according to their repeating components as either heteropolymers or homopolymers.

The compounds' bioaccessibility within the food matrix

Bioaccessibility refers to the fraction of a compound that is released from the food matrix during digestion and becomes available for absorption in the gastrointestinal tract. (Liang et al., 2023; Ayvaz et al., 2022; Eker et al., 2019). Anthocyanins are produced in the endoplasmic reticulum of plant cells and transported to vacuoles. Their synthesis occurs via the phenylpropanoid and flavonoid pathways (Jaakola et al., 2002). In the phenylpropanoid pathway, phenylalanine from the shikimate pathway is converted to cinnamic acid by the enzyme PAL, which is then hydroxylated to p-coumaric acid by C4H and activated to form 4-coumaroyl CoA. The flavonoid pathway begins with the condensation of 4-coumaroyl-CoA and malonyl-CoA, catalysed by CHS to produce chalcone, which is then converted to naringenin by CHI. Naringenin is hydroxylated to dihydrokaempferol by F3H, reduced to leucoanthocyanidin by DFR, and finally converted to anthocyanidin (e.g., cyanidin, delphinidin, pelargonidin) by ANS. Further modifications like acylation, methylation, and glycosylation can yield additional anthocyanin compounds (Jaakola et al., 2002). These pathways are controlled in response to different developmental and environmental factors.

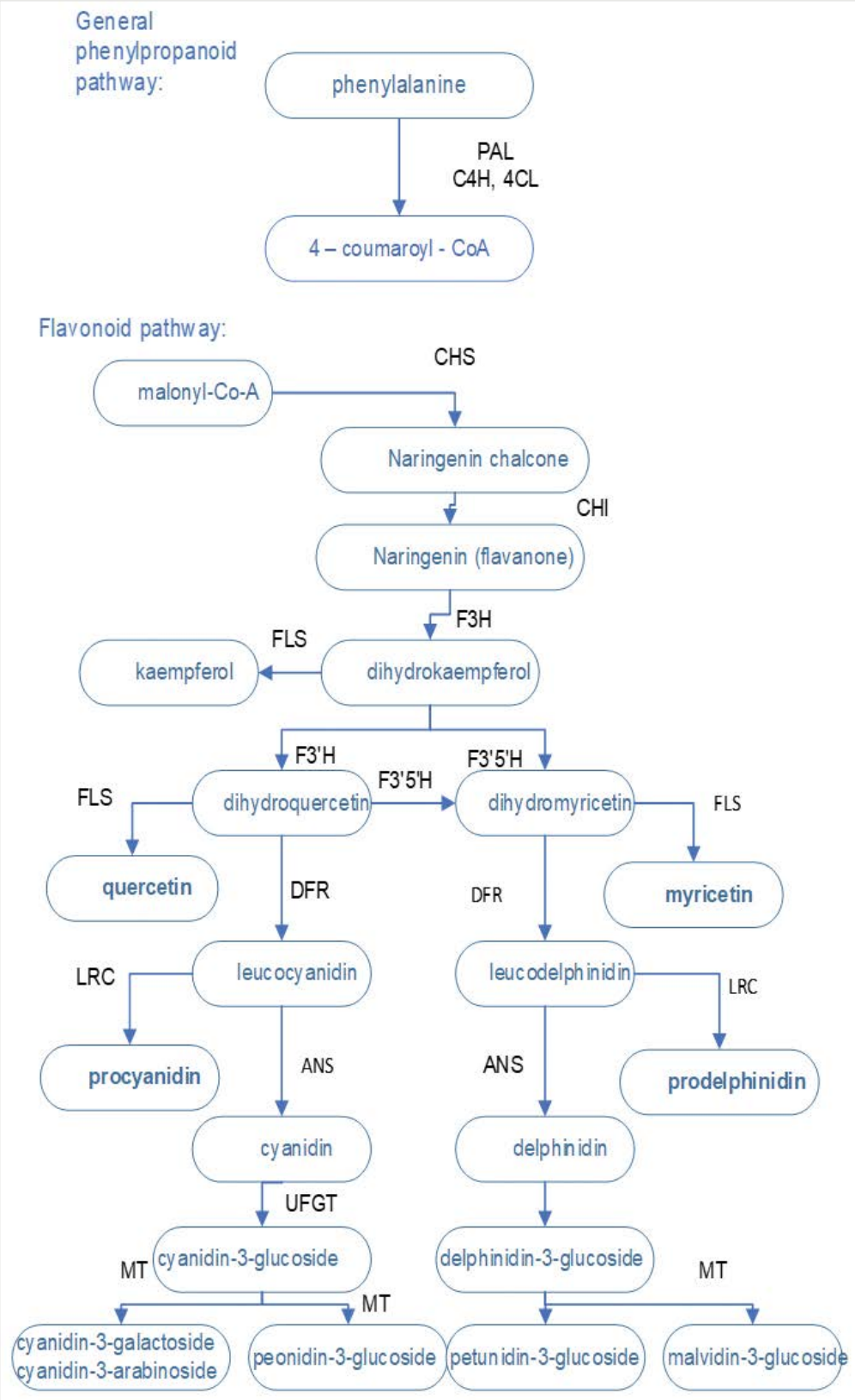

Figure 3. Biosynthesis pathways of anthocyanins. Abbreviations of enzymes involved in pathways: PAL – phenylalanine ammonia lyase, C4H – cinnamate 4-hydroxylase, 4CL – 4-coumaroyl CoA ligase, CHS - chalcone synthase, CHI – chalcone isomerase, FLS – flavonol synthase, F3H – flavanone- 3-hydroxylase, F3'H – flavonoid 3'-hydroxylase, F3'5'H – flavonoid 3',5'-hydroxylase, DFR – dihydroflavonol 4-reductase, ANS – anthocyanidin synthase, LRC – leucoanthocyanidin reductase, UFGT – UDP flavonoid glycosyltransferase, MT – methyltransferase

Anthocyanins, primarily located in cranberry fruit skin, vary in concentration among *Vaccinium* species and ripeness levels. Environmental factors such as sunlight, water, and temperature stress influence fruit size and, consequently, total phenolic content, anthocyanins, and procyanidins (Riihinen et al., 2008). While bilberry (*Vaccinium corymbosum* L.) and rabbiteye (*Vaccinium virgatum* Ait.) produce anthocyanins only in the fruit skin, the wild European bilberry (*Vaccinium myrtillus* L.) has deeply pigmented flesh. Over 150 anthocyanin types have been identified in *Vaccinium* berries, with variations attributed to allelic differences in structural or regulatory genes governing the biosynthesis pathway. Certain anthocyanins have a higher affinity for glycosylation enzymes, leading to preferential glycoside formation; for instance, UDP glucose: 3-*O*-glucosyltransferase exhibits greater activity with cyanidin than with peonidin. After forming anthocyanin 3-glucosides, further modifications occur via glycosyltransferases. Variations in biosynthesis pathway genes result in high substrate specificity for anthocyanins to sugar donors, including galactosyltransferase, arabinosyltransferase, and glucosyltransferase. Additionally, it has been suggested that the expression of arabinosyltransferase and glucosyltransferase is not essential for forming glucose and arabinose conjugates, as both sugars have identical stereochemistry for hydroxyl groups, allowing conjugation to anthocyanidins by either enzyme (Vorsa et al., 2003). PACs and anthocyanidins share the same flavonoid route, according to research (He et al., 2008; Albert et al., 2023). After being reduced to leucoanthocyanidins by dihydroflavonol 4-reductase, dihydroflavonols are oxidized to form anthocyanidins. By using ANR (anthocyanidin reductase), formed anthocyanidins (pelargonidin, cyanidin, and delphinidin, respectively) can be transformed into derivatives of flavan-3-ol, namely (-)-epiafzelechin, (-)-epicatechin, and (-)-epigallocatechin. This pathway has a second branch, where leucoanthocyanidins are converted into (2*R*,3*S*)-flavan-3-ols [(+)-afzelechin, (+)-catechin and (+)-gallocatechin, respectively], by the enzyme leucoanthocyanidin reductase (LAR).

Flavan-3-ols and flavan-3,4-diols, which are produced in the pathway, are precursors for PAC synthesis. The enzyme that enables the polymerization of the units is still unknown (He et al., 2008). Precursors are synthesized in the endoplasmic reticulum or cytosol, while PACs are stored in plant vacuoles. The mechanisms for transporting precursors to vacuoles are also unclear, but a study suggests that MATE transporter factors play a role (Albert et al., 2023). Vesicles with stable starter units form a pre-vacuolar vesicle, which then enters the central vacuole for polymerization (Dixon and Sarnala, 2020).

Anthocyanidins do not undergo the process of polymerization, however they do self-associate and form co-pigments. Phenolic nuclei have intrinsic ability to form non-covalent interactions with other aromatic nuclei. Considering they also have hydroxyl groups, they can both act as H-bond donors and acceptors. Anthocyanin chromophores can develop π-stacking interactions which favour the release of water molecules from the solvation shells of the interacting nuclei. This hydrophobic effect allows anthocyanidins to bind to one another, as well as to bind to other phenols. This process is called co-pigmentation (Dangles and Fenger, 2018).

PACs include proanthocyanins, prodelphinidins, and propelargonidins. Prodelphinidins are polymers of gallocatechin, and propelargonidins are polymers of epiafzelechin. In *Vaccinium* sp., the most present is proanthocyanin. Therefore, proanthocyanidins are often referred to as proanthocyanins. The distinguishing factor between type A and type B proanthocyanidins lies in their connection method. Type A proanthocyanidins feature at least one double linkage that includes a C-C bond along with an additional ether bond. The most common A-type compounds are A1 and A2. Type B consists of a single interflavan bond between carbon-4 of the B-ring and either C-8 or C-6 of the C-ring. They are the most abundant, with types B1, B2, B3, and B4 occurring most frequently (Rue et al., 2018). Most food exclusively contains PAC type B. In contrast to this statement, the profile of cranberry is distinct from that of other berry fruits, being rich in A-type PACs. Cranberry has PAC consisting of (+)-catechin and (−)-epicatechin, and such PAC form is called procyanidin.

Pharmacokinetic parameters of anthocyanins and procyanidins

Cranberries are commonly consumed in various forms, including fresh whole berries, gelatinized products, juices, and capsules. Pure cranberry juice is often too acidic (pH<2.5) and unappetizing, even when sweetened (Jensen et al., 2017).

Traditionally, many women seeking to prevent urinary tract infections (UTIs) have preferred cranberry juice cocktails, typically with around 25% cranberry juice content.

Anthocyanins are highly unstable and susceptible to oxygen, temperature, light, pH value, and enzyme activity. Acylated anthocyanins exhibit much lower absorption than their non-acylated counterparts due to low polarity. Acylated forms are much more resistant to heat and light and as such are used as food colorants (Liang et al., 2023).

Anthocyanins of varying sizes, sugar conjugation types, and functional groups can be absorbed by the gastrointestinal system due to their water-solubility. The rate of absorption, and consequently their bioavailability, are determined by the type of aglycone, sugar molecule, and acylated groups (Fang, 2014). The most efficient way for absorption is through nasal mucosa when administered to patients with nasal tubes. The concentration of anthocyanins in urine is five times higher when introduced nasally compared to ingested molecules in the GI tract (Cai et al., 2011).

Anthocyanins are efficiently absorbed in the stomach due to their most stable form, flavylium cation, in highly acidic pH of about 2. It is suggested that anthocyanins are absorbed by the bilitranslocase-mediated mechanism in the small intestine after passing through acidic gastric juice (Fallingborg, 1999). The small intestine's pH shifts notably from the stomach's acidity, starting at pH 6 in the duodenum and reaching pH 7.4 in the terminal ileum. This change affects the structure of anthocyanins, transforming them from a positively charged flavylium ion to a negatively charged quinoid base. Consequently, this transformation favours their interaction with bilitranslocase. Bilitranslocase, found in both gastric epithelial cells and the liver, facilitates the uptake of organic anions via an ATP-dependent transport mechanism. Recently, anthocyanins have been identified as substrates for this protein (Passamonti et al., 2002).The first interaction with the protein carrier is via hydrophilic moieties. Increasing the level of glycosylation enhances their water solubility. Mono- and di-glycosides exhibit stronger interaction with bilitranslocase compared to aglycone forms. Anthocyanins easily penetrate the gastrointestinal membrane, accumulating in intestinal tissues at micromolar concentrations. Yet, their bioavailability remains low due to extensive first-pass metabolism (Passamonti et al., 2002). To investigate the impact of GI factors on bioavailability, researchers conducted studies where humans were intravenously given anthocyanins. The plasma concentration of cyanidin-3-galactoside drastically decreased in 24 minutes after the oral administration (de Ferrars et al., 2014). The mechanism by which the sugar conjugate of cyanidin-3-galactoside is cleaved remains unclear. Its concentration did not decrease in epithelial cells of the small intestine, indicating that it has not been processed by cytosolic beta-glucosidase (Berrin et al., 2002). It is possible that anthocyanins may only exhibit their health benefits in the cells of intestinal tissue, rather than other parts of the human body, due to their poor distribution.

Anthocyanins are excreted in urine either intact or as glucuronic and sulfoconjugates. Deglycosylation precedes the conjugation process. The glycosyl moiety is often cleaved by enzymes such as β-glucosidase. The aglycone form is then available for phase II conjugation, including glucuronidation, sulfation, or methylation. C3GI is transformed into the methylated product of peonidin-3-glucoside and eliminated through urine as glucuronide or methyl-conjugate. UDP-glucuronosyltransferase facilitates the conjugation of anthocyanin with glucuronic acid in the liver, specifically attaching to the hydroxyl group located at the 3-position of the anthocyanin aglycone. Liver sulfotransferase creates water-soluble sulfoconjugates, which are then excreted by the kidneys (Felgines et al., 2003).

Procyanidins (proanthocyanidins containing + catechin and - epicatechin isomers) that are bound to the solid food matrix are not available for absorption. Only water-soluble procyanidins interact with enterocytes in the small intestine diffusion. Oligomers with more than four monomer units are unabsorbable (Ou and Gu, 2014). When consumed, some procyanidins are broken down in the acidic stomach due to their integration into food and varying polymerization. Passing into the duodenum, they encounter pancreatic juice. While stable against stomach acid and pancreatic juice, gut bacteria trigger dehydroxylation, converting procyanidins to γ-valerolactones (Niwano et al., 2022). Apart from valerolactones, phenolic acids are formed, which may be absorbed or conjugated in the liver and excreted through urine. However, bacteria struggle to ferment the large procyanidin molecule, impeding degradation. Procyanidin polymers can also bind to GI mucosa proteins, competing with smaller procyanidins and hindering their absorption (Nie and Stürzenbaum, 2019). The primary site for the glucuronidation of procyanidins is the endoplasmic reticulum of enterocytes, through UGTs (uridine 5'-diphosphate glucuronosyltransferases). Once they pass the GI tract, a small portion of procyanidins is subjected to phase II of metabolism in the liver, where a smaller rate of glucuronidation can happen, as well as sulfation and methylation via SULT (sulfotransferases) and COMT (catechol-O-methyltransferase). Once conjugated in the liver, procyanidins can be re-excreted to the small intestine via bile secretion (Choy and Waterhouse, 2014). Procyanidins type A (A1 and A2), which are present in the cranberry more than other berry fruits, are better absorbed than B2 procyanidins (Choy and Waterhouse, 2014).

Pharmacological properties of cranberry ingredients

Antibacterial effect of anthocyanins

The antibacterial effect of xenobiotics and plant extracts is generally expressed at one or more phases in bacterial metabolism. These compounds can affect the synthesis of the cell wall, and synthesis of nucleic acids and can interfere with intermediary metabolism. The most inquired target for the antibacterial activity is the bacterial cell wall. This complex structure is responsible for maintaining the shape and integrity of the bacteria. It consists of peptidoglycan, a large polymer made of glycan strands intertwined with peptide chains, forming a mesh-like structure. Glycan strands are made of repeating disaccharide units and peptide structure contains two to five amino acid residues (Garde et al., 2021). Disaccharides contain N-acetylmuramic acid and N-acetylglucosamine linked by *β*-1,4 glycosidic bonds. Lactoyl structures of N-acetylmuramic acid are covalently linked to amino acid residues (Dörr et al., 2019). It is a solid defense mechanism from extreme environmental conditions. The composition of the peptidoglycan is the foundation of the Gram classification, by which the bacteria are classified into Gram-positive and Gram-negative bacteria. Gram-positive bacteria, once exposed to crystal violet dye, show a purple colour due to the thick peptidoglycan wall retaining the colour. On the other hand, Gram-negative bacteria have a monolayered peptidoglycan wall that is covered additionally by a lipid coating extracellularly, which makes it invulnerable to violet dye (Garde et al., 2021).

Escherichia coli is a Gram-negative species of bacteria. Its cell wall is a pentapeptide chain made of the following amino acids: L-alanine, gamma-D-glutamate, meso-diaminopimelic acid, and two D-alanines. Crosslinking of the amino acids is facilitated by meso-diaminopimelic acid (mDAP), which forms a cross-linkage between gamma-D-glutamate and D-alanine. On the other hand, in Gram-positive bacteria such as *Staphylococcus aureus*, the amino acid chain contains L-lysine in the third position. The N-terminus of L-alanine is linked to N-acetylmuramic acid via lactic moiety (Dörr et al., 2019). Anthocyanin interferes with the hydrophobic surface of *S. aureus*, increases intracellular K^+ ions, and reduces total soluble proteins by affecting their synthesis (Dong et al., 2022). Bacteria exhibit cell surface hydrophobicity (CSH) due to the presence of non-polar molecules (teichoic and lipoteichoic acids), lipopolysaccharides, and

surface proteins (Salas-Tovar et al., 2021). The higher the hydrophobicity of the bacteria is, the higher its immersion surroundings and growth. Treatment of *S. aureus* with different concentrations of anthocyanin has disrupted cell membrane processes and the increase of hydrophobicity, alongside the increase of anthocyanin concentration. Once the cell membrane has been disrupted, K^+ ions leak through the surroundings, leading to leakage of other electrolytes as well, while bigger molecules, such as nucleic acids, are still contained within the cell. Dysregulation of K^+ channels and sodium-potassium ATP pump system, complete transport-based metabolism is disabled, and cells are programmed to premature death (Dong et al., 2022). The structure of the anthocyanins allows them to intercalate between adjacent base pairs of RNA and DNA. In human cells, anthocyanins have shown protective effects on DNA molecules. Its cytostatic activity is explained by the binding of the anthocyanin to the DNA which is foreign or abnormal, such as those found in tumour cells, thus delaying or inhibiting DNA synthesis and suppressing tumour cell growth. The same effect applies to bacterial nucleic acid. Once bound, anthocyanins will inhibit the replication of nucleic material and, consequently, inhibit the expression of proteins (Webb et al., 2008). For the intercalation to occur, the pH of the surroundings needs to be acidic, because only at pH lower than 4, does the anthocyanin exist in its flavylium cation form, which, due to its planar structure and positive charge, can form bonds with adjacent nucleic base pairs. At physiological pH around 7.5, anthocyanins do not bind to nucleic acid. Thus, anthocyanins may show protective effects on DNA in more aggressive cancer phenotypes, which have lower pH surroundings. Considering that solid tumours usually have an intracellular pH of about 7.0-7.2, anthocyanins' protective effect is limited. Since bacteria are generally neutrophils with optimum growth around pH 7, intercalation of flavylium cation between nucleic acid base pairs is not the most favourable antimicrobial mechanism.

Antibacterial effect of procyanidins and their anti-biofilm forming property

The antibacterial effect of procyanidins is more versatile compared to that of anthocyanins. Studies have shown (Chen et al., 2022) that procyanidins can inhibit bacterial adhesion and biofilm formation, destroying the integrity of plasma membrane or wall, inhibiting extracellular microbial enzymes, and thus depriving substrates for bacterial growth. Due to procyanidin's ability to chelate metal ions, once they bind Ca^{2+} or Mg^{2+}, the plasma membrane of the bacterial cell is destabilized. Its permeability and lipopolysaccharides release are increased. Lipopolysaccharides (LPS) are located at the outer side of the membrane of Gram-negative bacteria. They are released during normal bacterial growth and expansion of bacterial infection. A consequence of LPS release is the stimulation of monocytes and macrophages, which produce abundant amounts of proinflammatory mediators like TNF-α (tumour necrosis factor-alpha) and IL-1β (interleukin 1 beta). Release of these mediators is a bacterial natural response when starting treatment with antibiotics, and it is an explanation of the paradox why some patients experience septic or circulatory shock after the treatment of infection starts (Van Langevelde et al., 1998). Cranberry procyanidins are effective inhibitors of the growth of all bacteria that exert a mechanism of oxidative phosphorylation, by the inhibition of bacterial F-ATPase. F-ATPase is responsible for secreting protons from the cytosol once the pH value has become too acidic (Sekiya et al., 2019). Acidic cytosol makes it impossible for the bacteria to survive.

Inhibition of bacterial adhesion and biofilm formation is the property of the proanthocyanins of clinical interest. There are two proposed mechanisms of antibiofilm formation, one that is unique to PACs A, especially A2, which directly binds to PapGII of *E. coli* and prevents its adhesion to urethral epithelium; and the second one is that component from *V. macrocarpon* causes a change in gene expression that leads to the increased synthesis of

THP, a Tamm-Horsefall protein, also known as uromodulin (UMOD). THP is rich in mannose and has an affinity to FimH of type 1 pili. Once bound to the FimH, it prevents the binding of *E. coli* to the renal cells of the descending Henli loop (Ribić et al., 2018; Hannon et al., 2016).

Other pharmacological properties of cranberries, which are derived from antioxidative activity

Other potentially useful pharmacological properties of cranberries include anti-cancer properties, blood sugar regulation, promoting gastrointestinal and cardiovascular health, and antiviral and anti-inflammatory properties. The potential for cancer prevention is based on the antioxidative properties of cranberry ingredients. Due to the reduction of oxidative stress, cranberries potentiate cytoprotective effects in Caco-2 cells (Slemmer et al., 2013). Animal model studies show that cranberry extract can reduce insulin resistance (Kowalska and Olejnik, 2016), and its blood glucose regulation is dependent on the genetic material, diet, and sex of mice (Amer-Sarsour et al., 2023). The cardioprotective effect of cranberries is evident *in vitro* studies with cultured hepatocytes showing that active ingredients in cranberries can increase the surface expression of LDL cholesterol, and thus lower its plasma concentration (Chu and Liu, 2005). Also, anthocyanins inhibit cholesterol ester transfer protein (CETP), which would increase HDL cholesterol, and consequently stimulate LDL resorption (Qin et al., 2009). A study by Bernier et al. (2021) shows that cranberry extract in low concentration (9.6 µg/mL) has antiviral properties against *Herpes simplex* 2 virus, by inhibiting its replication by half, one hour after exposure at 37 °C, and Influenza B virus, in the concentration of 4.2 µg/mL. Its antiviral property is attributed to proanthocyanins which have affinity for the surface receptor of the virus. Once bound, virus attachment is prevented. The anti-inflammatory effect of cranberries is due to the inhibition of LPS-induced production of nitric oxide in macrophages (Han et al., 2019). In adipose tissue, cranberry ingredients exhibit anti-inflammatory properties by inhibiting the stimulatory effect of H_2O_2, which would mediate the expression of pro-inflammatory adipokines (Kowalska and Olejnik, 2016).

AIMS

The primary aim of this review paper is to provide a comprehensive understanding of the limitations in the therapeutic use of cranberries and related berries for health improvement. This study focuses on:

1. Analyzing how gene expression variability within the genus *Vaccinium* affects biosynthesis of anthocyanins and proanthocyanidins, leading to variable concentrations of active ingredients in the plant material;
2. Examining pharmacokinetic limitations in order to evaluate the impact of suboptimal parameters on the therapeutic efficacy of cranberry-derived formulations;
3. Identifying research gaps with the purpose of synthesizing and critically analysing existing literature, identifying key gaps and inconsistencies in current knowledge regarding cranberry usage for human health;
4. Highlighting challenges in the practical implications of cranberry products, which are related to standardization, patient adherence, and long-term efficacy in clinical contexts.

METHODOLOGY

The literature searches targeted articles on cranberry active ingredients, synthesis pathways, and clinical trials. PubMed was searched using keywords like "cranberry," "*Vaccinium macrocarpon*," along with terms such as "antioxidative," "pharmacokinetic parameters," "clinical studies," "animal studies," and "*in vitro*," up to 2012. Google Scholar, ScienceDirect, and The Cochrane Library (up to 2012) were additional databases searched. Further publications were found by scanning reference lists of relevant journal articles and books.

The inclusion criteria are various *Vaccinium* sp., both ripe and unripe, diverse environmental conditions such as light, soil, and geography, research on plant transcriptome analysis, and clinical study findings on cranberries.

The exclusion criteria are that only the results of original articles will be considered.

The search criteria involve reviewing changes in biosynthetic pathways that impact the bioavailability of anthocyanins and proanthocyanins across various *Vaccinium* species, as well as assessing differences in pharmacokinetic parameters based on available data.

RESULTS AND DISCUSSION

Indications suggest that the regulation of anthocyanin and proanthocyanin biosynthesis may vary in the genus *Vaccinium* compared to other studied species. In the study by Sun et al. (2015), gene expression is compared between two developmental stages: unripe fruits (white berries, W) and fully ripe fruits (red berries, R). The main aim is to pinpoint genes linked to anthocyanin metabolic pathways and analyse their expression in both W and R stages of *V. macrocarpon* Ait. The methodology used is Next Generation Sequencing, particularly *de novo* RNA-Seq, via Illumina HiSeq 2000. The result is *de novo* assembly of the *V. macrocarpon* transcriptome, with different gene expression between W and R berries. Once identified unigenes were aligned against the databases: NCBI non-redundant protein (NR), Swiss-Prot protein, Kyoto Encyclopedia of Genes and Genomes (KEGG), Clusters of Orthologous Group (COG), and Gene Ontology (GO) using BLASTx, and the nucleotide database (NT) by BlastN with an E-value threshold of 1e-5. A total of 38 460 unigenes (6708%) could be matched to the public databases. Identified unigenes had the greatest number of matches with the genes of *Vitis vinifera* (37.5%), *Prunus persica* (9.5%), *Solanum lycopersicum* (9.3%), *Ricinus communis* (7.1%), *Populus trichocarpa* (6.9%), *Fragaria vesca* subsp. *vesca* (4.0%) and *Glycine max* (2,8%). The remaining 22.9% had hits with other species.

Key findings in the study Sun et al. (2015) impacting anthocyanins and proanthocyanins' bioavailability include the discovery of candidate genes engaged in flavonoid biosynthesis and transportation. Two transport mechanisms are proposed for flavonoid movement: membrane transporter-mediated transport (MTT) and membrane vesicle-mediated transport (MVT). Part of the MTT system are proton-gradient H^+-ATPases and H^+-PPases, ATP-binding cassette (ABC) transporters, and multidrug and toxic compound extrusion protein (MATE) transporters. The MVT transport mechanism includes vacuolar sorting receptor (VSR) proteins, soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNARE), and glutathione *S*-transferase (GST) gene, which codes for the synthesis of flavonoid-binding protein responsible for uploading the vesicles. The study by Yang et al. (2018) explores colour development in ripe white bog bilberry fruits (*V. uliginosum* L.) from Wangqing County, Jilin Province, China. It investigates variations in the expression of key structural genes and transcription factors affecting anthocyanin biosynthesis, utilizing transcriptome sequencing and RT-PCR analysis. The see-through berry lacked anthocyanins and had lower phenolic and flavonoid content compared to the wild type. Yet, it showed higher levels of vitamin C and titrable acids. Structural genes were mainly down-regulated in the white-fruited variant, while transcription factors in anthocyanin and sugar metabolism pathways were mostly up-regulated. Results are summarized in Table 1.

A study conducted in 2021 by Guo et al. investigates the effects of light on the transcriptome of rabbiteye blueberries, or *V. ashei* Reade, which are grown in Kaili, Guizhou, China. To create cDNA libraries and align them with the reference genome of the highbush blueberry (*V. corymbosum*), nine blueberry samples were gathered and sequenced. Light exposure raised the amount of sugar and anthocyanins but lowered the amount of titrable acid. Significant variations in gene expression were found by transcriptome analysis of berries exposed to different light levels; these differences are shown in Table 2.

Early biosynthetic genes (EBGs) are responsible for the synthesis of flavonols, while late biosynthetic genes (LBGs) are responsible for the synthesis of anthocyanins.

According to Yang et al.'s (2018) study, compared to other plant genomes currently available in databases, the transcriptome of *V. macrocarpon* is more similar to *V. vinifera*. It's possible that some cranberry unigenes are shared by several plant species. The data presented in Table 2 demonstrate that cranberries contain both MTT and MVT transport pathways. Nevertheless,

bilitranslocase (BTL) unigenes could not be located. Genes involved in anthocyanin biosynthesis can be divided into two primary categories: transcription factors such as MYB, bHLH, and WD40, and structural genes that encode the pathway's enzymes. Together, these elements create a protein complex that binds to structural gene promoters to control the production of anthocyanins (Yang et al., 2018). Table 2 summarizes the findings from the mentioned study.

The study's Guo et al. (2021) results are consistent with earlier research (table 3). Low phenolic and flavonoid content is similar to the elevated anthocyanin and sugar content and lower titratable acid levels seen in naturally exposed *V. ashei*.

According to data from the controlled clinical experiment conducted by Milbury et al. (2010), the T max and C max of the cranberry anthocyanins (C3Ga, C3Gl, C3Ar, P3Ga, P3Gl, and P3Ar) vary from one to two hours and 0.56 to 4.64 nmol/L, respectively. These findings show that following acute cranberry juice ingestion, cranberry anthocyanins were in fact bioavailable. Regarding the maximal concentration and area under the curve of anthocyanins in their plasma and urine, there were significant variations among the subjects. This variation raises the possibility that people metabolize and excrete anthocyanins in different ways. It was reported that the total amount of urine anthocyanin recovered was 0.79 ± 0.90% of the administered dose.

Table 1. The expression of genes, transcription factors, and enzymes in flavonoid pathways

Structural genes	*VuPOD*	Cinnamoyl-CoA reductase (*VuCCR*), *VuCHI*, *VuCHS*	*VuCHS*	*VuFHT*, *VuF3'H* *VuDFR*, *VuANS*, *(VuANR) VuUFGT*	*VuF3'5'H VuLAR*
Upregulated	+	+			
Downregulated			+	+	
Genes and transcription factors	Genes *VubHLH63* *VuTDR4*	Transcription factors *VubHLH130*, *VuMADS-box*, transcription factor B3	*VubHLH93*	*VubHLH92* *VuMYB2*, *VuMYB4*, *VuMYB7*, *VuMYB8*, *VuMYB10*	*VuMYBB6*, *VuMYBPA1*, *VuMYB12*
Upregulated	++	++	No significant change compared to wild-type *V. uliginosum*	++	
Downregulated				++	++
Sugar metabolism	Beta –glucosidase, glycosyl transferases group 1,	Sugar transporter c130693	Sucrose synthase		
Upregulated	++		No significant change compared to wild-type *V. uliginosum*		
Downregulated		++			

Legend: + upregulated/downregulated, ++ significantly upregulated /downregulated genes, transcription factors and enzymes in flavonoid pathways (Yang et al., 2018). Results from the study by Yang et al., 2018 indicate that the structural genes *VuF3'5'H* and *VuLAR* do not exert an influence on anthocyanin biosynthesis, as their expression in white berries did not significantly differ from that in coloured berries. Conversely, the expression levels of *VuCHS*, *VuFHT*, *VuF3'H*, *VuDFR*, *VuANS*, *VuANR*, and *VuUFGT* were markedly downregulated compared to their expression in red berries, suggesting a close association with anthocyanin synthesis. The analysis across various ripening stages of *V. uliginosum* reveals that only *VuMYB6* and *VuMYBPA1* expression correlates with anthocyanin accumulation. The main reason why white berries lack anthocyanins is because of their downregulation. Reduced expression of transcription factor B3 may be associated with downregulation, which could impact the accumulation of anthocyanins. (Yang et al., 2018) demonstrated considerable up-regulation of *VubHLH130*, *VuMADS-box*, and transcription factor B3, suggesting their involvement in other developmental processes, even if there is currently no data supporting B3's role in colouring.

This implies that there was some degree of absorption and metabolism even though only a small portion of the anthocyanins that were taken were eliminated in the urine.

The results of the study by Roth et al. (2016) would be applicable for comparing the anthocyanin effect to changes in signal transduction and gene expression because bilberries are likewise high in anthocyanins. In this study, it has been proven that anthocyanins from bilberries (*V. myrtillus* L.), have the potential to inhibit IFN-γ-induced pro-inflammatory signalling pathways and reduce the secretion of cytokines in monocytic cells, after the consumption of 160 g of bilberries four times a day, for a total of six weeks. The preparation of the samples used is described in another study (Biedermann et al., 2013). However, no concentration of the plasma anthocyanins has been determined in this research. It can be implied that even at relatively low concentrations, anthocyanins could potentially influence certain physiological responses in the body.

Table 2. The expression of the genes in the flavonoid pathway

Light exposure	Natural (100%)	Moderate (50%)	Severe (20%)
Total of upregulated genes	1.176		
	7.715		
Common genes	671		
PAL gene	+	-	-
C4H	+	-	-
F3H	+	-	-
CHS	+	-	-
F3'5'H	+	-	-
MYB, *HY5*, *bHLH* and *WD40*	+	-	-
GST	+	-	-

Table 2 shows the legend for the flavonoid pathway genes: + upregulated, - no substantial upregulation (Guo et al., 2021). Along with other anthocyanin synthesis genes, such as C4H, F3H, F3'5'H, MYB, HY5, bHLH, and WD40, plants exposed to natural light displayed increased expression of the PAL gene, which is in charge of the first step in the phenylpropanoid pathway. The expression of the GST gene, which is involved in the transport of anthocyanins, also increased when exposed to natural light

Another study by McKay et al. (2011) reported that the relative concentration in the urine for cyanidin and peonidin glycosides ranged from 0.2 to 0.9 ng per 1 mg of creatinine, occurring at 2.2 to 3.4 hours. In contrast, their glucuronide metabolites exhibited concentrations of 0.9 to 41.1 ng/mg creatinine, observed at 3.0 to 5.1 hours. Also, a study by Sano et al. (2003) shows the serum concentration of procyanidin B1 was 0.0106 µmol/L after intake of 2.0 g grape seed extract, which contains 18 mg of procyanidin B1.

In another study (Zampariello et al., 2012), the maximal concentration of A2 in urine in the study was 24.4 ng/mg creatinine at 11.0 h post-ingestion, while A2 was detected in plasma at concentrations below the limit of quantification.

After receiving an intraperitoneal injection of flavonoids and 100% cranberry juice rich in anthocyanins, methanolic extracts of the liver, kidney, heart, bladder, and brain of rats and hamsters have demonstrated antioxidative capacity (Bariexca et al., 2019).

The work by Diaz et al. (2024) utilizes a human model, specifically human fecal microorganisms from either healthy individuals or those with ulcerative colitis to investigate the metabolism of cranberry proanthocyanidins (PACs). Inflammatory bowel illnesses (IBD) such as ulcerative colitis are linked to dysbiosis, which is defined by changes in the composition of the gut microbial community (Scott et al., 2020). According to the study, compared to microbiomes with ulcerative colitis, healthy microbiomes yield higher amounts of certain phenolic acid metabolites from cranberry extract. This demonstrates how dysbiosis affects the gut microbiome's ability to metabolize particular substances.

According to a recent study by Souissi et al. (2021), the commercialized berry polyphenolic fraction Orophenol®, which is sourced from wild blueberries (*Vaccinium angustifolium* Ait.), cranberries (*V. macrocarpon* Ait.), and strawberries (*Fragaria virginiana* L.), significantly inhibits adhesion of *Streptococcus mutans* to saliva-coated surfaces, such as hydroxyapatite and nickel-chrome alloy, which mimic dental enamel. It is commonly recognized

that this bacterium contributes to dental cavities. This antimicrobial action is due to the downregulation of the *luxS* gene, which is essential for controlling *Streptococcus mutans* quorum sensing. Additionally, a great deal of research has been done in animals and clinical trials on the immune system-modulating effects of proanthocyanidins and flavan-3-ols in the prevention and treatment of periodontal disorders (Nawrot-Hadzik et al., 2021). These studies emphasize the wide-ranging advantages of these substances in maintaining oral health. In addition to their direct antibacterial characteristics, these compounds also assist in regulating the immune response to address periodontal problems.

Men undergoing radiation treatment for prostate cancer commonly experience a side effect known as acute radiation cystitis, involving inflammation of the bladder. In a pilot study, men who took cranberry capsules with 72 mg PACs had a lower incidence of cystitis (65%) than men who took placebo capsules (90%). This information was reported by Hamilton et al. (2015). According to the study, choosing cranberry capsules over antibiotics or anti-inflammatory medications may help men receiving radiation therapy for prostate cancer.

In a 2012 Cochrane review, 24 randomized trials using cranberry juice or capsules were assessed. The results showed a high dropout rate, which was probably caused by the participants' inability to stick to a daily juice regimen, but there was some evidence that cranberry juice may reduce the frequency of UTI in susceptible women (Asma et al., 2018). In the study by Asma et al. (2018), a double blind, prospective randomized controlled trial was performed with comparing the mean number of new UTIs in 126 sexually active healthy women. Women were given a standardized cranberry extract containing 37 mg type-A linkage PACs per day, compared to a control dose of 2 mg PACs per day. The study estimates that 35% of patients in the control group would present at least one UTI during the 6-month follow-up period. Risk factors for developing a complicated UTIs that may affect the study would include pelvic floor disorders and diabetes. According to a research by Hormoznejad et al., (2020), treating non-alcoholic fatty liver disease (NAFLD) with 288 mg of cranberry extract or 26 g of dried cranberry for 12 weeks, may be more effective. This improvement is linked to increased insulin resistance and decreased blood alanine aminotransferase (ALT) levels ($P < 0.05$), which are important indicators of liver health in patients with nonalcoholic fatty liver disease (NAFLD). Furthermore, when comparing patients with NAFLD who took cranberry supplements to those who got a placebo, the data show a substantial decrease in ALT levels. An improvement in liver health and function is indicated by this drop in ALT levels. Although anthropometric measurements and steatosis grade improved in both groups (cranberry supplements and placebo), there was no statistically significant difference between the two groups for these variables. This suggests that as compared to the placebo, cranberry treatment did not significantly alter anthropometric parameters. The very small sample size in the research on the combination of cranberry supplements with a weight-loss plan in non-alcoholic fatty liver disease (NAFLD) represents a possible weakness. Forty-one of the fifty patients who were enrolled in the trial finished it. While this sample size may be adequate for a preliminary investigation, larger sample sizes are generally preferred in clinical trials to enhance the statistical power and generalizability of the findings. Furthermore, the study duration of 12 weeks may be considered relatively short for assessing the long-term effects of cranberry supplementation and a weight loss diet on NAFLD.

Larger sample sizes are typically preferable in clinical studies to improve the statistical power and generalizability of the results, even though this size may be sufficient for an initial study. Additionally, it should be noted that the 12-week trial period may be deemed brief in evaluating the long-term impacts of cranberry supplementation and a diet plan for weight loss on non-alcoholic fatty liver disease.

Furthermore, the molecular mechanisms behind cranberry extracts' anticancer properties have been the subject of contemporary research. Research has

demonstrated that cranberry extracts can cause cancer cells to undergo intrinsic apoptosis by influencing important signalling pathways, such as BAD activity and AKT phosphorylation, which results in cell death (Mansouri and Percival, 2020). HL-60 cells were subjected to 25 µg/ml cranberry extract for a whole day as part of this *in vitro* investigation. As a result, an increase in caspase-3/7 activity was observed. This increase can lead to the initiation of apoptosis pathways. Cranberry extract was found to increase mitochondrial outer membrane permeabilization (MOMP), which activates caspase-9 and triggers the committed execution phase of apoptosis. Cranberry extract has the potential to counteract the harmful effects of ethylene oxide on essential organs such as the heart, kidney, liver, lung, stomach, and testis in rats, according to histopathological investigations (Rasool et al., 2021). The antioxidative qualities of the components of cranberries serve as the foundation for the assertion. These characteristics have the ability to counteract the reactive oxygen species (ROS) that ethylene oxide produces, lowering oxidative stress and averting cellular harm. Cranberry extract also has the ability to boost the activity of antioxidant enzymes like catalase (CAT) and superoxide dismutase (SOD). In scavenging free radicals and shielding cells from oxidative damage, these enzymes are essential. Cranberry extract's phytochemicals can also aid in preserving the structural integrity of cells and tissues by blocking ethylene oxide-induced DNA damage, protein carbonylation, and lipid peroxidation. Procyanidins' capacity to alter the stiffness and fluidity of the plasma membrane by interfering with its permeability is thought to be the source of their antibacterial qualities (Khoo et al., 2017). Research on whether procyanidins can block β-lactamase, an enzyme that gives resistance to *β*-lactam antibiotics, is one possible avenue for investigation. This could destabilize the bacterial cell membrane and lower the minimum inhibitory doses of antibiotics. Ultimately, despite a wealth of studies on cranberries' antimicrobial qualities, little is known about the entire range of chemicals that cranberries contain and how they contribute to their antimicrobial activities. To learn more about the antibacterial processes of cranberries and maybe find new antimicrobial agents for a range of uses, more research should be done to identify and characterize these molecules. Proanthocyanidin A2, which has interflavanyl linkages that function as a receptor analogue on the surface of *E. coli* P-pili, is linked to the antibiofilm characteristic of cranberry extract (Vasudevan et al., 2020). By modifying gene expression and encouraging the manufacture of Tamm-Horsfall protein, PACs inhibit biofilm formation in the second way while treating uropathogenic *E. coli* (UPEC) (Hannon et al., 2017). The glycoprotein known as Tamm-Horsfall protein, or uromodulin (UMOD), is only synthesized in the renal cells of the descending Henle loop. A component of the innate immune system is its secretion. THP has a strong affinity for FimH of type 1 pili and is rich in mannose. By modulating intestinal microbiota, cranberry flavonoids and phenolic acids may interact with extra-intestinal bacteria, such as *E. coli*, reducing their transient intestinal colonization and lowering the risk of UTI incidence (González De Llano et al., 2020).

Although the antibacterial activities of cranberries have been explained by numerous studies, there seems to be a lack of information in the literature about the precise processes that underlie the effects of *Vaccinium* berries on viral pathogens. Few studies have examined the direct interactions between components from *Vaccinium* sp. and viral nucleic acids, compared to the studies looking into the effects of cranberries on bacterial adhesion and biofilm development. The antiviral qualities of cranberry extract against the Hazara virus (HAZV) and the Crimean-Congo Haemorrhagic Fever Virus (CCHFV) are investigated in the study by Mirandola et al. (2021). By concentrating on the early phases of replication, including attachment to host cells, the extract prevents HAZV infection. Its virucidal property is exhibited by engaging with HAZV particles and preventing them from attaching to cell receptors. Moreover, the extract prevents CCHFV infection. These results point to cranberry extract as a viable option for the creation of antivirals that combat CCHFV and potentially other viruses.

A-type proanthocyanidins have been demonstrated to have no effect on *Porphyromonas gingivalis* in its planktonic condition in the study conducted by Sánchez et al., 2020. Conversely, the research conducted by Ho et al. (2010) indicates that tannins that were separated from *Vaccinium vitis-idaea* L. had antibacterial action against *Prevotella intermedia* and *P. gingivalis*. Likely, *P. gingivalis's* growth and activity were not sufficiently inhibited by the study's usage of an A-type proanthocyanidin concentration. If the proanthocyanidin concentration in the trial was below the threshold required for it to have antimicrobial effects, that could account for the lack of effect. Furthermore, *P. gingivalis* may have evolved defenses against or a way around the antibacterial properties of A-type proanthocyanidins. *P. gingivalis* may have used virulence factors, including protein-arginine deiminases and fimbriae, to elude the host immune response and maintain chronic inflammatory activation of host cells, which could account for why the bacteria is unaffected by *Vaccinium components*. It appears from the research that *E. coli* does not use protein-arginine deaminases to increase its pathogenicity.

Based on available information, no indication of antimicrobial resistance of *Vaccinium* sp. components has been found thus far. Antibiotics' minimum inhibitory concentration (MIC) can be lowered by *Vaccinium* sp. components. According to the study by Nikolaev et al. (2020), when 4-hexylresorcinol was employed at 50% of the MIC, the MIC of antibiotics of different classes decreased by up to 50 times. This implies that by lowering the MIC values of antibiotics, 4-hexylresorcinol can increase their efficacy. The reported heterogeneous results in clinical studies may be attributed to the use of various cranberry products that may not have defined dosages, strengths, or active component compositions. Clinical research has shown that standardized cranberry products are required to prove efficacy since study results could have been impacted by underdosed bioactive proanthocyanidins. The potential for cranberry extracts to be tampered with because of their expensive manufacture is one problem that can affect how clinical trials turn out. A number of techniques have been put up to confirm the legitimacy of cranberry material. These techniques include measuring the quinic to malic acid ratio, analyzing the anthocyanins using liquid chromatography (LC), identifying proanthocyanidins (PAC) using LC-MS (liquid chromatography coupled with mass spectrometry), densitometry using High-Performance Thin-Layer Chromatography (HPTLC), DNA analysis, and anti-adhesion activity evaluation.

Gardana et al., 2020, have suggested particular markers and ratios to assess if the dietary supplements and extracts fulfil the necessary criteria for real cranberry fruit. The ratios of procyanidins to anthocyanins, epicatechin to catechin, and procyanidin A2 to total procyanidin concentration are the markers identified by the study. These markers and ratios are then analyzed using principal component analysis (PCA) to ensure compliance. It has been found that most cranberries are mostly fabricated with Morus nigra and *Hibiscus* extract, which contain mostly cyanidin-glucoside and cyanidin-rutinoside. This study also revealed that only four products contained the declared amount of procyanidin, necessary for effective UTI treatment. However, a potential gap that might influence the interpretation of the results is whether the manufacturer of the supplement and the researcher have used the same method for determining PAC content. The total PAC content results vary greatly depending on extraction, purification, and quantification processes. Low extraction efficiency leads to low procyanidin yields, which can be improved by optimizing the solvent composition, temperature, and time to enhance extraction efficiency, or by using different solvents and adjusting the extraction conditions. The mentioned enhancements may apply to reducing the procyanidin loss during the purification phase. For the accurate quantification of PACs, it is advisable to employ validated methods along with suitable standards and calibration curves.

The findings of the study by Gardana et al. (2020) contribute to quality control measures in the cranberry industry, emphasizing the need for accurate labelling, adherence to declared PAC content, and prevention of adulteration in cranberry-based products.

Bearing in mind that the interaction between environmental factors and gene expression can impact the biosynthesis of key compounds in berries, ultimately affecting their overall quality, the need for optimal standardization of the dose of PACs is crucial for improving the efficacy of cranberry products in preventing recurrent UTIs. Understanding the molecular mechanisms underlying these factors is essential for optimizing berry production and ensuring consistent quality in terms of nutritional content. Understanding the mechanisms by which *Vaccinium components* may inhibit viral attachment, replication, or other stages of the viral life cycle could provide valuable insights into the potential antiviral properties of *Vaccinium* sp. and contribute to the development of novel antiviral strategies. The potential anti-cancer properties of cranberries suggest the importance of standardizing cranberry products.

These investigations show that cranberry chemicals have the ability to suppress the growth of tumour cells, trigger apoptosis, and have anti-proliferative effects on a variety of cancer cell lines. These results demonstrate the potential utility of cranberry extracts in the prevention and treatment of cancer, underscoring the need for more investigation and study in this area.

Every study that has been examined has shown similar results that emphasize the possible health advantages of cranberries. However, due to factors such as the different concentration of active substances, the impact of individual metabolism, the requirement for continuous consumption, and the risk of people stopping supplement treatment, the practical implementation of this potential is restricted.

CONCLUSION

Cranberry-derived formulations demonstrate significant therapeutic potential, particularly in managing urinary tract infections and addressing microbial challenges. The distinctive pharmacological profile of cranberries, characterized by high concentrations of A-type proanthocyanidins and anthocyanins, underpins their antibacterial, antioxidative, and anti-inflammatory activities. However, the bioavailability and pharmacokinetics of these compounds remain significant challenges, limiting their therapeutic potential. Clinical studies consistently highlight low absorption rates, rapid metabolism, and urinary excretion of cranberry metabolites, as well as substantial inter-individual variability. For instance, urinary recovery of anthocyanins has been reported to be as low as 0.79% of the administered dose, while pharmacokinetic studies confirm that most active ingredients reach their peak plasma concentrations within 2–4 hours' post-ingestion, followed by a sharp decline. These data suggest that continuous supplementation or alternative delivery methods may be required for sustained therapeutic efficacy.

Variability in gene expression among different *Vaccinium* species further complicates the standardization of cranberry-based formulations. Genes regulating flavonoid biosynthesis pathways, such as *VuMYB* and *VuDFR*, are significantly influenced by environmental factors like light exposure and ripening stages, leading to fluctuations in active ingredient concentrations. For example, natural light exposure increases *PAL* gene expression and anthocyanin accumulation, while shaded conditions diminish these effects. These findings emphasize the need for optimized agricultural practices and genetic screening to ensure consistent quality in cranberry-derived products.

Clinical evidence also points to the critical need for standardized cranberry formulations. Several studies report mixed results due to inconsistencies in proanthocyanidin (PAC) concentrations across products, with only a minority meeting the minimum active ingredient thresholds necessary for efficacy. Furthermore, the influence of patient factors, such as gut microbiota composition and metabolic variability, underscores the importance of personalized approaches in cranberry supplementation. Dysbiosis, for instance, has been shown to reduce the metabolism of cranberry PACs into bioactive phenolic acids, which could limit their efficacy in individuals with conditions like ulcerative colitis or obesity-related metabolic disorders.

Emerging research highlights exciting prospects for cranberry applications beyond urinary tract health. Studies on cranberry's potential to modulate lipid profiles, regulate blood glucose levels, and exert antiviral properties against pathogens like *Herpes simplex* virus and influenza B warrant further exploration. Moreover, the discovery of novel mechanisms, such as PAC-mediated inhibition of bacterial biofilm formation through FimH or PapGII binding, paves the way for innovative therapeutic strategies against antibiotic-resistant pathogens.

Despite these advancements, challenges persist, particularly in ensuring patient adherence, determining optimal dosing regimens, and addressing the long-term safety and efficacy of cranberry-based therapies. Future efforts should focus on improving the bioavailability of active compounds through advanced delivery systems, such as encapsulation or conjugation with nanoparticles, and developing standardized, high-potency formulations supported by robust clinical trials. Additionally, molecular studies exploring the interaction between cranberry metabolites and host genetic factors could open new avenues for personalized nutrition and therapeutics.

In conclusion, while the therapeutic potential of cranberry formulations is evident, translating these benefits into widespread clinical practice will require addressing the complexities of bioavailability, standardization, and personalized efficacy. Collaborative efforts across disciplines, including genetics, pharmacology, and clinical sciences, are essential to fully harness the health benefits of cranberries and establish them as a cornerstone of evidence-based integrative medicine.

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