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https://doi.org/10.31925/farmacia.2025.6.3 **ORIGINAL ARTICLE**

MECHANISMS UNDERLYING THE POTENTIAL ROLE OF CRANBERRY-DERIVED PHYTOCHEMICALS IN PREVENTING URINARY TRACT INFECTIONS IN DIABETIC PATIENTS

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Abstract

The constant increase of bacterial resistance to antibiotics over time is an issue that requires finding therapeutic alternatives for the prevention and treatment of infections. Diabetes mellitus (DM) increases the predisposition to urinary tract infections (UTIs) through induced alterations in the urothelium secondary to high glucose concentrations and by affecting the immune response. Pharmacological formulas containing cranberry-derived compounds could represent a choice for the prophylaxis of UTIs in diabetics, but this possibility needs to be further analysed. Certain constituents of cranberry, especially polyphenols, have been shown to decrease bacterial adhesion to the urothelium, stimulate the secretion of Tamm-Horsfall protein, improve the integrity of the urothelium barrier and exert anti-inflammatory, antioxidant and antibacterial actions. The aim of this work is to evaluate potential pathogenetic mechanisms that could be interfered with by cranberry-derived compounds to prevent UTIs in diabetics.

Rezumat

Creșterea constantă a rezistenței bacteriene impune identificarea unor alternative terapeutice eficiente pentru prevenirea și tratamentul infecțiilor. Diabetul zaharat (DZ) este asociat cu o susceptibilitate crescută la infecțiile tractului urinar (ITU), determinată atât de modificările uroteliale induse de concentrațiile crescute de glucoză, cât și de afectarea răspunsului imun. În acest context, formulele farmacologice care conțin compuși derivați din merișor ar putea reprezenta o opțiune promițătoare pentru profilaxia ITU la pacienții cu diabet zaharat, însă această ipoteză necesită evaluări suplimentare. Studiile au demonstrat că anumiți constituenți ai merișorului, în special polifenolii, pot reduce aderența bacteriană la nivelul uroteliului, pot stimula secreția proteinei Tamm–Horsfall, pot îmbunătăți integritatea barierei uroteliale și pot exercita efecte antiinflamatorii, antioxidante și antibacteriene. Scopul prezentei lucrări este de a evalua mecanismele patogenetice potențial susceptibile de a fi modulate de compușii derivați din merișor, în vederea prevenirii infecțiilor tractului urinar la pacienții cu diabet zaharat.

Keywords: urinary tract infection, diabetes mellitus, cranberry, polyphenols

Introduction

Among the types of infections more frequently encountered in diabetics are UTIs. The prevalence [12, 22, 65, 75] and recurrence rate [16, 58] of UTIs are higher in diabetic than in non-diabetic population, especially in women, and the outcome of this condition less favourable due to local and systemic factors that may complicate UTI [16, 55, 60]. Glucosuria, bladder dysfunction with urinary retention and impaired humoral and cellular immune responses facilitate urinary bacterial overgrowth [51, 55, 60], and thus, a higher risk of UTI in patients with DM. Some research has revealed that the risk of UTI is associated with the duration of DM [12, 75] and poor glycaemic control [1, 37, 70, 75, 85], whereas the correlation with glycated haemoglobin A_{1c} (Hb_{A1c}) level has not been found in other studies [25, 83]. Moreover, diabetic patients may have UTIs with antibiotic-resistant uropathogens [2, 12, 47, 70, 73], making therapy even more difficult. Few investigations have found that the rate of multidrug resistance is higher in diabetics compared with non-diabetics [73, 74], and drug resistance has been observed to be correlated with glycaemic control [70, 73, 74] and duration of DM [2].

The global prevalence of DM in adults in 2021 was estimated at 10.5% (536.6 million), with the prospect of an increasing trend in the coming years, such that in 2045 the prevalence of DM would reach 12.2% (783.2 million) [76]. On the other hand, analysis of data from the 2019 Global Burden of Disease Study estimated that, globally, the number of cases of UTIs increased from 252.25 million in 1990 to 404.61 million in 2019, while global deaths due to UTIs increased from 98,590 in 1990 to 236,790 in 2019 [90]. UTIs in patients with type 2 DM were associated with higher annual medical costs compared with matched patients without UTI [91]. Recurrent UTIs in diabetic patients increase the risk of renal complications and antibiotic prescription, which further contributes to higher healthcare costs.

Therefore, prevention strategies, beyond antibiotics, require urgent evaluation.

Materials and Methods

The literature review was performed using the keywords "urinary tract infection" or "recurrent urinary tract infections" and "diabetes" or "diabetes mellitus" or "type 2 diabetes mellitus", "cranberry", "*Vaccinium macrocarpon*", "uropathogenic *Escherichia coli* (UPEC)", "diabetic urothelial changes", "polyphenols" and related metabolites from the PubMed, Science Direct databases. The titles and abstracts of the articles were searched, followed by a full analysis of relevant publications. Original research and reviews in English were selected. Inclusion criteria were: experimental or clinical studies evaluating urothelial changes in DM, bioactive compounds of cranberries, urinary excretion of cranberry metabolites, antiadhesive properties, effects on the urothelial barrier, antioxidant/anti-inflammatory actions, or interactions with antibiotics. Case reports or studies that do not directly address the pathogenesis or prevention of UTI by cranberry-derived compounds were excluded.

Results and Discussion

Changes in the urothelium that may increase the susceptibility of diabetic patients to urinary tract infections

Studies conducted on diabetic and non-diabetic patients with UTIs have reported that *Escherichia coli* is the most common germ isolated from urine samples [41, 58, 70, 86]. Other microorganisms involved in the ethology of UTIs, isolated with a higher frequency, were some species of bacteria, such as: *Klebsiella spp.*, *Enterococcus spp.*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus spp.*, *Acinetobacter* [37, 41, 70, 72, 80] and fungi (*Candida albicans*) [1, 5, 37, 55, 80]. In a multi-regional study on the bacterial aetiology of UTIs in the Romanian population [64] and in another Romanian retrospective study on the resistance profile of multi-drug-resistant UTIs [48], *Escherichia coli* was also identified in the highest percentage, followed by *Klebsiella spp.*

Uropathogenic *Escherichia coli* (UPEC) strains are equipped with virulence factors that enable them to evade the host's immune defence, colonise, invade, proliferate in the urothelium and ultimately cause UTI [69, 80, 86]. UPEC fimbriae mediate adhesion to uroepithelial cells, prevent mechanical removal of bacteria by the urinary stream, and protect against the action of antibiotics [69, 80, 86]. Type 1 fimbriae have specificity for D-mannose-containing host cell receptors, found particularly in the lower urinary tract [57, 86]. Attachment to specific receptors on the mucosal surface is mediated by FimH, a protein located at the tip of type 1 fimbriae [32, 57]. In studies of *Escherichia coli* strains isolated from patients with UTIs, the FimH gene was found in over 90% of UPEC strains analysed [32, 52]. Uroepithelial internalization of bacteria and their persistence in intracellular bacterial communities (IBCs) is preceded by UPEC adherence to bladder cells by type 1 fimbriae [86]. IBCs represent a reservoir of antibiotic-resistant bacteria that may contribute to relapse of infection [86].

Type 1 fimbriated *Escherichia coli* has been shown to adhere more strongly to uroepithelial cells harvested from diabetic women than to non-diabetic control cells [24] and to bladder cells from streptozotocin-induced diabetic female mice than to age-matched controls [57]. This may be related to the change in the carbohydrate content of the urothelial surface [31, 57] or to a different composition (different glycosylation) of the type 1 fimbriae receptor of diabetic urothelial cells [24]. An increased number of mannose-containing binding sites for type 1 fimbriae on bladder cells of diabetic mice compared with control mice has also been reported [57], as has an upregulation of mannose-like receptors (Mrc1) in diabetic mice infected with *Escherichia coli* but not in control mice [51]. In addition, upregulation of caveolin 1, a protein involved in endocytic uptake of *Escherichia coli*, was evidenced in the bladders of diabetic mice as well as in TERT-NHUC uroepithelial cells treated with high glucose levels [51].

In the study by Ozer *et al.,* it was shown that increased type 1 fimbriated UPEC attachment to bladder cells in streptozotocin-induced diabetic female mice was determined by the accumulation of advanced glycation end products (AGEs) on the urothelial surface caused by high glucose levels [57]. Furthermore, the authors determined that pyridoxamine, a natural form of vitamin B_6 and an inhibitor of AGEs formation, blocked UPEC adherence to urothelial cells in diabetic mice but had no effect on UPEC adherence in control mice [57]. This finding may be relevant for the treatment of UTIs in patients with DM, because pyridoxamine removes reactive carbonyl species produced by lipid and glucose oxidation [57].

P fimbriae attach to non-mannose receptors, mainly on renal tubular epithelial cells. P-fimbriated UPEC strains are predominantly associated with upper UTI [34, 79, 86] and persistent UTI [19]. Circulating human neutrophils have small amounts of neutral glycosphingolipids on their surface [44] to which P-fimbriated bacteria can adhere. This may contribute to the reduced ability of polymorphonuclear cells to bind and phagocytose these bacteria [79].

Tamm-Horsfall protein (THP) is a high molecular weight mannosylated glycoprotein secreted into the urine by tubular cells of the thick ascending limb of the loop of Henle and the initial portion of the distal convoluted tubule [6, 10, 88]. It binds to the mannose-binding domain of FimH of UPEC and blocks its binding to the target cell surface [24, 67, 68]. The protective action of THP also extends to the

prevention of urinary tract colonization by *Candida albicans* [13] and UTI with *Proteus mirabilis* [61]. THP has a filamentous structure and forms a three-dimensional meshwork where bacteria are trapped and subsequently eliminated by bladder emptying [88]. Another potential role of THP is to reduce inflammatory response of neutrophils by binding to an inhibitory receptor on neutrophils and to modulate NETosis in the urinary tract [50]. Experiments performed on THP-deficient mice with UTI revealed an increased bacterial load in the urinary tract, increased neutrophil recruitment, more severe tissue damage and reduced urinary NETosis during UTI compared with wild-type mice [50].

Several studies have evidenced that THP secretion is decreased in DM [62, 81, 88] and its chemical composition is altered due to increased glucose content [24, 62], which affects UPEC binding to the uroepithelium [29]. Measurement of the urinary excretion rate of THP in patients with type 1 DM resulted in lower values than in the control group [81]. In addition, the excretion rate of THP was reduced in diabetic patients with diabetic nephropathy compared to those without nephropathy [81]. In non-proteinuric insulin-dependent diabetics, the chemical structure of THP was modified, indicating a significantly higher glucose content compared to control group, but a reduced N-acetyl-neuraminic acid content [62]. The latter aspect was correlated with a decreased surface charge density of THP [62]. Urinary THP concentration was found significantly diminished in post-menopausal insulin-dependent diabetic women compared with non-insulin dependent and control women [6]. Reduced renal secretion of THP in patients with diabetic nephropathy may lead to recurrent UTIs [88].

In DM, normal white blood cell activity and the innate immune response are impaired [1, 20, 51]. High glucose concentrations have been associated with reduced levels of the antimicrobial peptide psoriasin in the plasma and urinary bladder of patients with type 2 DM compared with non-diabetic subjects, downregulation of its expression in urine exfoliated cells, loss of uroepithelial barrier integrity and function and alteration in cell membrane proteins and cyto-skeletal structures [51]. Psoriasin protects against *Escherichia coli* by sequestering zinc required for bacterial growth [26, 51].

Experiments on human neutrophils have revealed that treatment of these cells with psoriasin caused their activation and secretion of a broad array of the inflammatory cytokines and chemokines *via* mitogen-activated protein kinase (MAPK) p38 and extracellular signal-regulated kinase (ERK), the production of reactive oxygen species (ROS), degranulation and stimulation of oxidative and non-oxidative destruction mechanisms in the studied neutrophils compared with unstimulated neutrophils [93]. In UTI, neutrophils are attracted to the urinary bladder by cytokines released in response to infection of urothelial cell [15]. Neutrophils from patients with recurrent UTIs demonstrated significantly reduced bactericidal activity compared with healthy controls, which resulted in inadequate bacterial clearance and predisposition to recurrence of UTI [15].

UPEC infection leads to loss of urinary barrier integrity [27]. High glucose stimulates the expression of caveolin 1 in bladder cells of mice, leading to increase bacterial load [51]. Psoriasin caused down-regulation of caveolin 1 in bladder cells of diabetic mice, contributing to fewer bacteria internalised in the uroepithelial cells and restored the expression of occludin, a tight junction protein [51].

Normal ureteral epithelial cells (SV-HUC-1 cell line) pretreated with increasing concentrations of glucose for 24 h and then incubated with UPEC induced a significantly higher frequency of infected cells for cells pretreated with high concentration of glucose (10 and 15 mM) compared to cells treated with 0 mM glucose [31]. Glucose-enhanced uroepithelial cell invasion and infection were mediated by upregulation of the JAK/STAT-1 signalling pathway and Toll-like receptor (TLR)-4 expression in a dose-dependent manner [31]. TLR-4 binds to UPEC lipopolysaccharide (LPS) and initiates the activation of a signalling cascade, resulting in the secretion of pro-inflammatory cytokines [40, 86]. The severe acute inflammatory response to UPEC bladder infection is thought to be a predisposing factor to chronic and recurrent UTIs, as demonstrated in an experimental mouse model [30]. The development of chronic cystitis in C3H mice was preceded by severe pyuria and bladder inflammation, increased serum cytokine concentration ((Interleukin (IL)-5, IL-6, IL-8 analogue KC (keratinocyte-derived cytokine)) and granulocyte colony-stimulating factor (G-CSF)) [30]. Mice deficient in TLR4 signalling were more resistant to the development of chronic cystitis [30].

Another aspect that should be mentioned in type 2 DM patients is that the occurrence of UTI augments oxidative stress in these patients [28]. Urinary catalase and superoxide dismutase activity were significantly lower in type 2 diabetics with UTI, and urinary level of lipid peroxidation (assessed by measuring of urinary malondialdehyde concentration) was higher than in diabetic patients without UTI or in non-diabetic patients with UTI and controls [28]. An elevated level of lipid peroxidation in urine samples collected from patients with UTI, compared with the level of the same parameter in negative urine culture, associated with reduced levels of antioxidant enzymes, is an indicator that ROS are generated in UTI, and anti-oxidant therapy might be helpful in UTI, in addition to antibiotic therapy [42].

At the same time, ROS production by UPEC-infected bladder epithelial cells causes nuclear translocation of

nuclear factor-erythroid 2-related factor (NRF_2) and UPEC exocytosis through $RAB_{27}B$ activation [40]. NRF_2 binds to antioxidant response elements in the nucleus of urothelial cells and induces transcription of antioxidant genes [40]. NRF_2 activation decreases ROS generation, inflammation, cell death in infected bladder cells and bacterial load [40]. Loss of NRF_2 *in vivo* led to oxidative stress, inflammation and exfoliation of urothelial cells, while high NRF_2 activity lowered pro-inflammatory cytokine secretion and facilitated UPEC expulsion [40].

These clinical and experimental data provide evidence that could explain the increased predisposition to UTIs in the diabetic patients and highlight the challenge of preventing and treating recurrent UTIs, as uncontrolled glycaemia may be a risk factor for the development and recurrence of UTIs in patients with type 2 DM [1, 51, 70]. Because repeated, long-term antibiotic treatments lead to antibiotic resistance and dysbiosis of the normal flora of the organism [18, 27], non-antibiotic remedies might reduce the need for antibiotics and the risk of increasing antibiotic resistance [34, 86]. A feasible alternative or complementary approach to conventional antibiotic prophylaxis could be the administration of natural products that inhibit bacterial adhesion to uroepithelial cells [18, 19, 34, 63], exert antimicrobial activity [18], or increase the body`s immune defence response [80] and, as an ancillary effect, have a positive impact on blood glucose level and complications of DM. One of the natural remedies that could be considered is cranberry, used in different pharmaceutical forms. However, it is not known with certainty what the results of administering cranberry-derived compounds would be in preventing UTIs in diabetics, therefore, in-depth investigations are needed to elucidate this opportunity.

Urinary excretion of bioactive compounds after consumption of cranberry-derived products

Cranberries (American species - *Vaccinium macrocarpon*) have long been known for their benefits in preventing UTIs, although studies have not yet provided unequivocal evidence of their effectiveness [19, 87]. The explanation might be related to the use of different cranberry products, obtained by different extraction methods, and therefore with non-identical chemical compositions, and the use of non-standardised derivatives, administered in variable doses, which has led to inconsistent results, making it more puzzling to interpret and compare [18, 87]. A previous meta-analysis included 24 studies on the effectiveness of cranberry products in preventing UTIs in susceptible subjects, concluded that cranberry products did not significantly reduce the occurrence of symptomatic UTIs overall [39], and, until studies establish the amount of active ingredient in the product administered, as measured by a standardised method, cranberry products cannot be recommended for the prevention of UTIs [39]. Nevertheless, a recent systematic review and network meta-analysis by Moro *et al.* reported that cranberry products decreased the rate of UTIs and antibiotic use and should be considered in the therapeutic approach of UTIs [53].

The main organic constituents of cranberries are glucose, fructose, polyphenolic compounds (anthocyanins, proanthocyanidins (PACs), flavonols), terpenoids, acids (citric, ascorbic, benzoic, glucuronic, quinic, malic, ursolic) [18, 19, 87, 92], liposoluble and hydro-soluble vitamins (vitamin A, E, K, C, B-complex) [54]. Inorganic compounds are water and minerals [54]. Cranberry products are delivered in liquid or dry form, such as juices, syrups, capsules, tablets, powders, extracts, but without the same concentration of active compounds and efficacy [14, 87]. Given that, most often, cranberries are consumed in processed form, not as fresh fruits, technological processes that remove the peel and seeds of the fruit lead to a decrease in the anthocyanin content [14]. High temperature also affects the amount of anthocyanins, although it changes the content of PACs and flavonols to a lesser extent [14].

Plant polyphenols are entrapped in a complex matrix of dietary fibres, from where they are released through digestion in the gastrointestinal tract [9]. Digestive enzymes and the microbiota largely influence bio-accessibility and metabolism of dietary polyphenols and determine the bioavailability of both parent poly-phenols and their catabolites [9]. Cranberry intake is followed by gastric absorption of low molecular weight cranberry-derived phenolic compounds, which are then excreted, resulting in the accumulation of conjugated phenolics in the urine, whereas high molecular weight compounds, such as quercetin and myricetin, although present in high amounts in cranberry products, have not been identified in plasma and urine samples [84]. PACs with a higher degree of polymerization enter the large intestine intact because they are poorly absorbed in the small intestine and are metabolised by the local microbiota [77, 82] to lower molecular weight metabolites that are absorbed into the host portal circulation [19, 77]. The absorbable metabolites are transported to the liver, where they are further metabolised and then released into the circulation [77].

Plasma and urinary concentrations of a range of phenolic compounds were measured by GS-MS (gas chromatography-mass spectrometry) after consumption of cranberry products (juices, sauces and fruits) by the healthy human volunteers and showed that the concentration of all the cranberry-derived phenolic compounds increased significantly in urine samples after ingestion of the cranberry product [84]. Feliciano *et al.* [21] identified and measured the plasma and urinary concentrations of sixty phenolic metabolites after healthy men consumed cranberry juice containing five different amounts of (poly)phenols and reported

that the plasma concentration of many (poly)phenol metabolites was linearly related to the amount of (poly)phenols ingested with the cranberry juice, but not for all metabolites [21]. However, linearity was not found for the urinary excretion of metabolites [21]. One of the factors explaining the interindividual variation in the metabolite profile is assumed to be the variation in the gut microbiota of the subjects [9, 21, 78, 82].

Assessment of urinary anthocyanin excretion after ingestion of cranberry juice containing 650.8 μg total anthocyanins by healthy volunteers revealed that one of the anthocyanins, peonidin 3-O-galactoside, which is the second most abundant anthocyanin in cranberry juice, was excreted in the largest amount in urine within 24 hours of juice consumption [56]. A variety of polyphenolic metabolites have also been identified in urine after ingestion of a single dose of cranberry syrup by humans [36] and after chronic consumption (12 weeks) of cranberry powder by healthy older subjects [82]. However, Baron *et al.* did not detect PACs in urine after the intake of highly standardised cranberry extract [5], while other researchers reported low concentrations of PAC-A2 dimers in the urine of healthy older adults after consumption of cranberry juice [49].

Although numerous studies have proven urinary excretion of cranberry-derived metabolites after consumption of cranberry juice, syrup or powder by humans, demonstrating variable bioavailability, more analyses are required to identify which compounds have the strongest action in preventing UTIs and at what dose. In addition, it would be relevant to be evaluated how the microbiota of diabetics might influence, compared to that of non-diabetic subjects, the digestion and metabolism of cranberry products and their excretion through urine.

Potential mechanisms by which cranberry-derived compounds might interfere with the pathogenesis of urinary tract infections in diabetics

Cranberry polyphenols and intermediate microbial metabolites derived from their digestion have been postulated to carry out antiadhesive action against UPEC [19, 27, 59, 78]. Tamargo *et al.* evaluated the transformation of cranberry polyphenols under dynamic conditions by simulating the gastrointestinal digestion of these compounds and reported that two-thirds of the total cranberry polyphenols were recovered after simulated gastrointestinal digestion [78]. Furthermore, the study showed that the simulator effluents had significant antiadhesive activity against UPEC [78].

It has been shown *ex vivo* that cranberry fruit juice dry extract containing 36 mg of PACs exerts anti-adhesive activity against both type 1- and P-fimbriated UPEC, and this action was more potent than that of D-mannose dietary supplement, which only prevented the adhesion of type 1 fimbriated UPEC [34]. Purified PAC extracts obtained from dried cranberry juice inhibited the adherence of multi-drug resistant UPEC strains to human bladder uroepithelial cells [29]. Another research reported that the intake of a single dose of three different cranberry extracts with a standardised level of 36 mg of PACs by human subjects caused a significant increase in the antiadhesive activity of urine against uropathogenic P-fimbriated *Escherichia coli* compared with placebo [33]. It appears that the mechanism explaining the decrease in adhesion force of cranberry juice is the change in the conformation of the surface macromolecules of P-fimbriated strain of *Escherichia coli* and the decrease in the length of the P-fimbriae [43].

Similar results were obtained on UPEC strains (P-fimbriated strains and mannose-resistant hemagglutination strains) incubated with urine collected at different interval of times (from 2 to 8 hours) after oral consumption of a single dose of cranberry juice cocktail (16 oz) by a volunteer [79]. It caused significantly lower adherence than that observed by incubation of the same strains with urine collected after water ingestion, inhibition which was proportionally greater with the time of urine collection [79]. This indicates that antiadhesive components of the cranberry juice cocktail reached the urinary tract after its ingestion, having a protective effect against UPEC adherence [79]. Other cranberry phenolic metabolites (catechol, benzoic acid, vanillic acid, phenylacetic acid and 3,4-dihydroxyphenylacetic acid) have proved anti-adhesive properties against UPEC *in vitro* in a concentration-dependent manner [19]. Urine metabolites of highly standardised cranberry extract have been shown to be effective in inhibiting the adhesion and biofilm formation of a reference strain of *Candida albicans*, which is a biofilm-forming strain [5]. This may have clinical application, as patients with type 2 DM are more prone to fungal infections.

Cranberry fruit extract demonstrated an indirect inhibitory effect on UPEC adhesion to host cells as well. It stimulates the secretion of THP by the kidneys [67, 68]. The amount of THP secreted into the urine after administration of a standardised cranberry extract was greater in males than in females [67]. Urine samples provided by volunteer subjects (males and females) who consumed cranberry extract for seven days showed that urine collected from males significantly inhibited UPEC adhesion to human T24 bladder cells, while urine obtained from females did not influence the attachment of the UPEC strain to the cells [68].

The prevention of bacterial penetration into the urothelium is determined by its structural integrity, ensured by tight junctions between epithelial cells. When the expression of tight junction proteins is altered, the permeability of urothelium increases [27]. In the case of UTI with UPEC, the urothelial barrier is disrupted [27]. Experimentally, it has been demonstrated that exposure of the TERT-NHUC cell line to high glucose levels contributed to the loss of structural

integrity of the urothelium by downregulating occludin [51]. In a urinary barrier model of bladder epithelial cells (T24 cells), either UPEC-infected or non-infected, incubation with two cranberry-derived metabolites, 3,4-dihydroxyphenylacetic acid and phenylacetic acid, resulted in increased expression of claudin-2 and zonula occludens-1 (ZO-1) proteins in tight junctions compared with control [27]. Cranberry-derived metabolites improved urinary barrier integrity and paracellular permeability, although not significantly [27].

Administration of commercial cranberry juice cocktail and fresh cranberry juice to a mouse model infected with a UPEC strain expressing type 1 fimbriae but not P fimbriae showed a significant decrease in the number of bacteria in the infected bladders compared with control mice that consumed water [38]. The action of four organic acids (quinic, malic, shikimic and citric acids) at concentrations similar to those found in fresh cranberry juice was tested on the bladder bacterial load, either in combination of four, two, or individually [38]. The experiment indicated that they had an antibacterial effect, both when all four acids were mixed and when malic and citric acids or malic and quinic acids were combined [38]. The organic acids in cranberry appear to be effective antibacterial compounds, even though they did not cure the infection, but only reduced the bacterial load [38].

The antimicrobial action of cranberry juice and three types of cranberry extracts (water soluble, apolar phenolic compounds and antocyanins) was examined against several bacterial strains (both Gram-positive and Gram-negative) and revealed that all strains were inhibited by cranberry phenolic compounds, with the greatest growth inhibition being obtained by the extract rich in water-soluble phenolic compounds [17]. However, in another *in vitro* study, a methanol extract of dehydrated cranberries did not directly inhibit the growth of two P-fimbriated *Escherichia coli* strains, but it inhibited cyclooxygenase-2 activity, transcriptional activation of nuclear factor κβ (NF-κβ) in human T lymphocytes, and inhibited the release of several ILs (IL-1β, IL-6, IL-8) and tumour necrosis factor-α (TNF-α) from human peripheral blood mononuclear cells stimulated with *Escherichia coli* LPS [35]. The compounds that induced these effects were ursolic acid and its derivatives [35]. By suppressing the release of inflammatory cytokins, the cranberry-derived extract may ameliorate the inflammatory symptoms of UTI caused by *Escherichia coli* [35].

Extracts obtained from whole cranberry fruit have been shown to have anti-inflammatory effect [89]. Although, these extracts varied in their phytochemical composition regarding polyphenols and triterpenoid content, all extracts reduced LPS-induced IL-6 production by human monocytes (THP-1 cells), and three extracts rich in anthocyanins, triterpenoids and total polyphenols decreased IL-6 and TNF-α at much lower concentrations compared with LPS-exposed control [89]. A multicentre study in women with a recent history of UTI (≥ 2 UTIs in the previous year) reported that after 24 weeks of drinking a cranberry juice beverage, the number of clinical episodes of UTI was significantly reduced compared with placebo group [46]. The result could be related to the anti-inflammatory action of cranberry, which prevented the progression of asymptomatic bacteriuria to symptomatic episodes of UTI [46].

In addition to inhibiting UPEC adhesion to the urothelium, cranberries exert a powerful antioxidant activity [3, 7, 8, 71] and may attenuate mitochondrial damage [8]. Caillet *et al*. found that the cranberry extract, rich in apolar phenolic compounds and anthocyanins, has the highest free radical scavenging activity [7]. Hypothetically, cranberry polyphenols perform antioxidant actions through two mechanisms: they directly neutralise ROS [3, 7, 8, 54] and, indirectly, stimulate NRF_2 transcription, which further activates the synthesis of the antioxidant enzymes (catalase, glutathione) [8].

The antioxidant capacity of three pure polyphenols (quercetin, catechin and hesperetin) administered intraperitoneally to rats and of 100% cranberry juice (rich in antocyanins) administered to hamsters was evaluated in several organs of experimental animals [4]. Research has demonstrated the presence of polyphenolic metabolites in organ extracts and that the antioxidant capacity was significantly higher in organs (liver, kidney, heart, brain, bladder) of the study animals compared to control animals that received water [4]. Dietary polyphenols may have benefits for the treatment of chronic complications of some diseases, including DM, and may counteract the oxidative impairment of organs [4].

Bioactive compounds from various natural products may act as multi-drug resistance inhibitors, which improves the outcome of antibiotic treatment [18]. It is considered that cranberry potentiating effect of antibiotics is achieved by two mechanisms: alteration of the permeability of the bacterial wall to the antibiotic, making it more permeable to the antibiotic, and interaction with the mechanism that pumps the antibiotic out of the bacteria, inhibiting multidrug resistance efflux pumps [45]. Maisuria *et al.* reported that purified cranberry PAC fraction enhanced the antimicrobial activity of many antibiotics against *Escherichia coli*, *Proteus mirabilis* and *Pseudomonas aeruginosa* and decreased biofilm formation [45]. Concomitant treatment of *Escherichia coli* and *Pseudomonas aeruginosa* with cranberry PAC and tetracycline resulted in no development of antibiotic resistance [45].

Moreover, cranberry-extracted proanthocyanidins (cPAC) have been shown potentiation of β-lactams against β-lactam-resistant *Enterobacteriaceae* [23]. cPAC proved *in vitro* inhibitory activity against different classes of b-lactamases and enhanced the

activity of oxacilin and carbenicilin against methicilin-resistant but not methicilin-sensitive staphylococci [23]. Capsules containing 240 mg of PACs reduced the expression of several genes encoding virulence factors in the cephalosporin-resistant *Escherichia coli* isolate CTXM-15 [66]. This extended-spectrum-β-lactamase-producing UPEC strain is resistant to several classes of antibiotics, including third-generation cephalosporins, and is the strain most commonly associated with UTIs [66]. Hydroalcoholic extracts of cranberry with different concentrations of PACs demonstrated potent *in vitro* inhibitory activity against *Escherichia coli* strains isolated from women with UTIs [11]. Cranberry extract proved superior efficiency in elimination of one of the multi-drug-resistant antibiotic isolates than any of the antibiotics used for testing the antimicrobial susceptibility [11]. Cranberry PAC can be an adjunct in the therapy of recurrent UTIs. Table I summarises the actions that could be exerted by different pharmacological forms of cranberry for the prevention of UTIs.

Table I

Mechanisms that cranberry could influence to prevent urinary tract infections

Pharmacologic form	Mechanism	References
cranberry fruit juice dry extract containing 36 mg of PACs purified PAC extracts from dried cranberry juice cranberry extracts with a standardised level of 36 mg of PACs cranberry juice cocktail cranberry phenolic metabolites	Prevent UPEC adhesion to the urothelium	[34] [29] [33] [79] [19]
cranberry extract	Stimulate secretion of Tamm-Horsfall protein	[67], [68]
cranberry-derived metabolites	Improve urinary barrier integrity; decrease its permeability	[27]
commercial cranberry juice cocktail and fresh cranberry juice	Decrease urinary bacterial load	[38]
cranberry juice cranberry extracts	Inhibit bacterial growth	[17]
methanol extract of dehydrated cranberries extracts from whole cranberry fruit cranberry juice beverage	Exert anti-inflammatory activity; supress the release of inflammatory cytokins	[35] [89] [46]
cranberry extract cranberry fruit extract cranberry juice pure polyphenols (quercetin, catechin and hesperidin)	Exert antioxidant activity	[7] [3] [71] [4]
purified cranberry PAC fraction cranberry-extracted proanthocyanidins (cPAC) capsules containing 240 mg of PACs hydroalcoholic extracts of cranberry	Potentiate the effect of antibiotics/Antimicrobial activity	[45] [23] [66] [11]

Conclusions

The data presented on the effects of cranberries on UTIs are the results of a limited number of studies that were not conducted in diabetic patients. Current understanding is largely extrapolated from non-diabetic subjects, experimental animal models and cell culture models, where cranberry-derived compounds have been shown to interfere with several processes associated with UTI. The main gaps in the field consist of the scarcity of prospective, controlled studies specifically conducted in the diabetic population with UTIs and assessment of specific interference with antibiotic therapy *in vivo*. Therefore, future research should focus primarily on conducting clinical trials exclusively targeting diabetic patients with UTI or recurrent UTIs. In addition to these clinical trials, *in vitro* and *in vivo* studies would be recommended to investigate the molecular interactions of cranberry phytochemicals with glucosuric urine models and diabetic urothelial cells, as well as to identify the most beneficial compounds, the optimal therapeutic dose and formulation and the metabolic impact of cranberry consumption on glycaemic control and renal function. The gaps in the literature do not allow definitive conclusions to be drawn regarding their benefits for UTIs in diabetics, therefore, extensive studies are required.

Conflict of interest

The authors declare no conflict of interest.

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