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# Urinary track health benefits and phytochemical characterization based on a narrative review on cranberry and its innovative formulation in phospholipids

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Cranberry is rich in nutritional components and numerous bioactive compounds with properties useful in a variety of physiological and clinical conditions. Both the American (*Vaccinium macrocarpon*) and European (*Vaccinium oxycoccus*) species are rich in (poly)phenols, including flavonoids and phenolic acids (anthocyanins, flavonoids, and polyphenols such as phenolic acids). Cranberry is one of the few fruits with a high content of type A proanthocyanidins, associated with numerous health benefits, such as reducing recurrent urinary tract infections (UTIs). This review analyses information on the chemical composition of cranberry, the beneficial impact on human health, and disease prevention after cranberry consumption. Specifically, the mechanism of action of its benefits against urinary tract infections (UTIs), the second most common type of infection worldwide, is explored. Finally, the review focuses on the characteristics of new formulation technologies to increase bioavailability, such as new phospholipid-based delivery systems capable of dispersing cranberry extract in sunflower lecithin, thus improving its stability, solubility, absorption, and biological efficacy at lower doses. In conclusion, the available literature suggests that cranberry products are widely supported for reducing recurrent urinary tract infections, especially in women and children. Their mechanisms include anti-adhesion, anti-biofilm, and antimicrobial effects. They are generally safe and well-tolerated, although some restrictions apply (drug interactions, pre-existing conditions). Innovative delivery systems (such as phospholipids, microcapsules, gel formulations) optimize application, allowing for lower effective doses and lasting benefits, primarily improving safety. Further large-scale, high-quality studies are needed, especially for uses in non-urolological areas, to confirm broader health impacts.

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## A brief history of cranberry

Cranberries belong to the Ericaceae family and are primarily represented by two species: the American cranberry (*Vaccinium macrocarpon*) and the European cranberry (*Vaccinium oxycoccus*). The “large” American cranberry is mainly cultivated in North America, especially in the northern United States and Canadian provinces, as well as in Chile and in commercial farms in parts of Europe.<sup>1,2</sup> The American variety is a low-growing evergreen shrub with slender stems and small, elliptical leaves. Its berries ripen from pale pink to dark purple, typically from late summer through early autumn. In contrast, the European cranberry is smaller, grows wild across parts of Europe and Asia, and is better adapted to colder climates.<sup>2,3</sup> The term “cranberry” is thought to have originated from early observations by Indigenous peoples of North America, who

noted the resemblance of the plant’s floral parts to a crane’s neck and beak.<sup>1</sup> Because of their intense tartness, only about 5% of cranberries are sold fresh; the vast majority are processed into juices, sauces, and dried products. In addition to their culinary uses, cranberries have a longstanding history as both a food and medicinal plant in North America, Europe, and Asia.

### Chemical composition

Cranberries have a complex and rich chemical composition, with essential nutrients alongside a variety of bioactive compounds. These chemical constituents can vary significantly between species and cultivars, influenced by both genetic and environmental factors.

Water is the predominant component of the fruit, comprising approximately more than 80% of the mass. Carbohydrates make up around 12%, primarily in the form of simple sugars such as glucose, fructose, and sucrose, with glucose typically being the most abundant.<sup>2</sup> Large-fruited cranberries tend to

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contain higher concentrations of both monosaccharides (ranging from 3% to 7%) and sucrose (3.9% to 5.3%) compared to their smaller European counterparts (*Vaccinium oxycoccos*), which exhibit lower sugar levels (2% to 6% for monosaccharides and 0.01% to 0.5% for sucrose).<sup>1,4</sup> Oligosaccharides represent an important component that could be responsible for some health benefits through prebiotic, anti-adhesive, anti-inflammatory and antioxidant activity.<sup>5</sup> The perceived sweetness of cranberries is largely attributed to these sugars, though it remains tempered by the fruit's high organic acid content. Among these organic acids, citric, malic, and quinic acids are predominant, contributing to the fruit's notable acidity. Titratable acidity, primarily from citric acid, ranges from 2.1% to 4.9% in smaller cranberries and is generally lower in larger varieties (1.9% to 2.4%).<sup>1</sup> These levels are influenced by a variety of factors, including cultivar, ripeness, climate, and soil conditions.

Cranberries are also recognized for their vitaminic profile, particularly their high content of vitamins C, E, and K, which underlie many of their antioxidant properties. The American cranberry contains higher levels of ascorbic acid, with reported values reaching up to 47.5%, compared to 15.3% to 30% in European species. Additionally, although present in small quantities, omega-3 and omega-6 fatty acids are also found in cranberry fruit, contributing further to its nutritional value.<sup>1,2</sup> Mineral content in cranberries is similarly notable. Potassium is the most abundant micronutrient in both major species, but trace elements such as manganese and boron can also be found.<sup>6</sup>

Beyond their nutritional constituents, cranberries are particularly rich in phytochemicals, many of which have been associated with potential health effects. Among the most prominent are phenolic acids, triterpenoids, and flavonoids.<sup>7,8</sup> Phenolic acids in cranberries include both hydroxybenzoic and hydroxycinnamic acids. Benzoic acid is especially abundant, accompanied by smaller quantities of caffeic, ferulic, *p*-coumaric, and chlorogenic acids.<sup>9</sup> Triterpenoids, another important class of cranberry phytochemicals, are found mainly in the skin. These include ursolic acid, oleanolic acid, and betulinic acid, with ursolic acid in particular garnering attention for its anti-inflammatory activity.<sup>8,10</sup>

Flavonoids are a major group of compounds found in cranberries, classified into subgroups including anthocyanins, flavonols, and proanthocyanidins (also known as flavan-3-ols when referring to their monomeric forms).<sup>4,8</sup> Anthocyanins, the pigments responsible for cranberries' vivid red coloration, are found in much higher concentrations in the skin than in the pulp. Their levels increase markedly as the berries ripen. Major anthocyanins include cyanidin-3-galactoside, cyanidin-3-glucoside, cyanidin-3-arabinoside, peonidin-3-galactoside, and peonidin-3-arabinoside.<sup>2,11</sup> Flavonols, primarily quercetin and myricetin derivatives, are present throughout ripening and show a modest increase as the fruit matures. These include compounds such as quercetin-3-*O*-galactoside and myricetin-3-*O*-galactoside, which contribute to the fruit's antioxidant capacity.<sup>9,10</sup> Among the most studied cranberry flavo-

noids are flavan-3-ols and their polymeric forms, proanthocyanidins (PACs). These compounds play critical roles in plant defence and are widely recognized for their antimicrobial, antioxidant, and anti-inflammatory properties.<sup>9</sup> Catechin and epicatechin are the principal flavan-3-ols identified in cranberries, with epicatechin being a dominant constituent of PACs. The concentration of these compounds tends to peak in early ripening stages and diminishes as the fruit overripens. Notably, American cranberries generally contain higher levels of A-type PACs compared to European varieties.<sup>2,7,8</sup> It is known that A-type PACs and oligosaccharides could act in a synergistic way to enhance their beneficial properties.<sup>5</sup>

### Cranberry health benefits

This rich source of bioactive compounds has been investigated in studies as a potential supplementation for different urological and even non-urological applications. Overall, cranberries have also been shown health benefits as following: inhibit progression of degenerative unhealthy conditions and loss of functionality as neural degeneration; promotion of cardiovascular health; promotion of gastrointestinal health; oral benefits linked also to antiviral potentials; prevention and inhibition of cancer; modulation of inflammatory responses, antioxidant properties.<sup>2,12</sup> A diagram showed a summary of potential cranberry benefits (Fig. 1).

The presence of antioxidants like flavonoids, anthocyanins, and tannins, as well as vitamins C, E, and K has raised interest for their activity in scavenging free radicals and neutralizing reactive oxygen species, helping to protect cells from oxidative damage.<sup>13</sup> On the contrary, (poly)phenol antioxidant action derives more from an indirect modulation of cellular signaling pathways related to antioxidant defence.<sup>14</sup> Their anti-inflammatory properties are also well documented and largely attributed to (poly)phenols and triterpenoids such as ursolic acid, which can modulate inflammatory pathways by downregulating pro-inflammatory cytokines like TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, while promoting anti-inflammatory mediators.<sup>15</sup>

Cranberries may further exert cardioprotective effects by improving lipid profiles,<sup>16</sup> and lowering both systolic and diastolic blood pressure, possibly through nitric oxide-mediated vasodilation.<sup>17</sup> Their positive effect on glycemia modulation potential has been demonstrated through improvements in insulin sensitivity, as well as other positive effects on metabolism in diet-induced obesity in mice.<sup>18–20</sup>

In the gastrointestinal tract, cranberry (poly)phenols modulate the gut microbiota by promoting growth of beneficial species like *Lactobacillus* and *Bifidobacterium*, suppressing harmful bacteria and exerting prebiotic and anti-inflammatory effects.<sup>21,22</sup>

Additionally, cranberry-derived phytochemicals, particularly proanthocyanidins (PACs) and flavonoids, have shown *in vitro* anticancer activity through inhibition of tumor cell proliferation, invasion, and metastasis, and by inducing apoptosis in various cancer cell lines.<sup>23,24</sup>

Neuroprotective properties have also been observed, with evidence suggesting cranberry intake may protect against neurodegenerative processes seen in disease models.<sup>25,26</sup>



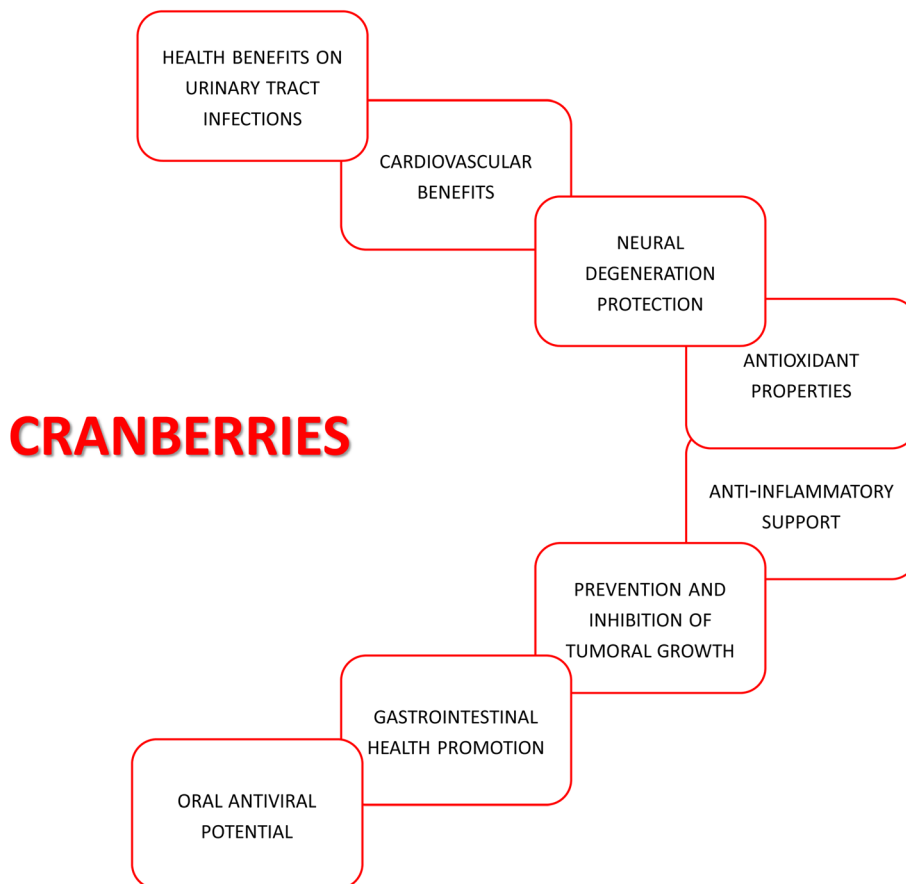


Fig. 1 Cranberry health benefits.

Collectively, these diverse bioactivities underscore the broad potential of cranberries in supporting human health against chronic disease.

#### Focus on urinary tract: mechanism of action

Among the various applications of cranberry, its most well-known and extensively studied role is in the management of urinary tract infections (UTIs). This activity is attributed to several complementary mechanisms involving different aforementioned bioactive compounds.

A-type proanthocyanidins (PACs) are unique polyphenols containing double linkages (A-type) that inhibit the adhesion of P-fimbriated *Escherichia coli* (*E. coli*) to urinary tract cells, helping to prevent urinary tract infections. These potent compounds also exhibit antioxidative, anti-inflammatory, and potential anti-cancer activities.<sup>27</sup> By preventing bacterial adhesion, cranberries interfere with the critical first step of infection development and progression.<sup>28,29</sup> A previous clinical study in healthy volunteers showed that administration of PAC-standardized cranberry powder (72 mg of PAC per day) may offer some protection against bacterial adhesion and virulence in the urinary tract.<sup>30</sup> These data were confirmed in a study where the phenyl- $\gamma$ -valerolactone cranberry metabolites and their conjugated forms (sulphated) were able to inhibit the adherence of uropathogenic *Escherichia coli* in bladder T24 epithelial cells.<sup>31</sup>

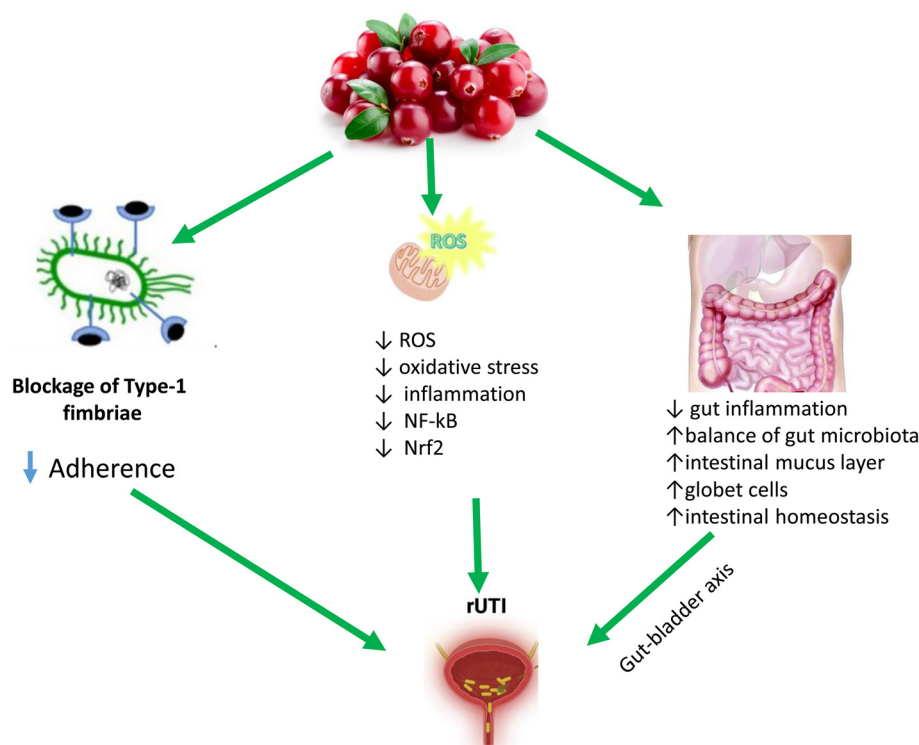
Second, in addition to preventing adhesion, cranberry compounds also demonstrate anti-biofilm properties. Flavonols and (poly)phenols have been shown to contribute to biofilm inhibition, with some showing synergistic effects with A-Type PACs.<sup>32</sup> (Poly)phenol-rich cranberry extracts have been shown to reduce the formation and stability of polymicrobial biofilms by decreasing biomass, acidogenicity, and the ratio of exopolysaccharide to microbial biovolume, as well as colony-forming unit counts. These effects target bacterial adhesion and biofilm development in its early stages.<sup>5,33,34</sup>

Third, cranberries possess broader antimicrobial activity, including bacteriostatic and bactericidal effects against various human pathogens.<sup>35–38</sup> This is partly reinforced by the presence of organic acids in cranberry juice, such as quinic, malic, shikimic, and citric acid, which may act synergistically. Some studies have suggested that combinations of these acids improve antibacterial efficacy.<sup>5,39</sup>

Furthermore, cranberry urinary metabolites [5-(3',4'-dihydroxyphenyl)- $\gamma$ -valerolactone and 4-hydroxybenzoic acid (4-HBA)] showed inhibitory activity of *Candida albicans* biofilm early-phase formation, possibly preventing genitourinary *Candida* infections.<sup>33,40</sup>

Lastly, cranberries may also impact microbial communities beyond the urinary tract. Intake of cranberry juice has been associated with a reduction in *Proteobacteria*, including *E. coli*,





**Fig. 2** Effects of cranberry extracts on recurrent urinary tract infections (rUTI). It is well known that cranberry contributes to UTIs prevention. Additionally, it shows anti-inflammatory, antioxidant, antiadhesive, and prebiotic effects of its phytochemicals. Cranberry may act in an impaired Nrf2/NF- $\kappa$ B system, mitochondrial dysfunction, and gut microbiota imbalance, alleviating oxidative stress and inflammation present in individuals suffering from rUTI. NF- $\kappa$ B: nuclear factor-kappa B, Nrf2: nuclear factor erythroid 2-related factor 2; ROS: reactive oxygen species.

and an increase in beneficial *Firmicutes* within the urinary microbiome of children.<sup>41</sup> Similarly, cranberry juice has been observed to lower levels of pathogenic *Streptococcus* species and increase commensal bacteria in the vaginal microbiota, suggesting a broader modulatory role in maintaining urogenital health.<sup>42</sup>

As summarized in Fig. 2, it is well known that cranberry contributes to UTIs prevention. Additionally, due to the biological effects of its phytochemicals, cranberry may act on an impaired Nrf2/NF- $\kappa$ B system, mitochondrial dysfunctions, and gut microbiota imbalance, alleviating oxidative stress and inflammation present in individuals suffering from recurrent UTIs (rUTI).

## Clinical use

### EMA monography

Interestingly, the European Medicines Agency (EMA) has developed a monograph for *Vaccinii macrocarpi fructus* as a traditional herbal medicinal product.<sup>43</sup> It recognizes the traditional use of a preparation made from the expressed juice of fresh cranberry fruits, administered orally in liquid form. This herbal preparation is indicated for two uses: first, for the relief of symptoms of mild, recurrent lower urinary tract infections in women, such as dysuria and/or pollakiuria, after serious

conditions have been excluded by a medical doctor; and second, for the prevention of recurrent, uncomplicated lower urinary tract infections in women, again following the exclusion of serious underlying conditions by a physician. Importantly, in both cases, the product is classified as a traditional herbal medicinal product, and its use is supported exclusively by long-standing tradition, without the requirement for pharmacokinetic or pharmacodynamic, in accordance with Directive 2001/83/EC (*Directive – 2001/83 – EN – EUR-Lex*). According to the monograph, the recommended dosage for adult and elderly women is 50–60 mL of expressed juice, taken two to four times daily for symptomatic relief, and 30 mL once daily for prophylaxis.

Use in children and adolescents is not recommended. Contraindications include hypersensitivity to cranberry and use in patients with kidney disorders who have experienced recurrent urinary tract infections, as these individuals require medical supervision. Concomitant use with warfarin or tacrolimus is also contraindicated;<sup>43</sup> in fact, cranberry juice has been reported to reduce serum levels of tacrolimus,<sup>44</sup> and to potentiate the effect of warfarin, increasing the risk of bleeding<sup>45,46</sup> although this last interaction has been discussed.<sup>47</sup>

The use of cranberry preparations in men and in pregnant women is not actually recommended, as lower urinary tract symptoms in these populations require clinical evaluation. Furthermore, cranberry concentrate has a high oxalate



content, raising concerns about the potential risk of stone formation in patients with a history of urolithiasis. Although no severe toxicity has been reported, mild adverse effects such as gastrointestinal discomfort, nausea, diarrhea, and dyspepsia, as well as hypersensitivity reactions like urticaria and rash, may occur.<sup>43</sup>

### Clinical evidence from meta-analysis

**Non-urological outcomes.** Main systematic reviews of cranberry use for non-urinary purposes are summarized in Table 1, Panel A. These reviews assessed outcomes related to cardiovascular and metabolic risk factors (e.g., lipid profiles, glycaemic markers, blood pressure, inflammatory status) as well as the efficacy of cranberry in *Helicobacter pylori* eradication. They focused on RCTs involving adult populations and various cranberry formulations (juice, capsules, extracts, etc.).

Regarding *H. pylori*, some reviews reported a trend toward improved eradication rates with cranberry supplementation, although statistical significance was not consistently reached. Overall, these findings suggest that standard cranberry formulations/products may provide limited but potentially clinically relevant effects in specific subgroups or outcomes. This warrants further investigation using standardized formulations and adequately powered trials.

While some systematic reviews reported modest benefits for certain outcomes, such as reductions in HOMA-IR, fasting blood glucose, or systolic blood pressure, results are not always consistent across different reviews. For some endpoints (e.g., LDL-C, TG), statistically significant positive effects have never been observed.

Overall, cranberries show: inhibited progression of degenerative unhealthy conditions and loss of functionality as neural degeneration; promotion of cardiovascular health; promotion of gastrointestinal health; oral benefits linked also to antiviral potentials; prevention and inhibition of cancer; modulation of inflammatory responses, antioxidant properties.<sup>2,12,24</sup> However, further well-designed clinical studies are needed to clearly define the non-urological effects of cranberry.

**Urological outcomes.** As expected, most systematic reviews have examined the efficacy of cranberry products in preventing and managing UTIs across a broad range of populations. The strength of evidence varies depending on patient characteristics, formulation (juice vs. capsule), PACs content, and comparator. Summaries of the main reviews are reported in Table 1, Panel B.

Overall, the reviews consistently show a benefit across different populations, though the magnitude and certainty of effect vary. In adults with prior UTIs or predisposing risk factors, meta-analyses report significant risk reductions of UTI's rate with cranberry.<sup>48,49</sup> Paediatric populations also appear to benefit: two reviews<sup>50,51</sup> found cranberry to be as effective as antibiotics or superior to placebo for preventing recurrent UTIs. Both pregnant women<sup>52</sup> and non-pregnant women<sup>53</sup> have been studied, with positive results.

Finally, reviews in other high-risk groups, such as catheter users, patients with spinal cord injury,<sup>54</sup> and including also those with neurogenic bladder,<sup>55</sup> suggest subgroup-specific efficacy.

Very useful and interesting are the Cochrane meta-analyses, updated on the assessments of the published clinical experiences. The evolution of the Cochrane meta-analyses on cranberry products for UTIs prevention is particularly illustrative, given its striking “up–down–up” trajectory (Fig. 3).

The first Cochrane review in 2000<sup>56</sup> included four RCTs assessing outcomes such as symptomatic and asymptomatic UTIs, side effects, and adherence. Data from three trials suggested some benefit for at least one outcome, but the review concluded that the small number and poor quality of trials provided no reliable evidence. High dropout rates indicated poor long-term acceptability of cranberry juice, though capsules might be more acceptable; cranberry juice could not be recommended for prevention. The 2001 update,<sup>57</sup> which added a fifth trial, reached the same conclusion.

In 2004,<sup>58</sup> the review included seven trials, with two good-quality RCTs showing a significant reduction in UTI incidence at 12 months with cranberry products in women (RR 0.61, 95% CI 0.40–0.91). The authors concluded there was some evidence that cranberry juice may reduce symptomatic UTIs over 12 months in women, though its effect in children, older adults, and men was unclear; dropout rates again raised concerns about long-term use. By 2008,<sup>59</sup> 10 studies ( $n = 1049$ ) were included, showing that cranberry products reduced UTI incidence at 12 months (RR 0.65, 95% CI 0.46–0.90) compared with placebo/control, with greater benefit in women with recurrent UTIs than in elderly adults or catheter users. Evidence for other groups remained uncertain, and dropout rates persisted.

The 2012 update changed this perspective.<sup>60</sup> This version expanded to 24 studies ( $n = 4473$ ) and found no significant reduction in symptomatic UTIs overall (RR 0.86, 95% CI 0.71–1.04) or in any subgroup, including women with recurrent UTIs, older adults, pregnant women, children, cancer patients, or people with neuropathic bladder/spinal injury. The addition of 14 new studies suggested cranberry juice was less effective than previously thought and given high dropout rates, mainly due to poor acceptability over long periods, and the small observed benefit, the authors concluded it could not be recommended.

By contrast, the 2023 update,<sup>61</sup> which is the last available version, included 50 studies ( $n = 8857$ ) and found moderate-certainty evidence that cranberry products reduced UTI risk overall (6211 participants: RR 0.70, 95% CI 0.58–0.84;  $I^2 = 69\%$ ). Subgroup analyses suggested benefit in women with recurrent UTIs (8 studies,  $n = 1555$ : RR 0.74, 95% CI 0.55–0.99;  $I^2 = 54\%$ ), children (5 studies,  $n = 504$ : RR 0.46, 95% CI 0.32–0.68;  $I^2 = 21\%$ ), and people susceptible due to an intervention (6 studies,  $n = 1434$ : RR 0.47, 95% CI 0.37–0.61;  $I^2 = 0\%$ ), but no benefit in elderly populations, those with bladder emptying problems, or pregnant women. The authors concluded cranberry products probably reduce the risk of sympto-





Table 1 Main systematic reviews on cranberry supplementation. Panel A: non-urinary topic; Panel B: urinary topic

Author	Title	Inclusion criteria	Exclusion criteria	N studies included	N participants	Population	Intervention	Comparator	Outcome	Setting	Findings
<b>Panel A</b> X. Li <i>et al.</i> , (2024) <sup>82</sup>	The effects of cranberry consumption on glycaemic and lipid profiles in humans: a systematic review and meta-analysis of randomized controlled trials	- RCTs (parallel or cross-over) - Participants >18 years - Cranberry supplementation used - Reported blood lipid/glucose indicators (TC, TG, HDL-C, LDL-C, FBG, insulin, HbA1c, HOMA-IR)	- <i>In vitro</i> , animal, non-interventional or non-RCTs - Duplicates - Incomplete data on lipids or glucose - Cranberry combined with other antioxidants (e.g., omega-3, L-citrulline) - Intervention <2 weeks	16	708	Adults	Cranberry supplements	Placebo or none	Blood lipid and glucose-related indicators	RCTs	- Significant reduction in TC/HDL-C ratio (4 studies, mean difference MD = -0.24; 95% CI: -0.45, -0.04; peffect = 0.02) - and HOMA-IR (5 studies, MD = -0.59; 95% CI: -1.05, -0.14; peffect = 0.01) - No effect on TG, HDL-C, LDL-C, TG, FBG, HbA1c, or fasting insulin overall - Subgroup analysis: dried form (capsules, powder, tablets) reduced fasting insulin (3 studies, 165 sixty-five participants, MD = -2.16; 95% CI: -4.24, -0.07; <i>p</i> effect = 0.04)
Delpino <i>et al.</i> , (2024) <sup>83</sup>	The effects of blueberry and cranberry supplementation on blood pressure in patients with cardiovascular diseases: a systematic review and meta-analysis of randomized clinical trials	- Original RCTs (cross-over or parallel) - Intervention ≥1 week - Participants ≥18 years - Used blueberry or cranberry (any form) - Reported SBP and DBP at baseline and endpoint - Participants had cardiometabolic diseases - Published in English, Portuguese, or Spanish	- Healthy individuals - <i>In vitro</i> or animal studies - No baseline or endpoint data - Non-controlled trials - Cranberry combined with other interventions without control comparison - Unpublished data, abstracts, patents, theses	17 (8 with cranberry)	835 (cranberry 373)	Adults with cardiometabolic disease	Cranberry or blueberry (any form)	Placebo or any intervention	SBP, DBP	RCTs	- No significant effect on SBP (MD = -0.81 mmHg, 95%CI -2.26-0.63) or DBP (MD = -0.15 mmHg, 95%CI -1.36-1.05) therefore blueberry/cranberry supplementation had neutral effect on BP in cardiometabolic disease patients - No significant results for cranberry alone after stratification (SBP/DBP MD = -1.39 mmHg)

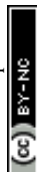


Table 1 (Contd.)

Author	Title	Inclusion criteria	Exclusion criteria	N studies included	N participants	Population	Intervention	Comparator	Outcome	Setting	Findings
Wang <i>et al.</i> , (2023) <sup>84</sup>	Effect of polyphenol compounds on <i>Helicobacter pylori</i> eradication: a systematic review with meta-analysis	- Published in English or Chinese - Adults with diagnosed <i>H. pylori</i> - Intervention: polyphenols (curcumin, cranberry, garlic, liquorice, broccoli) alone or with eradication therapy - Control: placebo or eradication therapy - Reported eradication rates and/or side effects - RCTs only	- Duplicate articles or same samples - Observational, narrative, basic research, meta-analyses, retrospective, case reports, conference presentations - Antibiotic/PPI/H2-antagonist use in prior 2 weeks - Polyphenols from non-cranberry sources (e.g., tea, coffee, wine)	12 (4 cranberry)	1251 (699 cranberry)	Adults with <i>H. pylori</i> infection	(Poly)phenol compounds alone or in addition to other treatments	Placebo/eradication therapy	<i>H. pylori</i> eradication rate	RCTs	- Polyphenol compounds significantly increased <i>H. pylori</i> eradication (RR = 1.19; 95% CI: 1.03–1.38; <i>p</i> = 0.02) - No significant difference in side effects between groups (RR = 1.47; 95% CI: 0.83–2.58, <i>p</i> = 0.18) - Cranberry subgroup eradication rate: 54.4% (vs. 45.4% in control); not statistically significant (RR = 1.24, 95% CI: 0.94–1.64, <i>p</i> = 0.13)
Delpino <i>et al.</i> , (2022) <sup>85</sup>	Effects of blueberry and cranberry on type 2 diabetes parameters in individuals with or without diabetes: a systematic review and meta-analysis of randomized clinical trials	- RCTs comparing blueberry or cranberry on T2DM parameters - Adult or older adult population (with or without diabetes) - Cranberry/blueberry used in any form - Control group included - Data reported before and after intervention	- Observational studies - Non-human studies - Non-RCTs - Grey literature	22 (9 cranberry)	993 (cranberry studies: 404)	Diabetic or non-diabetic adults and older adults	Blueberry or cranberry (capsule, juice, or other single-substance preparation)	Placebo usual care (non-pharmacological or pharmacological)	Fasting blood glucose, insulin resistance, glycated hemoglobin (HbA1c)	RCTs	- Cranberry/blueberry significantly reduced fasting blood glucose (MD = -17.72 mg dL <sup>-1</sup> , 95% CI: -29.62, -5.82) and HbA1c (MD = -0.32%, 95% CI: -0.57, -0.07), but not insulin resistance - Analyses stratified comparing blueberry vs. cranberry showed a small significant effect on insulin resistance (MD = -0.24, 95% CI -0.48, -0.01)



Table 1 (Contd.)

Author	Title	Inclusion criteria	Exclusion criteria	N studies included	N participants	Population	Intervention	Comparator	Outcome	Setting	Findings
Nikbazzm <i>et al.</i> , (2022) <sup>86</sup>	The effect of cranberry supplementation on <i>Helicobacter pylori</i> eradication in <i>H. pylori</i> positive subjects: a systematic review and meta-analysis of randomised controlled trials	- Parallel or crossover RCTs - <i>H. pylori</i> -positive by accepted diagnostic tests - Intervention: cranberry juice/extract/powder vs. placebo or control - Duration $\geq 1$ week - Outcome: <i>H. pylori</i> suppression/eradication - Adult participants (>18 years) - Multi-arm trials treated as separate studies	- Duplicate data - Cohort, cross-sectional, case-control, review, and ecological studies	4	1935	Adults with <i>H. pylori</i>	Cranberry	Placebo or non-placebo control	<i>H. pylori</i> eradication or suppression	RCTs	- Cranberry showed a non-significant increased odds of <i>H. pylori</i> eradication (OR = 1.27, 95% CI: 0.63–2.58) - Evidence inconclusive due to small number of studies and moderate heterogeneity
Pourmasumi <i>et al.</i> , (2020) <sup>17</sup>	The effects of cranberry on cardiovascular metabolic risk factors: a systematic review and meta-analysis	- Randomized clinical trials (RCTs) only - Cranberry used as a supplement - Adult participants ( $\geq 18$ years) - Reported CVD risk factors as outcomes	- Duplicate data - Cranberry combined with other supplements - Treatment duration <2 weeks - Postprandial studies - Unclear information and no author feedback	12	496	Adults	Cranberry supplements	Any	CVD metabolic risk factors (lipid profile, glycemic status, BP, BMI, inflammatory markers)	RCTs	- Cranberry significantly reduced systolic blood pressure (SBP) and body mass index (BMI) - No significant changes in triacylglycerol, total cholesterol, LDL, HDL, fasting glucose, insulin, HOMA-IR, DBP, waist circumference, CRP, or ICAM - Greater SBP reduction in studies with mean age $\geq 50$ - Subgroup analysis: increased HDL in <50 mean age group; increased triacylglycerol with juice form cranberry



Table 1 (Contd.)

Author	Title	Inclusion criteria	Exclusion criteria	<i>N</i> studies included	<i>N</i> participants	Population	Intervention	Comparator	Outcome	Setting	Findings
<b>Panel B</b> Han <i>et al.</i> , (2025) <sup>48</sup>	Nonantibiotic prophylaxis for urinary tract infections: a network meta-analysis of randomized controlled trials	- History or risk factors for UTIs - Investigated $\geq 1$ non-antibiotic UTI prevention intervention - Reported UTI incidence - RCT design - Antibiotics allowed as comparator	- Cohort, case-control, animal studies - Conference abstracts, editorials, letters - No usable outcomes - Sample size $< 10$ per group	50 (cranberry 18)	10 495 (cranberry 3262)	Individuals with a history of UTIs or UTI risk factors	Non-antibiotic intervention	Any other	Incidence of UTIs	RCTs	- Cranberry significantly reduced UTI incidence vs. placebo (RR = 0.72, 95%CI 0.60–0.87) - Triple therapy (cranberry + probiotics + vitamin A) most effective (RR = 0.27, 95%CI 0.09–0.87) - Cranberry vs. placebo: 16 studies, 2990 patients (87% female), RR = 0.80 (95%CI 0.69–0.92, $p = 0.002$ ) - Cranberry vs. antibiotics: 2 studies, 272 patients (100% female), RR = 1.38 (95%CI 0.82, 2.33, $p = 0.220$ )
Xiong <i>et al.</i> , (2024) <sup>57</sup>	Preventive effect of cranberries with high dose of proanthocyanidins on urinary tract infections: a meta-analysis and systematic review	- RCTs analysing cranberry and UTIs - Compared cranberry-containing products to placebo or non-placebo control - PAC content reported - Outcome: number of participants experiencing UTIs	- Animal studies, case studies, systematic reviews - Trials with incomplete evidence	10	2468	Any population	Cranberry with known PAC dose	Placebo or other treatment	- Number of UTI patients in treatment vs. control groups at study end	RCTs	- When daily intake of PACs $\geq 36$ mg/day: 18% UTI risk reduction (RR = 0.82, 95% CI = 0.69–0.98, $p = 0.03$ ) - No significant effect for PACs $< 36$ mg day <sup>-1</sup> - Subgroup analysis: significant UTI reduction with 12–24 weeks of cranberry use (RR = 0.75, 95% CI = 0.61–0.91, $p = 0.004$ ) - UTI risk reduction only in female-only subgroups (RR = 0.84, 95% CI = 0.71–0.98, $p = 0.02$ )



Table 1 (Contd.)

Author	Title	Inclusion criteria	Exclusion criteria	<i>N</i> studies included	<i>N</i> participants	Population	Intervention	Comparator	Outcome	Setting	Findings
Gkiortzis <i>et al.</i> , (2024) <sup>50</sup>	Prophylaxis options in children with a history of recurrent urinary tract infections: a systematic review	- RCTs only - Investigated antibiotics or dietary supplements as prophylaxis - Pediatric patients with recurrent UTI ( $\geq 2$ episodes)	- Non-English language studies - Included patients with congenital urogenital anomalies	23 (8 with cranberry)	3335 (871 randomised in a trial with cranberry)	Pediatric population	Antibiotics and dietary supplements as UTI prophylaxis	Other antibiotics or supplements	- Primary: incidence of symptomatic UTI in children with RUTI during prophylaxis - Secondary: febrile UTI episodes, kidney scarring, adverse events	RCTs	- Cranberry and nitrofurantoin reduced symptomatic UTI odds vs. control and antibiotics - Nitrofurantoin may be the best option for UTI incidence - Cranberry OR = 0.41 (95% CI: 0.23–0.74, $p < 0.01$ )
Moro <i>et al.</i> , (2024) <sup>59</sup>	Cranberry juice, cranberry tablets, or liquid therapies for urinary tract infection: a systematic review and network meta-analysis	- Individuals of any age/gender at risk of UTI - Compared at least two interventions, including cranberry (liquid/non-liquid), or other liquids, or no treatment	- Catheterised participants (unless data for non-catheterised participants reported separately)	20	3091	Individuals of any age and gender at risk for UTIs	Cranberry non-liquid (tablet, capsule, fruit) cranberry liquid (juice, cocktail, concentrate)	Placebo/no treatment/other cranberry formulation	- Primary: number of UTIs per group - Secondary: UTI symptoms (e.g., urgency, dysuria, frequency, pain), antimicrobial use	RCTs and non-randomised controlled clinical trials	18/20 studies highlighted cranberry juice reduced UTI rate by 54% vs. no treatment and 27% vs. placebo - Antibiotic use reduced by 49% vs. placebo and 59% vs. no treatment - Symptom prevalence reduced Subgroup analyses: - Cranberry tablet vs. comparator: RR = 5.22 (95% CI 1.26–21.55; 3 studies, 85 patients) - Cranberry juice vs. placebo: RR = 0.74 (95% CI 0.74–0.91, $p = 0.004$ ; 14 RCTs, 2400 participants) - Cranberry juice vs. no treatment: RR = 0.31 (95% CI 0.18–0.54, $p < 0.000$ ; 13 RCTs + 1 CCT, 234 participants)



Table 1 (Contd.)

Author	Title	Inclusion criteria	Exclusion criteria	N studies included	N participants	Population	Intervention	Comparator	Outcome	Setting	Findings
Bolgarina <i>et al.</i> , (2023) <sup>52</sup>	Cranberry supplements for urinary tract infection prophylaxis in pregnant women: a systematic review of clinical trials and observational studies on efficacy, acceptability, outcomes measurement methods, and studies' feasibility	- English-language primary studies - Pregnant women receiving cranberry supplements - Included data on efficacy, acceptability, outcome measurement methods, and feasibility - Human studies only	Non-primary studies	3	1156	Pregnant women	Cranberry supplements	Any comparator	- UTI prevention efficacy - Tolerance: side effects, pregnancy/neonatal safety, compliance - Feasibility: recruitment and retention rates - Methodology: study design and data collection	RCTs and observational	- UTI reduction trend noted - Cranberry juice caused GI intolerance in 23% (44/188) - Capsules reduced side effects (2%, 1/49) - Recruitment and retention issues: 33% and 59% dropout respectively
Xia <i>et al.</i> , (2021) <sup>55</sup>	Consumption of cranberry as adjuvant therapy for urinary tract infections in susceptible populations: a systematic review and meta-analysis with trial sequential analysis	- RCTs only - Compared cranberry products to placebo or control - Reported outcomes as number of UTI cases - Populations included: recurrent UTIs, elderly, pregnant women, children, catheterized, neuropathic bladder	- Cranberry combined with other bioactive compounds - Did not meet inclusion criteria - Animal studies, case reports, reviews, conference papers, editorials - Insufficient data	23	3979	Various susceptible populations	Cranberry-containing products	Placebo or non-placebo control	- Number of participants experiencing a UTI	RCTs	- Cranberry significantly reduced UTI incidence in susceptible populations (RR = 0.70; 95% CI: 0.59–0.83) - Relative risk reduction: 32% in women with recurrent UTIs (RR = 0.68; 95% CI: 0.56–0.81), 45% in children (RR = 0.55; 95% CI: 0.31–0.97), 51% in catheter users (RR = 0.49; 95% CI: 0.33–0.73) - Juice form had greater effect than capsules/tablets (RR = 0.65; 95% CI: 0.54–0.77)



Table 1 (Contd.)

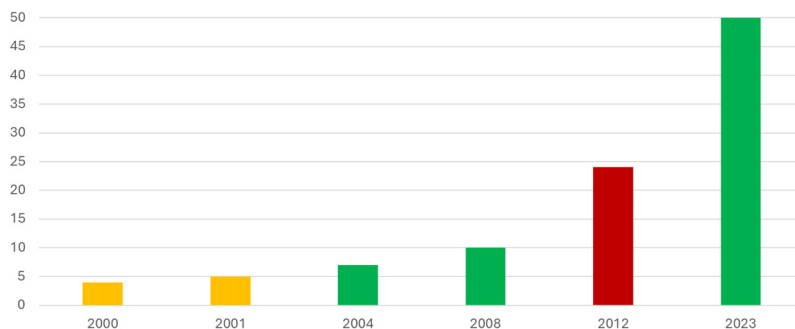
Author	Title	Inclusion criteria	Exclusion criteria	<i>N</i> studies included	<i>N</i> participants	Population	Intervention	Comparator	Outcome	Setting	Findings
Meena <i>et al.</i> , (2021) <sup>51</sup>	Non-antibiotic interventions for urinary tract infections in children: a systematic review and meta-analysis of randomized controlled trials	- Children <18 years - Non-antibiotic interventions for UTI prophylaxis - Reported outcome: UTI recurrence	- Included adults or kidney transplant patients - Did not report UTI recurrence as outcome	16 (9 cranberry)	1426 (769 cranberry studies)	Children (<18 years)	Any non-antibiotic interventions	Placebo or antibiotics	Recurrence of UTI	RCTs	- Cranberry was as effective as antibiotics prophylaxis (RR = 0.92; 95% CI: 0.56–1.50) but better than placebo/no therapy (RR = 0.48, 95% CI: 0.28–0.80) in reducing UTI recurrence - In children with normal urinary tracts, cranberry significantly reduced UTI recurrence over 6–12 months when compared to placebo/no therapy (5 trials, 466 participants, RR: 0.48; 95% CI: 0.28–0.80)
Gbinigie <i>et al.</i> , (2020) <sup>38</sup>	Cranberry extract for symptoms of acute, uncomplicated urinary tract infection: a systematic review	- RCTs (blinded/ open-label) comparing cranberry extract vs. any treatment for acute uncomplicated UTIs - Adults (≥18 years) - Cranberry used orally (juice, fruit, capsule, etc.) - If combined with other interventions, cranberry effect needed to be isolatable	- Exclusively complicated UTI (e.g., catheterised, spinal cord injury, renal tract abnormalities, male UTIs, pyelonephritis) - Animal studies, case reports, systematic reviews	3	688	Adults	Cranberry supplements	Any treatment or placebo	Participant symptoms, clinical cure, microbiological/biochemical outcomes, and wellbeing	RCTs	- One RCT ( <i>n</i> = 309) found no effect of cranberry juice on UTI symptoms or antibiotic use vs. water (MD: -0.01, 95% CI: -0.37 to 0.34) - One RCT ( <i>n</i> = 319) found no added benefit from cranberry juice with immediate antibiotics for acute UTI - One RCT ( <i>n</i> = 60) showed within-group symptom and <i>E. coli</i> load improvement with cranberry extract, not seen in controls



Table 1 (Contd.)

Author	Title	Inclusion criteria	Exclusion criteria	<i>N</i> studies included	<i>N</i> participants	Population	Intervention	Comparator	Outcome	Setting	Findings
Raguzzini <i>et al.</i> , (2020) <sup>54</sup>	Cranberry for bacteriuria in individuals with spinal cord injury: a systematic review and meta-analysis	- Reported at least one primary or secondary outcome (symptoms, antibiotic use, clinical cure, microbiological/biochemical outcomes, harms) - Peer-reviewed studies - Published in English - Focused on cranberry's effect on bacteriuria or UTI vs. control - Included regardless of cranberry bioactive source/dose or study design	- Subjects with spina bifida or myelomeningocele	6	477	Patients with spinal cord injury	Cranberry supplements	Placebo or no treatment	Bacteriuria or UTI prevention	Observational and interventional studies	- No significant difference in bacteriuria prevention (RR = 0.85; 95% CI: 0.60–1.21) - Low study quality; unable to recommend or exclude cranberry for individuals with spinal cord injury
Fu <i>et al.</i> , (2017) <sup>53</sup>	Cranberry reduces the risk of urinary tract infection recurrence in otherwise healthy women: a systematic review and meta-analysis	- RCTs in healthy, nonpregnant women ( $\geq 18$ years) with UTI history - Compared cranberry to placebo or no treatment - Reported outcome: number of UTI cases	- Not peer-reviewed full-text articles - Special populations (elderly, children, pregnant women) - Institutionalized subjects - Complicated UTIs ( <i>e.g.</i> , renal impairment, MS, dementia, spinal injury, abnormal urinary tract, neuropathic bladder, catheter, stones)	7	1498	Generally healthy nonpregnant women $\geq 18$ years with history of UTI	Cranberry supplements	Placebo or control	- Number of participants experiencing a UTI	RCTs	- Cranberry reduced UTI risk by 26% (RR = 0.74; 95% CI: 0.55–0.98) - Risk of bias in 2 studies due to high attrition or selective reporting - Only 2 studies had >300 participants - Cranberry may help prevent UTI recurrence in healthy women; larger trials needed

BP: blood pressure; CI: confidence interval; CVD: cardiovascular disease; DBP: diastolic blood pressure; FBG: fasting blood glucose; HbA1c: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; HOMA-I: homeostatic model assessment of insulin resistance; LDL-C: low-density lipoprotein cholesterol; MD: mean difference; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; CI: confidence interval; MD: mean difference; PAC: proanthocyanidin; RCT: randomized controlled trial; RR: relative risk; UTI: urinary tract infection.



**Fig. 3** Evolution of Cochrane meta-analyses conclusions on cranberry products for UTI prevention. Y-Axis: number of included studies per review. Colours: yellow – no reliable evidence; red – no significant effect; green – probable effect.

matic, cell culture-verified UTIs in specific groups. Cochrane has also addressed cranberries for UTIs. The 2000 review<sup>62</sup> found no RCTs or quasi-RCTs meeting inclusion criteria, and the 2023 update<sup>63</sup> reached the same conclusion, highlighting the persistent lack of high-quality, double-blind, placebo-controlled trials assessing cranberry products for this indication.

In summary, Cochrane's stance on cranberries for UTI prevention has evolved from no reliable evidence (2000–2001), to some benefit in women with recurrent UTIs (2004–2008), to no significant effect (2012), and back to probable benefit in select groups (2023), while for acute UTIs, robust RCT evidence remains entirely absent. These findings are in line with European Association of Urology 2025 Guidelines on Urological Infections, which report that a highly standardised cranberry extract formulated with phospholipids and high-dose proanthocyanidins appears effective in preventing cystitis recurrence episodes.<sup>64</sup>

## Cranberry formulations

Several delivery systems are nowadays available. The most studied in literature were developed by the need to improve the bioavailability of active compounds related to cranberry activities. The most common are represented by: microencapsulation using Whey Protein Isolate (WPI) developed to improve bioavailability, liposomal/bile salt formulations where cranberry extract loaded into bile salt activated liposomes (BSALs) shows a sustained release pattern (61%–93% release); chitosan-based gels or carboxymethylcellulose formulations for a sustained and slower release of anthocyanins; phospholipids formulations.<sup>65–69</sup> Cranberry extract was also microencapsulated in poly(lactide-*co*-glycolide) PLGA, to generate formulations able to inhibit salivary biofilm.<sup>70</sup> More research has been performed on cranberry phospholipids (Anthocran™ Phytosome™) which is a rational formulation of cranberry extract based on lecithin using Phytosome™ technology, an innovative food-grade delivery system, which optimizes the solubility, the absorption and biological properties of nutraceuticals, such as cranberry extracts, by creating a solid dispersion of the botanical ingredient within a sunflower lecithin

(phospholipid)-based matrix. This technology has been used for various bioactive molecules and botanical extracts, including quercetin, *Berberis aristata* extract, Coenzyme Q10, Palmitoylethanolamide (PEA), bergamot, *Melissa officinalis*, green tea from *Camelia sinensis*, *Boswellia serrata* extract and curcuminoids from *Curcuma longa* L.<sup>71–78</sup>

Natural compounds, and botanical extracts in general, often have low solubility, poor stability, and complex chemical structures that limit their diffusion through intestinal membranes. Formulation with the phospholipids solid dispersion was reported to prevent self-aggregation of phytochemicals during gastrointestinal transit, to promote dispersion and absorption in the small intestine, to optimize their tolerability and interaction with biological membranes and the intestinal microbiota.

This could pose an interesting rationale, as a better absorption could lead to similar results by administering a lower dosage, with consequent minimization of potential off-target adverse events.

Regarding specifically cranberry formulated in phospholipids, the rationale of the formulation was mostly linked to the target organ, thanks to the delivery of most of the active metabolites in urine after cranberry intake. Cranberry phospholipids contained the full bouquet of (poly)phenols presented in natural cranberry juice, thanks to a rigorous supply chain from fruits harvest to manufacturing of the final health food ingredient.<sup>33</sup> From PACs to anthocyanins and organic acids, cranberry in phospholipids mimics the composition of natural cranberry juice that was the original ingredient consumed in the traditional medicine of Native American for urinary health and later investigated by modern science and ethnopharmacology. This cranberry formulation is standardized to contain 6–9% of PACs as measured by spectrophotometry using the DMAC method. Its pharmacokinetic profile was studied in urines rather than human plasma, as urines are the target for *Vaccinium macrocarpon* ingredient benefits for urinary health (Baron *et al.*, 2020<sup>33</sup>). This in-depth investigation provided new insights into the absorption, metabolism, and excretion of cranberry compounds when formulated with phospholipids compared to the standard cranberry extract. In-depth, that investigation allowed detection of up to 42 com-



pounds in human urines after supplementation with cranberry formulated with phospholipids, confirming that PACs are almost absent in the urine after cranberry intake; on the other hand, PACs metabolites were detected and identified.<sup>33</sup> The study tested urine samples from individuals who consumed standardized cranberry extract formulated with phospholipids and compared them to those who took unformulated cranberry extract, focusing on antimicrobial activity against *Candida albicans*, which is key in determining infection outcomes. The analysis revealed that urine fractions richer in proanthocyanidins metabolites, derived from consumption of cranberry formulated with phospholipids, were the most effective in inhibiting *Candida albicans* adhesion and biofilm formation, attributing the health benefits to PACs metabolites rather than the parent PACs. This research contradicted the belief that PACs themselves are the main active compounds for health benefits, showing instead that intestinal microbiota converts PACs into beneficial and active metabolites with significant antimicrobial activity. Remarkably, the study showed that cranberry phospholipids, containing ~9 mg of PACs in a 120 mg dose, demonstrated bioequivalence to 120 mg of

unformulated cranberry extract (~36 mg PACs) in terms of inhibiting *Candida albicans* adhesion. This highlights the equivalence efficacy of cranberry phospholipids formulation to cranberry extracts at 36% PACs, as it achieves the same effect with a significantly lower PACs content, thus proving its optimized bioavailability and effectiveness with high antimicrobial activity, firstly described in human urines. Moreover, cranberry formulated with phospholipids has been reported to allow to reach active concentrations of phenyl- $\gamma$ -valerolactone in urine, the active PACs metabolites, with a lower variability in absorption and an improved organ target accessibility, when compared to unformulated cranberry extract.<sup>33</sup> Furthermore, the concentrations of phenyl- $\gamma$ -valerolactones in urine permitted the inhibition of the adhesion and the biofilm formation of *Candida albicans* and are in line with inhibitory concentrations of *Escherichia coli*.<sup>31,33</sup> Human studies have demonstrated that cranberry formulated with phospholipids is effective in alleviating symptoms associated with urinary tract infections (UTIs), such as urinary frequency, urgency, dysuria, nocturia, ache, and haematuria, and it has been shown to reduce the recurrence of UTIs at dosages starting from 120 mg per day.<sup>79</sup>

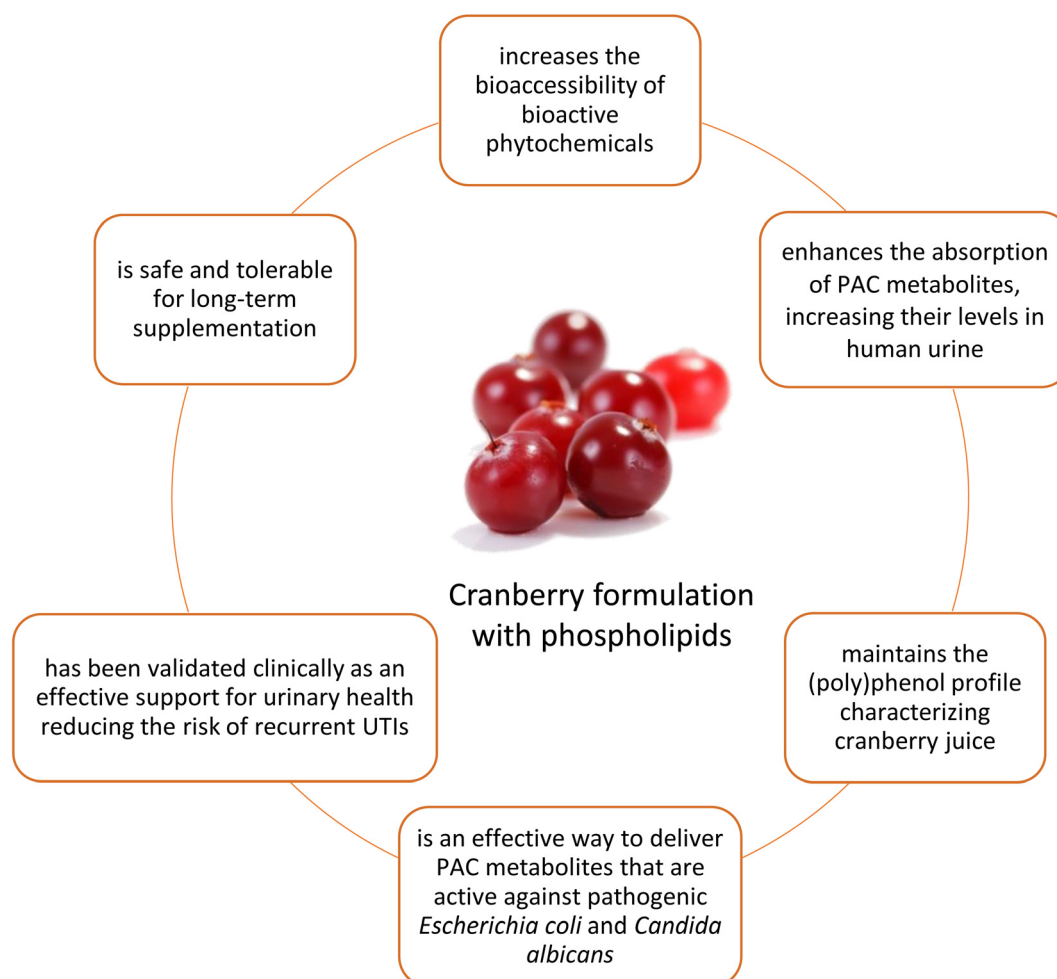


Fig. 4 Main features of cranberry formulated with phospholipids.



A randomized, double-blind, placebo-controlled study in postmenopausal women taking SGLT2 inhibitors (antidiabetic drugs linked to increased UTI risk) further confirms the efficacy of cranberry formulated with phospholipids in reducing UTI recurrence, positioning it as a beneficial supplement for those at high risk for UTIs<sup>80</sup> and included this as a valuable botanical support in the European Association of Urology guidelines on urological infections<sup>64</sup> (2025). Furthermore, cranberry formulated with phospholipids has been extensively studied and proven to be safe for long-term use, without any serious side effects reported.<sup>33,79,80</sup> This formulation also respects the natural balance of the intestinal microbiota, as demonstrated in *ex vivo* studies. It maintains the physiological transformation of (poly)phenols during microbial metabolism, supporting the production of biologically active colonic metabolites like phenyl- $\gamma$ -valerolactones.<sup>81</sup> Hence, cranberry formulated with phospholipids stands out for its dual advantage of supporting urinary health and maintaining intestinal health without disrupting the natural balance of gut microbiota. Taking into account all the above evidence, the main features of cranberry formulated with phospholipids are summarized in Fig. 4.

## Conclusion

Urologists are increasingly recommending cranberry products like juice or supplements for the prevention of recurrent urinary tract infections (UTIs), particularly in women. Cranberry is a rich source of bioactive compounds that exert anti-adhesion, anti-biofilm, and antimicrobial effects against uropathogenic *E. coli*, supporting its traditional and evidence-based role in preventing UTIs. meta-Analyses indicate consistent, although variable, efficacy across diverse populations, including women, children, and high-risk groups, in preventing UTIs. Beyond urology, modest effects on glycaemic control, blood pressure, *Helicobacter pylori* eradication, neural protection, antiviral potentials, cancer prevention, have been reported, but evidence remains inconsistent and further studies are needed.

Cranberry is generally well tolerated, with gastrointestinal discomfort the most common adverse event, though caution is warranted in patients on warfarin, tacrolimus, or with a history of oxalate stones. Cranberry extracts have shown to be effective against recurrent urinary tract infections and in addition, their lecithin-based formulation with an ameliorated urinary absorption, may present potential advantages compared to traditional non-formulated extracts. Of note, cranberry formulated with phospholipids is one of the few standardized cranberry ingredients with a rigorous characterization.<sup>33,81</sup> Nonetheless, large, well-designed randomized controlled trials of cranberry preparations (including phospholipids-based formulation), are essential to clarify its full potential on health benefits.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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