

The Effect of Cranberry (*Vaccinium macrocarpon*) Fruit Extract on VEGF Levels in Wistar Rats (*Rattus norvegicus*) with Cystitis Model

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ABSTRACT

Cystitis, often caused by Escherichia coli, triggers inflammation and tissue damage in the bladder. While the anti-adhesion properties of cranberry (Vaccinium macrocarpon) against uropathogenic bacteria are well known, its role in the subsequent healing phase, particularly through modulation of Vascular Endothelial Growth Factor (VEGF), remains poorly understood. This study aims to investigate the effect of cranberry fruit extract on VEGF levels and the degree of histopathological inflammation in a cystitis model. Fosfomycin trometamol is an effective antibiotic for treating urinary tract infections, particularly bacterial cystitis. However, the observed increase in Vascular Endothelial Growth Factor (VEGF) levels during treatment is not a direct effect of the drug but rather a biological response associated with the body's natural healing process. In cystitis, inflammation and tissue damage in the bladder wall trigger the release of various cytokines and chemokines, including VEGF, which plays a key role in angiogenesis and tissue regeneration. Fosfomycin works by reducing bacterial load and inflammation, thereby allowing the body to enter the active healing phase. During this phase, increased VEGF levels reflect ongoing tissue repair and new blood vessel formation. Therefore, the elevation of VEGF should be interpreted not as a side effect of fosfomycin but as a biological marker of bladder tissue recovery following successful infection clearance.

Keywords: Fosfomycin trometamol, VEGF, cystitis, angiogenesis, tissue healing.

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INTRODUCTION

Cystitis is a lower urinary tract infection, specifically affecting the bladder, and can be classified into uncomplicated and complicated infections (Wagenlehner et al., 2020). Uncomplicated cystitis occurs in healthy, non-pregnant men or women, while complicated cystitis involves risk factors that increase the likelihood of infection or antibiotic therapy failure (Li & Leslie, 2023). Acute cystitis is usually caused by a bacterial infection of the bladder, with women being more susceptible due to the proximity of the rectum to the urethral meatus and the shorter urethral length (Gyftopoulos et al., 2019). *Escherichia coli* is the primary cause of uncomplicated urinary tract infections (UTIs) in women (approximately 75–95% of cases), followed by *Klebsiella* (Jalil & Al Atbee, 2022). Other common pathogens include members of the *Enterobacteriaceae* family such as *Proteus mirabilis*, while bacteria like Group B *Streptococcus*, *Lactobacillus*, and coagulase-negative *Staphylococcus* rarely cause UTIs and usually represent contamination from urine cultures of healthy individuals (Li & Leslie, 2023).

Urinary tract infection (UTI) is the most common bacterial infection in women, with about 40% to 60% of women experiencing it at some point in their lives—half of them by age

32 (Czajkowski et al., 2021). This leads to eight million emergency department visits, 100,000 hospitalizations, and healthcare costs amounting to \$3 (Moore & Liang, 2021).5 billion annually in the United States. Additionally, 27% to 46% of women experience recurrent UTIs within a year after an acute infection. In men, the incidence is much lower, with similar symptoms, though recurrent or persistent cases may suggest prostatitis. Men possess additional protective factors such as a longer urethra and a urethral meatus located farther from the anus. Although UTIs in men are often considered complicated, some infections in men aged 15 to 30 years without specific risk factors can be treated as uncomplicated infections (Lala et al., 2023).

Cranberry, with over 200 years of history as a urinary antiseptic, has become one of the most widely used non-antibiotic approaches for UTIs (Wawrysiuk et al., 2019). When used as a prophylaxis for UTIs, cranberry compounds such as type A proanthocyanidins and other polyphenols can inhibit bacterial adhesion, including the P fimbriae of uropathogens (Tambunan & Rahardjo, 2019).

Cranberry fruit (Vaccinium macrocarpon) is a distinctive source of polyphenols such as flavonoids and phenolic acids, which possess high antioxidant properties and are known to have positive health effects (de Llano et al., 2020). Proanthocyanidins (PACs) with type A linkages or metabolites are considered the active ingredients in cranberry (Feldman et al., 2022). Several studies have suggested that cranberry extract could be a potential alternative to antibiotics for treating acute uncomplicated UTIs, particularly due to its ability to inhibit *E. coli* adhesion to the bladder urothelium (Güven et al., 2024).

Previous research has extensively documented the anti-adhesion and anti-inflammatory properties of cranberry. For instance, Study A (Gupta et al., 2017) demonstrated that cranberry products significantly inhibit the adherence of P-fimbriated *Escherichia coli* to primary cultured bladder and vaginal epithelial cells. Furthermore, Study B (Shi et al., 2022) highlighted the anti-inflammatory and antioxidant mechanisms of cranberry extract, showing its capacity to reduce pro-inflammatory cytokines and oxidative stress in urinary tract tissues. However, while the initial phases of infection control are well covered, the subsequent healing and tissue regeneration phase remains less explored (Mihai et al., 2019) .

Conversely, studies focusing on the role of Vascular Endothelial Growth Factor (VEGF) in *cystitis* have advanced our understanding of tissue repair (Abreu-Mendes et al., 2022). Study C (Abreu-Mendes et al., 2022) systematically reviewed the role of urinary VEGF in bladder pain syndrome/interstitial *cystitis* (BPS/IC), identifying VEGF as a key biomarker for angiogenesis and tissue regeneration in inflamed bladder tissue. Similarly, Study D (Li et al., 2023) investigated VEGF-mediated angiogenesis in bladder tissue regeneration, emphasizing its importance in restoring vascular integrity and epithelial structure post-inflammation (Tornese et al., 2024).

This creates a clear knowledge gap: while the anti-adhesive and anti-inflammatory effects of cranberry are established, its specific contribution to the tissue regeneration phase of *cystitis*, particularly through the modulation of VEGF and subsequent angiogenesis, remains understudied. No prior research has directly examined the effect of cranberry fruit extract on VEGF levels and the correlation with histopathological improvement in a *cystitis* model.

Specifically, previous studies have investigated the effectiveness of cranberry in treating UTIs; however, no studies have yet explored its efficacy in influencing VEGF levels, the degree of inflammation based on histopathological analysis, and bacterial colony counts in

Wistar rats. This study aims to evaluate the effects of cranberry fruit extract on VEGF levels and the degree of histopathological inflammation in Wistar strain rats with *cystitis* models.

This study proposes the following hypotheses:

H₀ (Null Hypothesis): Cranberry (*Vaccinium macrocarpon*) extract has no significant effect on VEGF levels and the degree of histopathological inflammation in Wistar rats (*Rattus norvegicus*) with urinary tract infection induced by *E. coli*.

H₁ (Alternative Hypothesis): Cranberry (*Vaccinium macrocarpon*) extract has a significant effect on VEGF levels and the degree of histopathological inflammation in Wistar rats (*Rattus norvegicus*) with urinary tract infection induced by *E. coli*.

METHOD

This study was true experimental research using a posttest-only control group design conducted on male Wistar rats. The rats were randomly divided into seven groups: negative control, positive control, and five treatment groups receiving cranberry extract at different doses (100–400 mg/kg BW). The research was carried out at the Cendikia Laboratory, Medan City, from May to June 2025. Ethical approval was granted by the Health Research Ethics Committee of Universitas Prima Indonesia (No. 128/KEPK/UNPRI/III/2025). The samples consisted of 35 male Wistar rats aged 8–10 weeks (180–220 g). They were acclimatized before treatment and maintained under standard laboratory conditions. Cranberry extract (*Vaccinium macrocarpon*) was used as the main test material. The independent variable was the dose of cranberry extract, while the dependent variables were VEGF levels and the degree of inflammation in bladder histopathology. The instruments included an ELISA reader, syringes, test tubes, microscope, and microtome. Materials used were cranberry extract, *E. coli*, Fosfomycin Trometamol, VEGF reagents, alcohol, xylol, paraffin, and ketamine. Rats were divided into seven groups: negative control, *E. coli* control, positive control (Fosfomycin Trometamol), and four treatment groups receiving different doses of cranberry extract. VEGF levels were measured using the ELISA method, while bladder tissue inflammation was examined microscopically after Hematoxylin–Eosin (HE) staining. Data were analyzed using one-way ANOVA at a 0.05 significance level, followed by Tukey's post-hoc test to identify significant differences between groups.

RESULTS AND DISCUSSION

In this study, tests were conducted on a cystitis rat model treated with cranberry extract. The study consisted of six groups, with each group containing five rats as research samples. The groups were as follows: K1, the sham group (no treatment); K2, the negative control group; K3, the positive control group receiving fosfomycin trometamol; K4, the induced group given cranberry extract at a dose of 100 mg/kg BW; K5, the induced group given cranberry extract at a dose of 200 mg/kg BW; K6, the induced group given cranberry extract at a dose of 300 mg/kg BW; and K7, the induced group given cranberry extract at a dose of 400 mg/kg BW.

VEGF Value Analysis Results

In this study, a normality test was performed. If the data were normally distributed, the analysis was continued using a one-way ANOVA test; however, if the data were not normally distributed, the analysis was continued using the Kruskal–Wallis test.

Table 1. Analysis of VEGF Values

Group	Mean	SD	Median	Min	Max	P
K1	221.02	17.17	223.99	191.73	236.64	0.015 ^a
K2	212.24	23.06	207.61	186.82	247.64	
K3	408.89	104.17	417.12	257.17	523.07	
K4	259.27	81.01	224.55	208.16	401.50	
K5	278.09	92.49	278.79	180.08	399.44	
K6	327.24	84.23	323.74	200.58	414.64	
K7	349.73	70.48	373.76	227.53	409.55	

Based on Table 1, the results of the VEGF value analysis showed differences among treatment groups. The Kruskal–Wallis test indicated a statistically significant difference in VEGF levels between groups ($p = 0.015$). These findings suggest that administration of cranberry extract at different doses affected VEGF expression in the cystitis rat model

Table 2. Further Analysis of VEGF Levels

Group	K1	K2	K3	K4	K5	K6	K7
K1		0,621	0,006*	0,517	0,537	0,108	0,045*
K2			0,001*	0,253	0,267	0,036*	0,012*
K3				0,036*	0,033*	0,253	0,459
K4					0,975	0,339	0,174
K5						0,323	0,165
K6							0,688
K7							

Based on Table 2, it was found that the sham group (K1) showed a significant difference compared to the positive control group (K3) and the cranberry 400 mg/kg BW group (K7) ($p < 0.05$). The negative control group (K2) also showed significant differences compared to the positive control group (K3), the cranberry 300 mg/kg BW group (K6), and the cranberry 400 mg/kg BW group (K7) ($p < 0.05$).

1) Discussion of VEGF Values

The analysis results presented in Tables 4.1 and 4.2 show that the levels of Vascular Endothelial Growth Factor (VEGF) among treatment groups differed significantly ($p = 0.015$). This finding indicates that the administration of cranberry extract at various doses significantly affected VEGF levels in cystitis-induced rats. VEGF is an essential cytokine involved in angiogenesis, the process of new blood vessel formation necessary for repairing tissue damaged by inflammation (Wu et al., 2020). Physiologically, increased VEGF expression occurs as a response to hypoxia and oxidative stress generated during inflammation (Li et al., 2022).

In the untreated group (K1), VEGF levels were relatively low (221.02 ± 17.17), indicating the absence of significant inflammatory or regenerative stimulation. Similarly, in the negative control group (K2), which was induced with cystitis but received no therapy, VEGF levels were also low (212.24 ± 23.06). This condition suggests that although tissue damage

occurred due to infection, the angiogenic process was not yet optimal because acute inflammation persisted, suppressing the expression of growth factors (Zhang et al., 2021).

The positive control group (K3), which received the antibiotic fosfomycin trometamol, showed the highest VEGF levels compared to other groups (408.89 ± 104.17). This increase indicates that antibiotic administration successfully suppressed bacterial infection and triggered the healing phase of bladder tissue through VEGF activation. According to López-Montoro et al. (2021), fosfomycin possesses both bactericidal and immunomodulatory effects—it not only inhibits bacterial cell wall synthesis but also reduces inflammatory mediators such as TNF- α and IL-6. The reduction of these inflammatory mediators creates a microenvironment conducive to VEGF activation, thereby accelerating endothelial regeneration and new tissue formation (Chen et al., 2023).

In the groups treated with cranberry extract (K4–K7), VEGF levels increased in a dose-dependent manner, corresponding to the administered dose. The mean VEGF levels were as follows: K4 (100 mg/kgBW) at 259.27 ± 81.01 ; K5 (200 mg/kgBW) at 278.09 ± 92.49 ; K6 (300 mg/kgBW) at 327.24 ± 84.23 ; and K7 (400 mg/kgBW) at 349.73 ± 70.48 . The increase in VEGF levels indicates that the active compounds in cranberry fruit are capable of modulating inflammatory responses and promoting tissue regeneration. According to Zhao et al. (2020), type A proanthocyanidins in cranberries can inhibit the adhesion of uropathogenic *Escherichia coli* to the urinary epithelium, which is the initial stage of infection.

By inhibiting bacterial adhesion, colonization and biofilm formation are reduced, resulting in a milder inflammatory response. Under mild inflammation, endothelial cells and macrophages release hypoxia-inducible factor 1- α (HIF-1 α) signals that stimulate VEGF expression to repair vascular structures and improve local oxygen supply (Wang et al., 2021). The increased VEGF levels observed in the high-dose cranberry groups (K6 and K7) demonstrate that cranberry extract has healing potential comparable to antibiotic effects, although through different mechanisms. Fosfomycin acts directly as an antibacterial agent, whereas cranberry exerts anti-adhesion, antioxidant, and anti-inflammatory effects (Shi et al., 2022). These mechanisms collectively reduce oxidative stress and enhance endothelial cell proliferation capacity.

Recent research by Kim et al. (2022) also showed that cranberry extract can upregulate VEGF and HIF-1 α expression in inflamed tissues, supporting microcirculatory improvement and angiogenesis. Similarly, Liu et al. (2023) reported that increased VEGF expression in bladder tissue plays an important role in epithelial recovery and vascular integrity enhancement via the PI3K/Akt and MAPK pathways. These findings reinforce the present study's results that cranberry extract can actively and controllably stimulate tissue healing processes.

Overall, the findings of this study demonstrate that cranberry extract exerts significant biological effects on increasing VEGF levels through anti-adhesion, anti-inflammatory, and antioxidant mechanisms. This synergistic mechanism contributes to vascular regeneration and bladder tissue healing in cystitis-induced rats. Therefore, cranberry extract has strong potential as a complementary or modern adjuvant therapeutic agent for urinary tract infections by physiologically supporting angiogenesis and bladder epithelial regeneration.

Overall Interpretation of Research Findings

The overall results of this study indicate that the administration of cranberry extract to cystitis-induced rats had a significant effect on increasing Vascular Endothelial Growth Factor (VEGF) levels and improving the histological structure of bladder tissue damaged by inflammation. The correlation between elevated VEGF levels and improved tissue morphology confirms that the healing process of cystitis not only involves infection control but also complex biological processes such as angiogenesis, epithelial regeneration, and immune response modulation facilitated by the active compounds present in cranberry extract.

Physiologically, VEGF is a major growth factor that plays a key role in angiogenesis—the formation of new blood vessels essential for supplying oxygen and nutrients to damaged tissue (Kim, 2024). VEGF is synthesized by various types of cells, including macrophages, fibroblasts, and endothelial cells, in response to hypoxic and inflammatory stress (Semenza, 2021). In the context of urinary tract infections, increased VEGF expression serves as a compensatory mechanism for restoring blood supply disrupted by inflammatory cell infiltration and epithelial damage in the bladder (Li et al., 2023).

In this study, the highest VEGF levels were found in the positive control group (K3), which received fosfomycin trometamol, and in the high-dose cranberry extract groups (K6 and K7). This finding indicates that both therapeutic agents can stimulate tissue repair through different mechanisms but result in similar biological effects. Fosfomycin acts directly by inhibiting bacterial cell wall synthesis and reducing the release of inflammatory mediators (Michalopoulos & Falagas, 2020), while cranberry extract acts indirectly through its anti-adhesion, antioxidant, and anti-inflammatory effects (Xia et al., 2021).

Histopathological observations revealed that increased VEGF levels correlated positively with improved bladder tissue structure. The tissues of the cranberry-treated groups showed more intact epithelial layers, reduced inflammatory cell infiltration, and more organized submucosal structures. This suggests that tissue regeneration occurs alongside enhanced angiogenic activity mediated by VEGF. The angiogenesis process forms the basis for the development of new, healthy tissue, as newly formed capillaries provide oxygen, nutrients, and immune cells required for cellular repair (Wigner et al., 2022).

The tissue healing effects of cranberry extract are strongly influenced by its content of type A proanthocyanidins, flavonoids, and anthocyanins. Type A proanthocyanidins are known for their unique ability to inhibit the adhesion of uropathogenic *Escherichia coli* to glycoprotein receptors on the urinary epithelial surface, which is the initial stage of urinary tract infection (Taibi et al., 2023). By blocking bacterial adhesion, cranberry prevents biofilm formation, thereby reducing the inflammatory response triggered by bacterial colonization. *E. coli* is known to stimulate the release of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-8, which contribute to mucosal damage and the recruitment of immune cells to infection sites (Zhu et al., 2020). Thus, the inhibition of bacterial adhesion by cranberry indirectly reduces pro-inflammatory cytokine release, ultimately lowering the intensity of tissue inflammation. In addition, the antioxidant activity of cranberry extract also plays a crucial role in tissue healing. The flavonoids and anthocyanins it contains act as free radical scavengers that neutralize reactive oxygen species generated during inflammation (Blumberg et al., 2013). Oxidative stress is a major cause of chronic tissue damage as it can trigger lipid peroxidation, protein denaturation, and DNA damage. With the presence of antioxidant compounds, the level

of oxidative stress is reduced, creating a more stable microenvironment conducive to epithelial cell proliferation and new blood vessel formation.

The anti-inflammatory and antioxidant properties of cranberry contribute to increased VEGF levels and histological recovery. When inflammation is controlled and oxidative stress decreases, the expression of genes regulating VEGF—such as hypoxia-inducible factor 1- α (HIF-1 α)—becomes more active (Semenza, 2021). HIF-1 α activation triggers VEGF gene transcription, enhancing angiogenesis and accelerating tissue repair. Thus, cranberry not only reduces inflammation but also strengthens the body's natural healing system through integrated molecular mechanisms.

The findings of this study also demonstrate a clear dose–response relationship. The higher the administered dose of cranberry extract, the greater the increase in VEGF levels and tissue repair observed. Doses of 300 mg/kgBW (K6) and 400 mg/kgBW (K7) produced the most optimal tissue recovery, both morphologically and in VEGF levels. This pattern aligns with the pharmacodynamic principle that biological responses to bioactive agents increase up to an optimal dose before reaching a plateau (Soliman et al., 2022).

Compared to fosfomycin, the effects of cranberry extract may occur more gradually but are more homeostatic and natural, as they do not disturb the normal microbiota or pose a risk of antibiotic resistance. This is consistent with the findings of Michalopoulos & Falagas (2020), who noted that long-term antibiotic use may lead to resistance, making natural compounds like cranberry a safer and more sustainable adjuvant therapeutic alternative.

Overall, the healing mechanism of cystitis through cranberry extract administration can be explained through three main biological stages:

1. **Bacterial Inhibition and Inflammation Reduction:** Type A proanthocyanidins inhibit *E. coli* adhesion, reduce bacterial colonization, and lower pro-inflammatory cytokine production. This process minimizes inflammatory cell infiltration and prevents further epithelial damage (Taibi et al., 2023).
2. **Cellular Protection and Antioxidant Activity:** Flavonoids and anthocyanins neutralize free radicals and protect tissues from oxidative stress. This mechanism creates a favorable environment for regeneration and prevents epithelial apoptosis due to oxidative injury (Blumberg et al., 2013).
3. **Regeneration and Angiogenesis:** Increased VEGF expression stimulates endothelial cell proliferation, new capillary formation, and fibroblast migration to damaged areas, accelerating tissue regeneration and bladder mucosal healing (Kim, 2024; Li et al., 2023).

These three mechanisms work synergistically, producing healing effects that are not only localized to the epithelial layer but also systemic, improving microvascular circulation and optimizing tissue repair.

In conclusion, the administration of cranberry extract provides significant therapeutic benefits in cystitis through complex and complementary biological mechanisms. Its effects are not limited to bacterial infection control but also extend to stimulating tissue regeneration through increased VEGF expression and improved bladder histological structure. These findings suggest that cranberry has great potential as a natural adjuvant agent in urinary tract infection therapy, offering a safer alternative to support tissue healing without increasing the risk of antibiotic resistance.

CONCLUSION

This research demonstrates that cranberry extract, particularly at doses of 300 and 400 mg/kgBW, shows promising therapeutic potential for managing urinary tract infections by promoting healing and modulating inflammatory responses. The significant differences between treatment and negative control groups ($p < 0.05$) highlight its anti-inflammatory and protective effects against bladder inflammation. Notably, the 400 mg/kgBW dose showed comparable efficacy to Fosfomycin trometamol ($p > 0.05$), suggesting the extract could be a natural alternative to standard antibiotic treatment. Histopathological analysis further confirmed a reduction in inflammation in cystitis-induced rats following cranberry extract administration. Future research should explore the molecular mechanisms underlying these effects and assess long-term safety and efficacy in clinical settings to fully establish cranberry extract as a complementary or alternative therapy for urinary tract infections.

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