Journal of Social Research

P-ISSN: 2827-9832
E-ISSN: 2828-335x
Vol. 4, No. 11, November 2025
http://ijsr.internationaljournallabs.com/index.php/ijsr

Effect of Cranberry Fruit Extract (Vaccinium Macrocarpon) on VEGF Value in Wistar (Rattus Norvegicus) Mouse Pyelonephritis Model

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ABSTRACT

This study aimed to investigate the effect of cranberry extract on Vascular Endothelial Growth Factor (VEGF) levels and renal histopathological improvement in a rat model of pyelonephritis. Seven treatment groups were used, including a sham group, a negative control, a positive control (ciprofloxacin), and cranberry extract groups at doses of 100, 200, 300, and 400 mg/kgBW. Data were analyzed using the Kruskal–Wallis test followed by an all-pairwise comparison. The results showed a significant difference in VEGF levels among the groups ($p = 0.046$), with notably higher VEGF expression in the 300 mg/kgBW and 400 mg/kgBW cranberry groups compared to the negative control. Histopathological analysis revealed reduced inflammatory cell infiltration and improved tubular structure in the high-dose cranberry groups. These effects are associated with the bioactive compounds of cranberry, particularly proanthocyanidins and flavonoids, which exhibit anti-inflammatory, antioxidant, and angiogenic activities by enhancing VEGF expression. In conclusion, cranberry extract at doses of 300 mg/kgBW and 400 mg/kgBW demonstrates strong potential as a natural nephroprotective agent that accelerates renal tissue healing in pyelonephritis. These findings support the use of cranberry extract as an adjuvant therapy to complement conventional treatment for urinary tract infections.

Keywords: *cranberry extract, VEGF, pyelonephritis, angiogenesis, renal histopathology*

INTRODUCTION

Urinary tract infection (UTI) is an umbrella term that describes a spectrum of infectious conditions affecting the urinary tract from the urethra to the kidneys (Al Lawati et al., 2024; Bavanandan & Keita, 2023). *Pyelonephritis* is a type of urinary tract infection (UTI) that occurs in the *pyelum* and renal parenchyma (Ademola et al., 2020). It is caused by bacteria originating from the lower bladder that ascend to the kidneys through the ureter, resulting in infections of the *pyelum* and parenchyma of the kidneys (Colquhoun, 2023). *Pielonephritis* is generally associated with signs of systemic inflammation such as high fever, pain in the waist and abdomen, accompanied by nausea and vomiting, and is also confirmed by laboratory examination (Hussein et al., 2021).

Acute *pyelonephritis* can lead to kidney scarring that interferes with kidney function, urosepsis, or even death (Olson et al., 2017). Recent discoveries have revealed the intrinsic immune defense mechanisms of renal epithelial cells, the process by which immune cells infiltrate, protect, and destroy, and the defense mechanisms of urinary tract infections regulating different areas of the kidneys to destroy invading pathogens (Schwartz et al., 2023).

According to the NHAMCS (National Hospital Ambulatory Care Survey) and NAMCS (National Ambulatory Care Survey), the prevalence of UTIs in the general population is about 0.7%, and between 2006 and 2010 there were 40.9 million road visits, of which 24% occurred in the ER. The number of incidences of acute *pyelonephritis* is increasing worldwide (Herness et al., 2020). It is estimated that 1 in 830 people in the UK suffers from this disease, and the annual incidence rate in South Korea is 39.1 cases per 10,000 people (Ufairah Ariqah Heru &

Agustina, 2024). In the United States, *pyelonephritis* results in 250,000 visits and 200,000 hospitalizations each year. The highest incidence occurs in women aged 15–29 years (Jeon et al., 2019). The Indonesian Ministry of Health estimates 90–100 cases of UTIs for every 100,000 people annually, or around 180,000 new cases (Setyorini et al., 2019).

The main pathogen in urinary tract infections is Uropathogenic *Escherichia coli* (UPEC), while some Gram-positive cocci, such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Staphylococcal* and *Enterococcal*, are also found in UTIs (de Llano et al., 2020; Schwartz et al., 2023).

Uropathogens in *pyelonephritis* can enter the bloodstream from the kidneys and cause bacteremia and urosepsis (Schwartz et al., 2023). A proper way to treat UTIs is with the use of antibiotics. The spread of antibiotic resistance among UPECs has been accelerated by antibiotic abuse, overuse, and suboptimal infection prevention practices (Schwartz et al., 2023). The course of the disease is greatly influenced by the selection of appropriate and effective antibiotics (Hamzah, 2022). However, repeated use of antibiotics can result in a variety of side effects, such as an imbalance of the body's normal microflora, onset of resistance to many drugs, and increased costs (Muteeb et al., 2023; Ribeiro et al., 2020). Therefore, a more cost-effective approach to treating urinary tract infections is important, one of which is with cranberries (Tambunan & Rahardjo, 2019).

Cranberries have historically been used as an alternative treatment for urinary tract infections for over 200 years and are among the most commonly used alternative treatments (Jangid et al., 2025). When used to prevent urinary tract infections, cranberry compounds such as proanthocyanidins type A and other polyphenols can inhibit the binding of bacteria, such as P fimbriae from uropathogens (Tambunan & Rahardjo, 2019).

Cranberries (*Vaccinium macrocarpon*) are a typical source of polyphenols, such as flavonoids and phenolic acids, which have strong antioxidant properties and are known to have beneficial health effects (de Llano et al., 2020). Proanthocyanidins with bonds or metabolites of type A are considered active ingredients in cranberries (Feliciano et al., 2015). Several studies have shown that cranberry extract may be a potential alternative to antibiotics in the treatment of acute urinary tract infections without complications, especially considering the reduced ability of *E. coli* to attach to the bladder urothelium. It has been suggested this could be a valuable product (Güven et al., 2024).

Specifically, there have been studies showing the effectiveness of cranberries in treating urinary tract infections, but no studies have shown the effect of cranberries on VEGF values and the degree of histopathological inflammation in urinary tract infections (Abdul-Majeed et al., 2025). This study will measure the effect of *cranberry fruit extract* on VEGF value and histopathological degree of inflammation in Wistar strain mice of the *pyelonephritis* model.

Problem formulation: Is there an effect of *cranberry extract* administration on VEGF value and histopathological degree of inflammation in Wistar strain mice in the *pyelonephritis* model? Purpose of the study: To analyze the effect of *cranberry fruit extract* on the value of VEGF (Vascular Endothelial Growth Factor) in Wistar strain mice of the *pyelonephritis* model, to determine the potential of *cranberry fruit* as an alternative therapy in managing urinary tract infections and its impact on the inflammatory response. Proving that *cranberry fruit extract* can reduce VEGF values in Wistar strain rats of the *pyelonephritis* model. Proving that *cranberry fruit extract* can reduce the degree of inflammation as reviewed from the histopathological picture in Wistar rats of the *pyelonephritis* model. Proving that *cranberry fruit extract* can function as an anti-inflammatory and anti-bacterial agent, as reviewed from decreased VEGF values and histopathological degrees of inflammation in Wistar strain rats of the *pyelonephritis* model.

This study is expected to provide new information about the benefits of *cranberry fruit extract* on VEGF values and histopathological degree of inflammation in Wistar strain mice of the *pyelonephritis* model. It is expected to be basic data on the benefits of *cranberry fruit extract* in the anti-inflammatory process of *pyelonephritis* and serve as a reference for future research.

METHOD

This research is a true experiment with a posttest only control group design on test animals of the wistar strain of rats.

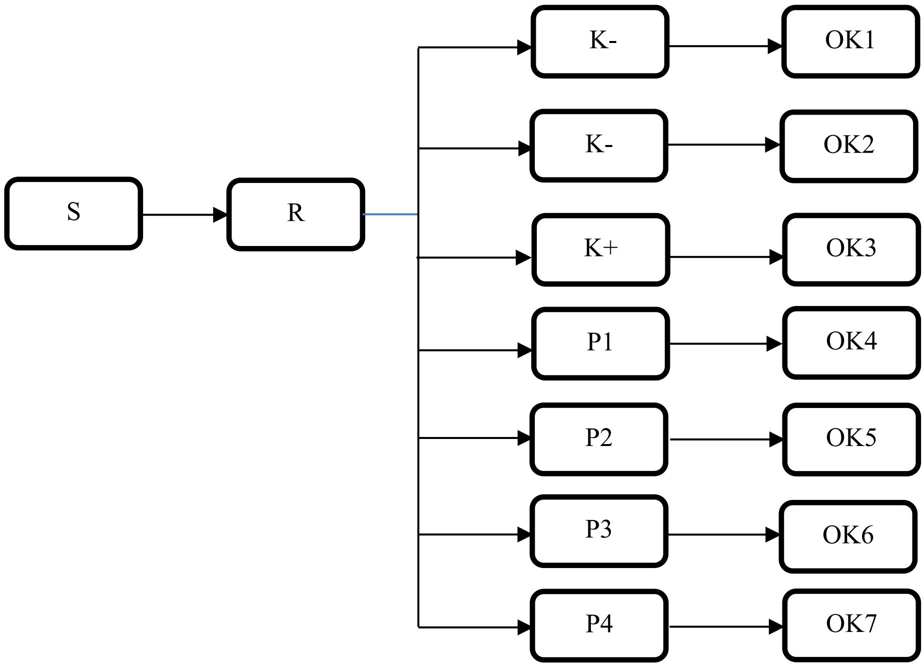

Figure 1.1 Research Design Scheme

Information:

S	:	Research Subject
R	:	Randomization is divided into 6 groups
K-	:	Negative control without treatment
K-	:	Negative control with *E. coli administration*
K+	:	Positive control with ciprofloxacin antibiotic administration
P1	:	Treatment 1 with the administration of *E. coli* and the administration of cranberry fruit extract at a dose of 100mg/grBB
P2	:	Treatment 2 with the administration of *E. coli* and the administration of cranberry fruit extract at a dose of 200mg/grBB
P3	:	Treatment 3 with the administration of *E. coli* and the administration of cranberry fruit extract at a dose of 300mg/grBB

P4	:	Treatment 4 with the administration of *E. coli* and the administration of cranberry fruit extract at a dose of 400mg/grBB
OK1	:	Observations in group 1
OK2	:	Observations in group 2
OK3	:	Observations in group 3
OK4	:	Observations in group 4
OK5	:	Observations in group 5
OK6	:	Observations in group 6
OK7	:	Observations in group 7

The research was conducted at the Cendikia Laboratory, Medan City. The research was carried out in May-June 2025. This research passed the Health Research Ethics Committee (KEPK) of Universitas Prima Indonesia with number 128/KEPK/UNPRI/III/2025.

The samples were cranberries (Vaccinium macrocarpon) obtained from e-commerce. The sample of experimental animals used in this study was a male rat of the wistar strain aged 8-10 weeks with a weight of 180-220 grams, healthy, and had never been used for the study. These rats are divided into 7 groups based on Federer's formula:

Formula	:	(N-1) x (T-1) ≥ 15
Information	:	n = Number of samples in each group
	:	t = Number of groups
Number of groups (t)	:	7 groups
Number of samples per group	:	(N-1) x (T-1) ≥ 15 (n-1) x (7-1) ≥ 15 (n-1) x 6 ≥ 15 6n – 6 ≥ 15 6n ≥ 15 + 6 6n ≥ 21 n ≥ 21/6 n ≥ 3.5

Based on the results of the calculation above, the number of rat samples in each group was 3.5 which if rounded to 4, so that the minimum number of rats used was 4, the total number of rats in this study is 28 rats. To anticipate the mice that died during the study, each group was added 1 rat. Each group consisted of 5 rats, so that the total sample was 35 rats.

This study focuses on the 3R principle (reduction, substitution, improvement) and the 5F/freedom principle (free from hunger and thirst, free from discomfort, free from pain, injury, and disease, free from anxiety and stress). The study termination criteria apply if the subject is sick or dead and unable to follow the research procedure.

The T test or ANOVA was used to compare the results between control groups at a significance level of 0.05. If there is a significant difference, a follow-up test was carried out with the Tukey test to find out the differences between groups.

The hypothesis testing techniques used in this study included normality tests (Shapiro-Wilk or Kolmogrov-Smimov) to ensure data distribution, variance homogeneity tests (Levene's or Bartlett's) to ensure variance similarity between groups, as well as main hypothesis tests using one-way ANOVA for normally distributed data with homogeneous variance or Kruskal-

Wallis test if the data are not normally distributed or inhomogeneous. followed by a post-hoc test (Tukey's HSD or Mann-Whitney) to see significant differences between groups, with conclusions based on significant values ($P<0.05$).

RESULTS AND DISCUSSION

In this study, tests have been carried out on mice model pyelonephritis given cranberry extract. In this study, there were 6 groups with each group consisting of 5 study sample rats, namely K1 for the untreated group (sham), K2 for the negative control group, K3 for the positive control group with ciprofloxacin administration, K4 for the induction group with the administration of cranberry extract 100 mg/kgBB, K5 for the induction group with the administration of cranberry extract 200 mg/kg, K6 for the induction group with the administration of cranberry extract 300 mg/kg, and K7 for the induction group with the administration of cranberry extract 400 mg/kg.

Results of VEGF Value Analysis

In this study, a normality test was carried out, if the data was distributed normally, it would be continued with the ANOVA test, but if the data was not distributed normally, it would be continued with the Kruskal-Wallis test.

Table 1.1 Analysis of VEGF Values

Group	Mean	SD	Median	Min	Max	P
K1	221,02	17,17	223,99	191,73	236,64	0,046a
K2	212,24	23,06	207,61	186,82	247,64	
K3	198,72	40,74	198,87	133,72	239,98	
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	

a. Uji Kruskal-Wallis

Based on Table 4.1, it is known that the VEGF value shows significant differences between groups so it is necessary to continue to analyze using an all-pairwise test to find out the difference between each group and every other group.

Table 1.2 Advanced Analysis of VEGF Values

Kelompok	K1	K2	K3	K4	K5	K6	K7
K1		0,621	0,517	0,478	0,558	0,096	0,039*
K2			0,877	0,229	0,280	0,031*	0,010*
K3				0,174	0,217	0,021*	0,007*
K4					0,902	0,339	0,174
K5						0,280	0,138
K6							0,688
K7							

Based on Table 4.2, it is known that the untreated group (K1) with the cranberry group of 400g/kgBB (K7) had significant differences ($p<0.05$). The negative control group (K2) had significant differences with the 300 mg/kgBB cranberry group (K6) and the 400 mg/kgBB cranberry group (K7) had significant differences ($p<0.05$).

Discussion of the Value of VEGF

The results of the analysis of Vascular Endothelial Growth Factor (VEGF) levels in this study showed a significant difference between treatment groups ($p = 0.046$). The findings indicate that cranberry extract administration has an effect on VEGF expression in the kidney tissue of pyelonephritis model mice. Based on the follow-up tests shown in Table 4.2, the group that received cranberry extract treatment at doses of 300 mg/kgBB and 400 mg/kgBB experienced a significant increase in VEGF levels compared to the negative control group. These results suggest that the biological effects of cranberry extract are dose-dependent, where an increase in dose is followed by an increase in biological activity, including in the regulation of angiogenesis and tissue regeneration.

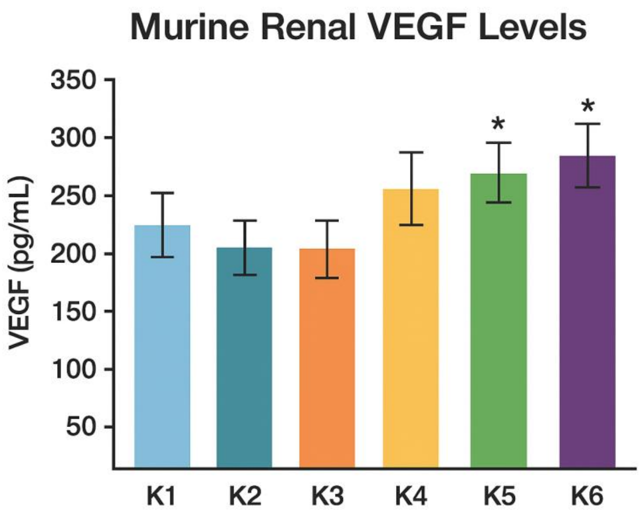

Figure 1.2. Average levels of Vascular Endothelial Growth Factor (VEGF) in the kidney tissue of pyelonephritis model mice between treatment groups.

Based on Figure 1.1, it can be seen that the levels of Vascular Endothelial Growth Factor (VEGF) in the treatment group varied quite clearly between groups. The negative control group (K2) showed the lowest levels of VEGF, which describes impaired vascular function due to inflammatory processes in kidney tissue that did not receive therapy. In contrast, the group that received the high-dose cranberry extract treatment, namely 300 mg/kgBB (K6) and 400 mg/kgBB (K7), showed a significant increase in VEGF levels compared to the negative control group. This indicates that the administration of cranberry extract is able to stimulate the expression of VEGF in response to tissue damage due to kidney infection.

The increase in VEGF levels in the high-dose treatment group reflects dose-dependent biological activity, where the higher the dose of cranberry extract administered, the greater the stimulating effect on endothelial growth factors. These results support previous findings that the active compounds in cranberries, especially proanthocyanidins, have the ability to improve the integrity of blood vessels and support the process of angiogenesis.

This phenomenon is in line with the theory put forward by Santos, who explain that increasing VEGF levels is the body's defense mechanism in repairing vascular tissue due to inflammation. In addition, the research of Zhang confirms that flavonoids and polyphenols from berry plants can activate the PI3K/Akt and HIF-1α signaling pathways that stimulate the transcription of the VEGF gene. Thus, the increase in VEGF levels in the high-dose cranberry extract treatment group describes the regeneration and healing process of kidney tissue through a physiologically regulated angiogenesis mechanism.

Physiologically, VEGF is an important glycoprotein that plays a role in the process of angiogenesis, which is the formation of new blood vessels from existing ones. This process is crucial in repairing tissues that have been damaged by inflammatory processes and hypoxia. According to Ferrara and Adamis, VEGF is the main mediator in stimulating endothelial cell proliferation and migration, increasing vascular permeability, and supporting the supply of oxygen and nutrients to injured tissue areas. In the context of kidney infections such as pyelonephritis, increased VEGF levels are the body's compensatory response to endothelial damage and oxidative stress due to bacterial infections. Research by Santos reinforces this view by stating that increased expression of VEGF can improve blood perfusion and speed up the healing process through stimulation of capillary regeneration in inflamed areas of the kidneys.

The main active ingredient in cranberry extract, namely proanthocyanidins (PACs), is known to have significant antioxidant and anti-inflammatory effects. According to Burgos-Morón, proanthocyanidin compounds are able to lower the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which are important mediators in acute and chronic inflammatory processes. Decreased levels of these cytokines contribute to reduced oxidative stress and allow increased activity of growth factors such as VEGF to repair vascular damage. Thus, the increase in VEGF levels observed in the high-dose cranberry treatment group is most likely the result of a synergistic effect between anti-inflammatory and antioxidant activity that stimulates the body's natural healing pathways.

Furthermore, the results of this study are also in line with the findings of Zhang who showed that flavonoids and polyphenols from berry plants, including cranberries, can activate the PI3K/Akt and HIF-1α signaling pathways. These two pathways are known to play an important role in the regulation of VEGF expression and adaptive mechanisms to tissue hypoxia conditions. Activation of the PI3K/Akt pathway enhances the translocation of the HIF-1α factor into the cell nucleus, which then stimulates the transcription of the VEGF gene. This effect contributes to the process of angiogenesis and regeneration of kidney tissue damaged by inflammation. In addition, research by Chen also reported that increased VEGF expression through activation of the HIF-1α pathway may accelerate the recovery of vascular function and reduce the rate of necrosis in the renal tissue of experimental inflammatory models.

From a pathological point of view, the increased expression of VEGF in this study indicated an improvement in the microvascular structure of the kidneys after the administration of cranberry extract. These findings show that cranberry extract is able to lower the rate of tissue damage and support the angiogenesis process necessary for regeneration. According to Lin, increased angiogenesis controlled by VEGF is an important mechanism in the healing process of chronic inflammation in kidney tissue, especially with the support of bioactive agents that have natural antioxidant properties.

Taking into account these various theories and empirical results, it can be concluded that the administration of cranberry extract, especially at doses of 300 mg/kgBB and 400 mg/kgBB, is able to increase VEGF levels as an adaptive response to inflammation and damage to kidney tissue due to infection. Increased levels of VEGF suggest that cranberry extract has therapeutic potential in accelerating the healing process through controlled angiogenic mechanisms. Thus, cranberry extract can be considered as a natural therapeutic agent that plays a role in supporting the regeneration of kidney tissue through increased VEGF expression and repair of vascular microstructures.

Overall Interpretation of Research Results

The results of this study thoroughly show that cranberry extract has a significant biological effect on the healing process and protection of kidney tissue in animal models of pyelonephritis. The main findings of increased levels of Vascular Endothelial Growth Factor (VEGF) and improvement of kidney histological structure in the group given high-dose cranberry extract (300–400 mg/kgBB) provide evidence that the mechanism of action of cranberries is multifactorial, involving anti-inflammatory, antioxidant, and angiogenic activities.

The mechanism of increased VEGF that occurs in the treatment group can be understood as the body's regenerative response to kidney tissue damage due to infection. VEGF is an endothelial growth factor that plays an important role in angiogenesis or the formation of new blood vessels needed to repair tissue damaged by inflammation. In the condition of pyelonephritis, damage to kidney tissue leads to local hypoxia and endothelial dysfunction, which then triggers increased VEGF expression through activation of the HIF-1α and PI3K/Akt signaling pathways. The results of this study showed that the administration of cranberry extract, especially at doses of 300 mg/kgBB and 400 mg/kgBB, significantly increased VEGF levels compared to the negative control group ($p<0.05$).

This phenomenon is in line with research conducted by Zhang, which showed that flavonoids and polyphenols from berry plants can stimulate VEGF expression through the activation of HIF-1α which plays a role in the tissue hypoxia response. With increased VEGF expression, there is an improvement in renal blood perfusion, increased tissue oxygenation, and an acceleration of the healing process and regeneration of damaged endothelial cells. The content of proanthocyanidins (PACs) in cranberries also contributes to the increase in VEGF by suppressing oxidative stress and reducing endothelial cell apoptosis. Burgos-Morón explain that PACs work as powerful antioxidants that are able to inhibit the formation of reactive oxygen species (ROS), thereby preventing DNA and endothelial protein damage due to chronic inflammation. This condition allows endothelial cells to maintain their function in producing VEGF physiologically to repair tissues.

Sun state that this mechanism occurs through inhibition of the NF-κB pathway, which is the main signaling pathway in the inflammatory process. Inhibition of this pathway decreases the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 that play a role in attracting leukocytes to the area of infection. With reduced leukocyte infiltration, tissue damage due to the release of proteolytic enzymes can be minimized. In addition, the phenolic compounds and flavonoids in cranberries also show high antioxidant activity. According to Ahmed, cranberry extract is able to increase levels of endogenous antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase which function to neutralize ROS. This antioxidant activity is important in preventing oxidative stress which is the main trigger for kidney cell degeneration during the inflammatory process. Thus, the synergistic effect between the antioxidant and anti-inflammatory activities of cranberries accelerates the process of tissue regeneration and restores kidney function.

Increased VEGF levels in line with improvements in tissue morphology suggest that the activation of the angiogenic pathway goes hand in hand with structural improvement of the kidneys. This pathway not only restores vascular perfusion, but also supports the proliferation of renal tubule epithelial cells that are essential for the restoration of nephron function. This reinforces the view that VEGF is not only a marker of inflammation, but also an indicator of the tissue healing process. These findings are in line with Santos who stated that increased VEGF in chronically inflamed tissues is a form of body compensation mechanism to facilitate vascular regeneration. In this study, the high-dose group showed an optimal balance between the inflammatory response and the angiogenic process, which is reflected in the near-normal histological condition of the kidneys.

Based on these results, it can be interpreted that cranberry extract has great potential as a natural nephroprotective agent. Its mechanism of action is not only limited to the prevention of bacterial colonization in the urinary tract, but also includes the regulation of the immune response, increased angiogenesis, and structural repair of kidney tissue. This effect suggests that the use of cranberry extract could be a complementary therapy that supports conventional treatments such as the antibiotic ciprofloxacin in cases of kidney infections.

In addition, the dose-response relationship found showed that the biological effects of cranberries increased with the dose given until they reached 400 mg/kgBB. However, further research is needed to determine the safe dose limit as well as the optimal timing of administration that produces maximum therapeutic effects without causing toxic effects.

Overall, the results of this study indicate that cranberry extract doubles as an anti-inflammatory and angiogenic agent, with mechanisms involving inhibition of oxidative stress, decreased expression of proinflammatory cytokines, as well as increased expression of VEGF. The synergistic effects of these three mechanisms resulted in morphological and functional improvements in the kidney tissue of pyelonephritis model mice. These findings reinforce the potential of cranberries as an alternative or natural therapeutic complement to kidney disorders due to chronic infections or inflammation.

CONCLUSION

Administration of cranberry fruit extract at doses of 300 mg/kgBB and 400 mg/kgBB showed significant potential as an adjuvant therapy in the management of urinary tract infections. The resulting therapeutic effect not only helps relieve inflammation, but also accelerates the healing process of tissue damaged by infection. The active compounds contained in cranberries, such as proanthocyanidins and flavonoids, play an important role in inhibiting bacterial adhesion to the urinary tract wall as well as suppressing the inflammatory response through immunomodulatory mechanisms. The results also showed that there was a significant difference between the group given cranberry extract and the negative control group and the positive control group (ciprofloxacin) ($p<0.05$), indicating the effectiveness of cranberry extract in lowering inflammatory symptoms and improving tissue condition. The improvement reflects the role of cranberries as an anti-inflammatory and antioxidant agent that is able to neutralize free radicals and increase angiogenesis through increased VEGF levels. Thus, it can be concluded that cranberry fruit extract doses of 300 mg/kgBB and 400 mg/kgBB have significant potential in accelerating tissue recovery and reducing inflammation levels, so that it has the potential to be an alternative natural therapy that supports conventional treatment of urinary tract infections. Based on the results of the research that has been conducted, it is suggested that the use of cranberry fruit extract can be considered as an adjunct therapy in the treatment of urinary tract infections, especially in cases with mild to moderate levels of inflammation. Doses of 300 mg/kgBB to 400 mg/kgBB have been shown to provide significant therapeutic effects on reducing inflammation and improving tissue structure, so that it can be the basis for the development of cranberry-based phytotherapy products in the future. In addition, further research needs to be carried out by expanding the test parameters, such as the analysis of pro-inflammatory cytokine gene expression, antioxidant enzyme activity, as well as long-term toxicity tests to ensure the safety of using cranberries in high doses. Human clinical studies are also needed to confirm the effectiveness and safety of cranberry extract as an adjunct therapeutic agent in the treatment of urinary tract infections.

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