Role of Lycopene in Benign Urologic Conditions

Subjects: Biology

Contributor: Piotr Kutwin

Benign prostatic hyperplasia (BPH) is a proliferative disorder of the prostate gland arising from its epithelial cells and smooth muscle within the transitional zone. Prostatitis is a common urologic condition that in 1999 was subdivided into four categories—acute bacterial prostatitis, chronic bacterial prostatitis, chronic non-bacterial prostatitis/chronic pelvic pain syndrome (CPPS), and asymptomatic inflammatory prostatitis. Urinary tract infection (UTI) is one of the most common bacterial infections affecting women. Benign prostatic hyperplasia, urolithiasis, recurrent urinary tract infections, and chronic prostatitis are diseases that are commonly diagnosed worldwide. Carotenoids, including lycopene, are widely available in fruits and vegetables, and it is postulated that they can be used in the prevention and treatment of benign urological conditions.

Keywords: urinary tract infections ; benign prostate hyperplasia ; lycopene

1. Benign Prostatic Hyperplasia

Prostate growth is induced by androgen stimulation and dihydrotestosterone (DHT), produced from testosterone by 5-alpha-reductase, which is a hormone that primes this phenomenon [1].

After lifestyle modifications, which are a first-line treatment in mildly symptomatic disease, administration of medications is the mainstay in the treatment of most men with symptomatic BPH. For this purpose, two drug classes, i.e., 5-alpha-reductase inhibitors and Alpha-blockers have been adopted as the standard of care [2]. As these drugs are not free of adverse events, including a loss of libido, erectile dysfunction [3], and dizziness [4], it is advisable to seek alternative methods to treat and prevent BPH.

Lycopene appears to reach high levels in the prostate and human semen [5][6]. However, the mechanism itself by which lycopene is accumulated in prostatic tissue and excreted into semen remains unknown. High concentration levels of lycopene in prostatic tissue are linked with the prevention of pathologies, such as BPH. These actions are thought to be mediated through various mechanisms, including the inhibition of 5-alpha-reductase expression [7].

1.1. Benign Prostatic Hyperplasia Epidemiological Studies

The largest observational study, which primarily focused on dietary patterns and BPH occurrence, was performed by Tavani et al., who included 2820 men. Of this number, 1369 suffered from BPH. The authors concluded that the risk of BPH significantly decreased with an increasing intake of carotene, vitamin C, and iron. The intake of lycopene or zeaxanthin did not impact BPH incidence. These results contradict those of interventional studies conducted so far. However, as the authors noted, no uniform case definition of the disease has been established and only surgically treated men with BPH were included, which is a potential reason for the lack of dependency between lycopene consumption and BPH prevalence [8].

Kristal et al. examined dietary risk factors for incidence of benign prostatic hyperplasia in 4770 Prostate Cancer Prevention Trial placebo-arm participants who were free of BPH at baseline. BPH was assessed in this group of men over a 7-year period. The authors found that a dietary pattern low in vegetables and protein, and high in fat and red meat, was associated with the development of symptomatic BPH. There was also a weak association between lycopene, zinc, and supplemental vitamin D intake and decreased BPH occurrence [9].

1.2. Benign Prostatic Hyperplasia Experimental Studies

A few in vitro studies have shown that lycopene inhibits the proliferation of benign prostate epithelial cells [10] and suppresses inflammatory cascade [11]. The mechanism responsible for this effect might be the inhibition of 5-alpha-reductase and basal inflammatory signaling, assessed in benign prostate tissue of rats. However, a study performed by Herzog et al. did not show the influence of lycopene administration on prostate growth in young rats [12].

An experimental model showed that a combination of Selenium (Se), Serenoa Repens (SeR), and Lycopene (Ly) effectively reduces oxidative stress, prostate inflammatory response, and histological features [11]. Another study performed by Minutoli et al. also investigated the influence of SeR, Se, and Ly on the microscopic effects of supplementation on BPH tissue. Administering SeR, Se, and Ly significantly blunted prostate growth. Moreover, the combination of SeR–Se–Ly was most effective in reducing prostate enlargement and growth by 43.3% in treated animals [13].

Both in vitro and clinical studies indicate that lycopene potentially inhibits BPH progression. Kim et al. administered 30 mg of lycopene per day for three weeks before radical prostatectomy to 32 patients diagnosed with prostate cancer (PCa). Later on, they investigated the impact of lycopene consumption on histopathological changes found in prostate specimens assessed post-surgically. They revealed that lycopene induced apoptosis in cancer-free BPH tissue. Apoptosis affected both epithelial and myoepithelial cells [14].

Lycopene was not the only carotenoid that demonstrates antioxidant properties tested in pre-clinical trials aimed at BPH treatment. Hou et al. investigated astaxanthin (AST) in the BPH rat model. They studied the effects of tested carotenoid on prostate weights, superoxide dismutase (SOD) activity, and testosterone and dihydrotestosterone levels depending on the dose of the administered substance (20 mg/kg, 40 mg/kg and 80 mg/kg). The most pronounced decline in prostate weights was observed after delivering 80 mg/kg of AST, while noticeable changes in hormone levels and SOD activity started from the administered dosage of 40 mg/kg; they concluded that AST has an inhibitory effect on testosterone-induced rats [15].

2. Prostatitis

Chronic non-bacterial prostatitis/chronic pelvic pain syndrome (CPPS) accounts for 90–95% of all prostatitis cases. Patients usually report symptoms of discomfort in the pelvis, genital, and suprapubic area, urinary symptoms, and sexual dysfunction [16].

The etiopathogenesis of CPPS is still unclear. Since no invading infectious agent has been identified, many hypotheses have been put forward to explain the CPPS etiopathogenesis. They include defective urothelial integrity and function, autoimmune triggered inflammation state, endocrine imbalances, pelvic floor muscle spasm, peripheral and central sensitization, and psychosocial conditions [17]. In the latest research performed by Zhou et al., increased oxidative stress and oxidative damage induced by chronic bacterial prostatitis were found in patients, and such phenomena were closely related to the course of the disease [18].

CPPS is considered a challenge in outpatient clinics. As conventional treatment of CPPS seems hardly effective, more attention has been paid to alternative treatments, including carotenoid therapy.

2.1. Prostatitis Experimental Studies

The suppressive effect of antioxidant supplement (Prosta-Q) on inflammatory processes in prostatitis was assessed by Shahed et al. The product includes zinc, quercetin, cranberry, saw palmetto, bromelain, and papain. It is speculated that oxidative stress may be a key pathway in some men with CPPS, which can be targeted with antioxidant therapy [19]. Lycopene, which downregulates inflammatory regulators such as cytokines, enzymes, and transcription factors in cell culture systems [20], is also known to decrease expression markers for immune cell infiltration in rats' prostate tissue [12].

The synergistic effect of chronic bladder pain (CBP) treatment with lycopene and fluoroquinolones was demonstrated by Han et al. Their analysis of microbiological cultures of the prostate and urine as well as histological findings showed that the addition of lycopene to antibiotic treatment is associated with a statistically significant decrease in bacterial growth and improved prostatic inflammation compared with the ciprofloxacin group [21].

Morgia et al. evaluated the efficacy of the SeR–Se–LY combination in reducing chronic inflammation in patients with benign prostatic hyperplasia and/or prostate intraepithelial neoplasia or atypical small acinar proliferation (PIN/ASAP). This was a multicenter study involving nine Italian urological centers between January 2009 and December 2010. The influence of the test substances on the inflammatory state was measured by histo-biochemical methods. The anti-inflammatory effects were indirectly measured by evaluating the density of T-cells (CD3, CD8), B-cells (CD20), and macrophages (CD68). At the six-month follow-up, there were statistically significant reductions of extension and grading of inflammatory infiltration, mean values of CD20, CD3, and CD68, and mean PSA value in a group of patients with chronic prostatic inflammation taking SeR–Se–LY compared with the control group. It was concluded that patients with bladder outlet obstruction could benefit from this therapy acting on the inflammatory component of BPH [22].

2.2. Prostatitis Clinical Studies

The effects of SeR–Se–LY on IIIa CPPS were compared to Serenoa repens alone in a randomized study performed by Morgia et al. After eight weeks of treatment, S. repens + selenium and lycopene were found to ameliorate symptoms associated with chronic prostatitis, providing significant improvement in voiding dysfunctions compared to S. repens alone. As the treatment was safe and well tolerated, the authors pointed out its usefulness when long-term therapy is required [23].

Cai et al. assessed the influence of adding Serenoa repens, selenium, lycopene, bromelain, and methyl-sulfonyl-methane extracts to standard levofloxacin therapy for chronic bacterial prostatitis. They found that combination therapy had a significant effect on all three evaluated scores (QoL, NIH-CPSI, and IPSS) compared to antibiotic treatment alone. Moreover, as the authors pointed out, no adverse drug reactions have led to high compliance with the experimental protocol [24].

Based on evidence from observational and experimental studies, lycopene shows therapeutic activity against chronic prostatitis. Although its effect was assessed as a support to standard antibiotic treatment, the results of the studies are encouraging. Taking into account chronicity and the recurrent nature of the disease, which demands long-term drug usage, carotenoid supplementation seems to be a reasonable choice for such patients (**Table 1**).

Table 1. Characteristics of studies on chronic prostatitis treatment in which lycopene was used as a solitary drug or in combination with other substances.

Study	Year	Studied Population	Intervention	Results	Ref.
Cai et al.	**2016**	**79 patients suffering from CBP**	**The participants were assigned to one of two groups: Group A taking levofloxacin 500 mg once daily for two weeks with lycopene and methylsulfonylmethane addition; Group B receiving only the antibiotic**	**In group A there was a significant improvement in NIH-CPSI (−17.6 ± 2.65) and IPSS (−12.2 ± 2.33) scores versus Group B (mean difference: −9 ± 1.82; −8.33 ± 1.71, respectively)**	**[24]**
Morgia et al.	**2010**	**102 patients suffering from IIIa CP/CPPS, aged 23–49 years**	**Patients were randomly assigned into two groups: group A receiving Profluss (*S. repens*, selenium, and lycopene) or group B taking *S. repens* alone for two months**	**The NIH-CPSI score significantly improved ($p < 0.001$) in both groups; the decrease in IPSS score and improvement in the maximum peak flow rate was seen in both arms, but was more pronounced in group A. The decrease of PSA and WBC count ($p < 0.007$) was only reported in group A**	**[23]**
Morgia et al.	**2013**	**168 patients suffering from BPH submitted to prostate biopsy for PCa suspicion. Two additional cores were taken for PCI evaluation**	**The first group consisted of 108 participants with histological diagnosis of PCI randomized to Profluss group (I) or to control group (Ic). The second group consisted of 60 participants with histological diagnosis of BPH, randomized to Profluss + α-blocker treatment group (II) or to the control group (IIc)**	**Alleviation of inflammatory state, decrease in mean values of interleukins (CD20, CD3, CD68), and mean PSA levels in group I compared to group Ic. The extension and grading of inflammatory state in group II were also decreased compared to IIc, but not statistically significantly. A statistically significant difference in interleukin levels (CD20, CD3, CD68, CD8) was reported in group II compared to IIc**	**[22]**

CBP—chronic bladder pain; NIH-CPSI—National Institutes of Health—Chronic Prostatitis Symptom Index; IPSS—International Prostate Symptom Score; CP—chronic prostatitis; PCI—prostate chronic inflammation; CPPS—chronic pelvic pain syndrome; WBC—white blood cells; PCa—prostate cancer.

3. Urinary Tract Infection

Recurrent urinary tract infection (rUTI) is frequently defined as two or more episodes in the last six months or at least three episodes in the last 12 months [25]. The risk of developing a UTI in a lifetime has been estimated to be above 50% [26], with 25% having a recurrence [27]. Urinary tract infection may be confined to the lower urinary tract (cystitis), or it may also affect the upper urinary tract (acute pyelonephritis). A variety of oxidation products are found in urine participating in local and systemic oxidative stress reactions [28]. Furthermore, UTI severely increases oxidative stress in patients [29].

Prevention strategies, including the replacement of vaginal estrogens, taking D-mannose supplements, nitrofurantoin applied at a daily dose of 50 mg methenamine salts, and cranberry products, are major components of rUTI care. The management goal is to significantly reduce UTIs. However, it is not always possible to eliminate the infection completely despite strict adherence to medical recommendations [30].

There are a few described mechanisms by which the protective effect of vitamin A on the urinary tract can be observed. Vitamin A increases both immune response efficacy to infection once the epithelial barrier has been disrupted [31] and non-specific immunity, by supporting the physical and biological integrity of epithelial tissue as the first barrier to infection [32]. Furthermore, it can provide a more effective barrier against infection by restoring normally differentiated epithelium that coats the urinary tract, preventing pathogen adhesion [33].

3.1. Urinary Tract Infection Experimental Studies

Munday et al. studied vitamin A deficiency in rat models. They found pyelonephritis in 68% and cystitis in 66% of rats after 34 weeks of the experiment. The vitamin A deficiency in rats led to squamous metaplasia that was confined to the transitional epithelium, suggesting susceptibility of this epithelial type to vitamin A deficiency. Squamous metaplasia was thought to be the likely reason for bacterial infections observed within the rats' urinary tract [34].

3.2. Urinary Tract Infection Clinical Studies

Kahbazi et al. studied the addition of vitamin A to antibiotic therapy in the acute phase of pyelonephritis (APN). The results showed that oral vitamin A treatment during APN resolves some of the clinical symptoms of UTI more quickly and reduces renal scarring following APN compared to antibiotics alone. This was the first report to present the antipyretic and anti-urinary frequency effects of vitamin A [35]. It is thought that this effect arises from retinol's hormone-like activity as a growth factor for epithelial cells, and vitamin A's re-epithelialization properties of damaged mucosal surfaces [36].

Yilmaz et al. investigated the influence of vitamin A supplementation on recurrent urinary tract infection. UTI recurrence rates during the 12-month follow-up significantly decreased after a single dose of vitamin A given when the patients were enrolled in the study. This decrease was notably more prominent during the first six months [37]. The consequences of Vitamin A deficiency on urinary tract and possible effects of VitA supplementation are shown in **Figure 1**.

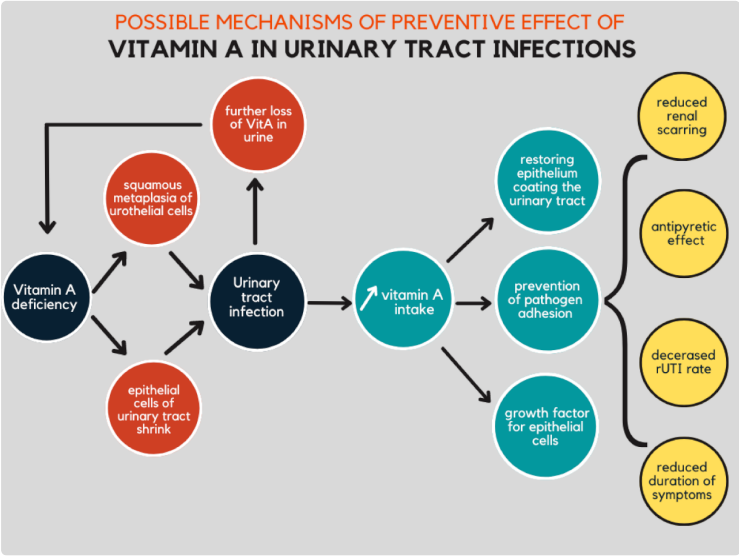

Figure 1. The possible cascade leading to urinary tract infection and preventive effects of vitamin A supplementation in the urinary tract infections.

Although evidence of vitamin A's effect on urinary tract infection is sparse, research thus far confirms its supportive role in managing acute and recurrent UTI (**Table 2**). To draw any final conclusions concerning carotenoid efficacy in the treatment and prevention of UTI, additional well-powered studies are still needed.

Table 2. Characteristics of studies assessing vitamin A effects on urinary tract infection treatment and prevention.

Study	Year	Material	Intervention	Results	Ref.
Kahbazi et al.	**2017**	**90 females aged 2–12 years diagnosed with UTIs and the first episode of APN**	**Participants were randomized into two groups: in addition to antibiotics the intervention group was given 10 days of oral vitamin A while the control group received 10 days of placebo**	**Duration of symptoms (fever, urinary frequency, and poor feeding) was significantly reduced in the intervention group. The second 99mTc-DMSA scan revealed worsening of patients' kidney status in 22.2% of participants in the vitamin A group and 44.7% of patients in the placebo group (p = 0.003)**	[35]
Yilmaz et al.	**2007**	**24 patients with uncomplicated rUTI were included**	**Patients were randomized into two groups: the first receiving a single dose of 200,000 IU vitamin A in addition to antibiotic treatment and the second being a control group**	**In the six months after treatment, the chance of suffering rUTI reduced from 3.58 to 0.75 in the intervention group. UTIs were statistically less frequent during the six months follow-up after vitamin A supplementation compared to the control group**	[37]

UTI—urinary tract infection; rUTI—recurrent urinary tract infection; APN—acute pyelonephritis.

References

1. Steers, W.D. 5α-Reductase Activity in the Prostate. Urology 2001, 58, 17–24.
2. Lepor, H. Medical Treatment of Benign Prostatic Hyperplasia. Rev. Urol. Dis. State Rev. 2011, 13, 20–33.
3. Hirshburg, J.M.; Kelsey, P.A.; Therrien, C.A.; Gavino, A.C.; Reichenberg, J.S. Adverse Effects and Safety of 5-Alpha Reductase Inhibitors (Finasteride, Dutasteride): A Systematic Review. J. Clin. Aesthetic Dermatol. 2016, 9, 56.
4. Dunn, C.J.; Matheson, A.; Faulds, D.M. Tamsulosin. Drugs Aging 2002, 19, 135–161.
5. Clinton, S.K.; Emenhiser, C.; Schwartz, S.J.; Bostwick, D.G.; Williams, A.W.; Moore, B.J.; Erdman, J.W.; El, J.W. Cis-Trans Lycopene Isomers, Carotenoids, and Retinol in the Human Prostate. Cancer Epidemiol. Biomark. Prev. 1996, 5, 823.
6. Palan, P.; Naz, R. Changes in Various Antioxidant Levels in Human Seminal Plasma Related to Immunoinfertility. Arch. Androl. 1996, 36, 139–143.
7. Siler, U.; Barella, L.; Spitzer, V.; Schnorr, J.; Lein, M.; Goralczyk, R.; Wertz, K. Lycopene and Vitamin E Interfere with Autocrine/Paracrine Loops in the Dunning Prostate Cancer Model. FASEB J. 2004, 18, 1019–1021.
8. Tavani, A.; Longoni, E.; Bosetti, C.; Maso, L.D.; Polesel, J.; Montella, M.; Ramazzotti, V.; Negri, E.; Franceschi, S.; Vecchia, C. la Intake of Selected Micronutrients and the Risk of Surgically Treated Benign Prostatic Hyperplasia: A Case-Control Study from Italy. Eur. Urol. 2006, 50, 549–554.
9. Kristal, A.R.; Arnold, K.B.; Schenk, J.M.; Neuhouser, M.L.; Goodman, P.; Penson, D.F.; Thompson, I.M. Dietary Patterns, Supplement Use, and the Risk of Symptomatic Benign Prostatic Hyperplasia: Results from the Prostate Cancer Prevention Trial. Am. J. Epidemiol. 2008, 167, 925–934.
10. Obermüller-Jevic, U.C.; Olano-Martin, E.; Corbacho, A.M.; Eiserich, J.P.; van der Vliet, A.; Valacchi, G.; Cross, C.E.; Packer, L. Lycopene Inhibits the Growth of Normal Human Prostate Epithelial Cells In Vitro. J. Nutr. 2003, 133, 3356–3360.
11. Bonvissuto, G.; Minutoli, L.; Morgia, G.; Bitto, A.; Polito, F.; Irrera, N.; Marini, H.; Squadrito, F.; Altavilla, D. Effect of Serenoa Repens, Lycopene, and Selenium on Proinflammatory Phenotype Activation: An In Vitro And In Vivo Comparison Study. Urology 2011, 77, 248.e9–248.e16.
12. Herzog, A.; Siler, U.; Spitzer, V.; Seifert, N.; Denelavas, A.; Hunziker, P.B.; Hunziker, W.; Goralczyk, R.; Wertz, K. Lycopene Reduced Gene Expression of Steroid Targets and Inflammatory Markers in Normal Rat Prostate. FASEB J. 2005, 19, 1–24.
13. Minutoli, L.; Altavilla, D.; Marini, H.; Rinaldi, M.; Irrera, N.; Pizzino, G.; Bitto, A.; Arena, S.; Cimino, S.; Squadrito, F.; et al. Inhibitors of Apoptosis Proteins in Experimental Benign Prostatic Hyperplasia: Effects of Serenoa Repens, Selenium and Lycopene. J. Biomed. Sci. 2014, 21, 19.
14. Kim, H.-S.; Bowen, P.; Chen, L.; Duncan, C.; Ghosh, L.; Sharifi, R.; Christov, K. Effects of Tomato Sauce Consumption on Apoptotic Cell Death in Prostate Benign Hyperplasia and Carcinoma. Nutr. Cancer 2003, 47, 40–47.
15. Wang, L.; Hou, Y.; Wang, R.; Pan, Q.; Li, D.; Yan, H.; Sun, Z. Inhibitory Effect of Astaxanthin on Testosterone-Induced Benign Prostatic Hyperplasia in Rats. Mar. Drugs 2021, 19, 652.

16. Habermacher, G.M.; Chason, J.T.; Schaeffer, A.J. Prostatitis/Chronic Pelvic Pain Syndrome. Annu. Rev. Med. 2006, 57, 195–206.
17. Pontari, M.A.; Ruggieri, M.R. Mechanisms in prostatitis/chronic pelvic pain syndrome. J. Urol. 2004, 172, 839–845.
18. Zou, Y.; Sun, Q.; Li, J.; Yang, C.; Yang, J.; Zhang, L. Effects of E/Z Isomers of Lycopene on Experimental Prostatic Hyperplasia in Mice. Fitoterapia 2014, 99, 211–217.
19. Shahed, A.R.; Shoskes, D.A. Oxidative Stress in Prostatic Fluid of Patients With Chronic Pelvic Pain Syndrome: Correlation With Gram Positive Bacterial Growth and Treatment Response. J. Androl. 2000, 21, 669–675.
20. de Stefano, D.; Maiuri, M.C.; Simeon, V.; Grassia, G.; Soscia, A.; Cinelli, M.P.; Carnuccio, R. Lycopene, Quercetin and Tyrosol Prevent Macrophage Activation Induced by Gliadin and IFN-γ. Eur. J. Pharmacol. 2007, 566, 192–199.
21. Han, C.H.; Yang, C.H.; Sohn, D.W.; Kim, S.W.; Kang, S.H.; Cho, Y.-H. Synergistic Effect between Lycopene and Ciprofloxacin on a Chronic Bacterial Prostatitis Rat Model. Int. J. Antimicrob. Agents 2008, 31, 102–107.
22. Morgia, G.; Cimino, S.; Favilla, V.; Russo, G.I.; Squadrito, F.; Mucciardi, G.; Masieri, L.; Minutoli, L.; Grosso, G.; Castelli, T. Effects of Serenoa Repens, Selenium and Lycopene (Profluss®) on Chronic Inflammation Associated with Benign Prostatic Hyperplasia: Results of “FLOG” (Flogosis and Profluss in Prostatic and Genital Disease), a Multicentre Italian Study. Int. Braz. J. Urol. 2013, 39, 214–221.
23. Morgia, G.; Mucciardi, G.; Galì, A.; Madonia, M.; Marchese, F.; di Benedetto, A.; Romano, G.; Bonvissuto, G.; Castelli, T.; Macchione, L.; et al. Treatment of chronic prostatitis/chronic pelvic pain syndrome category IIIA with Serenoa repens plus selenium and lycopene (profluss®) versus S. repens alone: An Italian randomized multicenter-controlled study. Urol. Int. 2010, 84, 400–406.
24. Cai, T.; Tiscione, D.; Gallelli, L.; Verze, P.; Palmieri, A.; Mirone, V.; Bartoletti, R.; Malossini, G. Serenoa Repens Associated with Selenium and Lycopene Extract and Bromelain and Methylsulfonylmethane Extract Are Able to Improve the Efficacy of Levofloxacin in Chronic Bacterial Prostatitis Patients. Arch. Ital. Urol. E Androl. 2016, 88, 177.
25. Epp, A.; Larochelle, A. Recurrent Urinary Tract Infection. J. Obstet. Gynaecol. Can. 2017, 39, e422–e431.
26. GRIEBLING, T.L. Urologic diseases in america project: Trends in resource use for urinary tract infections in women. J. Urol. 2005, 173, 1281–1287.
27. Scholes, D.; Hooton, T.M.; Roberts, P.L.; Stapleton, A.E.; Gupta, K.; Stamm, W.E. Risk Factors for Recurrent Urinary Tract Infection in Young Women. J. Infect. Dis. 2000, 182, 1177–1182.
28. Kurutas, E.B.; Ciragil, P.; Gul, M.; Kilinc, M. The Effects of Oxidative Stress in Urinary Tract Infection. Mediat. Inflamm. 2005, 2005, 242–244.
29. Gul, M.; Kurutas, E.; Ciragil, P.; Cetinkaya, A.; Kilinc, M.; Aral, M.; Buyukbese, M.A. Urinary Tract Infection Aggravates Oxidative Stress in Diabetic Patients. Tohoku J. Exp. Med. 2005, 206, 1–6.
30. Jung, C.; Brubaker, L. The Etiology and Management of Recurrent Urinary Tract Infections in Postmenopausal Women. Climacteric 2019, 22, 242–249.
31. Friedman, A.; Sklan, D. Antigen-Specific Immune Response Impairment in the Chick as Influenced by Dietary Vitamin A. J. Nutr. 1989, 119, 790–795.
32. Chandra, R.K. Increased Bacterial Binding to Respiratory Epithelial Cells in Vitamin A Deficiency. BMJ 1988, 297, 834–835.
33. McDowell, E.M.; DeSanti, A.M.; Newkirk, C.; Strum, J.M. Effects of Vitamin A-Deficiency and Inflammation on the Conducting Airway Epithelium of Syrian Golden Hamsters. Virchows Arch. B Cell Pathol. Incl. Mol. Pathol. 1990, 59, 231–242.
34. Munday, J.; McKinnon, H.; Aberdein, D. Cystitis, Pyelonephritis, and Urolithiasis in Rats Accidentally Fed a Diet Deficient in Vitamin A. J. Am. Assoc. Lab. Anim. Sci. 2009, 48, 790–794.
35. Kahbazi, M.; Sharafkhah, M.; Yousefichaijan, P.; Taherahmadi, H.; Rafiei, M.; Kaviani, P.; Abaszadeh, S.; Massoudifar, A.; Mohammadbeigi, A. Vitamin A Supplementation Is Effective for Improving the Clinical Symptoms of Urinary Tract Infections and Reducing Renal Scarring in Girls with Acute Pyelonephritis: A Randomized, Double-Blind Placebo-Controlled, Clinical Trial Study. Complementary Ther. Med. 2019, 42, 429–437.
36. Dalirani, R.; Zoshk, Y.; Sharifian, M.; Mohkam, M.; Karimi, A.; Fahimzad, A.; Varzandefar, M. Kidney Diseases Role of Vitamin A in Preventing Renal Scarring After Acute Pyelonephritis. Iran J. Kidney Dis. 2011, 5, 320–323.
37. Yilmaz, A.; Bahat, E.; Yilmaz, G.G.; Hasanoglu, A.; Akman, S.; Guven, A.G. Adjuvant Effect of Vitamin A on Recurrent Lower Urinary Tract Infections. Pediatrics Int. 2007, 49, 310–313.