Review Article

Use of antioxidants in urinary tract infection

Zahra Allameh¹, Jamshid Salamzadeh²

¹Department of Clinical Pharmacy and Pharmacy Practice, Isfahan University of Medical Sciences, Isfahan, Iran
²Department of Clinical Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

INTRODUCTION

Although oxidation reactions are crucial for life, they can also damage cells. Cells contain a complex network of antioxidant systems to prevent oxidative damage to cellular components. In general, antioxidant systems either prevent reactive species from being formed or remove them before they can damage vital components of the cell. When antioxidant defense mechanisms are decreased, or when the generation of reactive oxygen molecules is increased, oxidant injury results from the shift in the oxidant/antioxidant balance.

Oxidative stress seems to play a significant role in many human diseases including cancers and infections. Several renal diseases including glomerulonephritis, vasculitis, toxic nephropathies, pyelonephritis, acute renal failure, and others are likely to be mediated at least in part by oxidant injury.

Pyelonephritis is an inflammatory process, and oxidative stress plays a major role in it. Anti-inflammatory or antioxidant therapy given concomitantly with antibiotics should lower the risk of postpyelonephritic scarring. As the lack of review studies in the use of antioxidants in urinary tract infections was detected, this study was designed. We conducted a review of available articles in PubMed and Google Scholar with a simple review, using keywords of “antioxidant” and “pyelonephritis” with all their possible synonyms and combinations. Only interventional studies were collected. There were neither limitations on time, nor the location of the study, type of subjects, administration rout of the antioxidant drug, and the antioxidant drug used. After studying the abstracts or in some cases the full text of articles, they were categorized based on the type of antioxidant, type and number of subjects, rout of administration, dosing, duration of treatment, year of publication of the paper, and the results. A total of 66 articles published from 1991 to 2015 were found by studying just the title of the papers. Studying the abstracts reduced this number to 51 studies. Antioxidants used for this condition were Vitamins A, E, and C, cytoflavin, caffeic acid phenethyl ester, ebselen, allopurinol, melatonin, N-acetylcysteine, oleuropein, montelukast, oxytocin, ozon, dapsone, pentoxifyllin, tadalafil, bilirubin, cranberry, meloxicam, L-carnitine, colchicine, perfluoran, methylprednisolone, and dexamethasone. Studies show that antioxidants are capable of reducing oxidative stress and can be used effectively along with antibiotics to reduce the scar formation.

ABSTRACT

Pyelonephritis is an inflammatory process, and oxidative stress plays a major role in it. Anti-inflammatory or antioxidant therapy given concomitantly with antibiotics should lower the risk of postpyelonephritic scarring. As the lack of review studies in the use of antioxidants in urinary tract infections was detected, this study was designed. We conducted a review of available articles in PubMed and Google Scholar with a simple review, using keywords of “antioxidant” and “pyelonephritis” with all their possible synonyms and combinations. Only interventional studies were collected. There were neither limitations on time, nor the location of the study, type of subjects, administration rout of the antioxidant drug, and the antioxidant drug used. After studying the abstracts or in some cases the full text of articles, they were categorized based on the type of antioxidant, type and number of subjects, rout of administration, dosing, duration of treatment, year of publication of the paper, and the results. A total of 66 articles published from 1991 to 2015 were found by studying just the title of the papers. Studying the abstracts reduced this number to 51 studies. Antioxidants used for this condition were Vitamins A, E, and C, cytoflavin, caffeic acid phenethyl ester, ebselen, allopurinol, melatonin, N-acetylcysteine, oleuropein, montelukast, oxytocin, ozon, dapsone, pentoxifyllin, tadalafil, bilirubin, cranberry, meloxicam, L-carnitine, colchicine, perfluoran, methylprednisolone, and dexamethasone. Studies show that antioxidants are capable of reducing oxidative stress and can be used effectively along with antibiotics to reduce the scar formation.

Keywords: Antioxidant; pyelonephritis; urinary tract infection

Access this article online

Website: www.jrpp.net
DOI: 10.4103/2279-042X.179567

How to cite this article: Allameh Z, Salamzadeh J. Use of antioxidants in urinary tract infection. J Res Pharm Pract 2016;5:79-85.
failure, and lower urinary tract infections. These results suggest antioxidant therapy as a valuable option for children with kidney problems.[1]

In addition, it has been shown that in pyelonephritis (upper urinary tract infection), an infection-induced intoxication and oxidative stress can lead to cell death, and pyelonephritis can be treated by reducing mitochondrial reactive oxygen species, and thus by protecting the mitochondrial integrity and lowering kidney damage.[2]

In many studies, impaired balance between oxidant systems and antioxidant defense in patients with acute or chronic pyelonephritis is established, and some studies have declared this in the pathogenesis of tissue injury in this infection.[3-5] It seems logical that anti-inflammatory or antioxidant therapy given concomitantly with antibiotics to reduce the risk of postpyelonephritic scarring.[6]

**METHODS**

We conducted a review of available articles in PubMed and Google Scholar, using keywords of “antioxidant” and “pyelonephritis” with all their possible synonyms and combinations. Studies showed that antioxidants are capable of reducing oxidative stress and can be used effectively along with antibiotics to reduce the risk of pyelonephritis scarring.

Only interventional studies were collected. There were neither limitations on time nor the location of the study, type of subjects, administration route of the antioxidant drug, and the antioxidant drug used. After studying the abstracts or in some cases the full text of articles, they were categorized based on the type of antioxidant, type and number of subjects, route of administration, dosing, duration of treatment, year of publication of the paper, and results (whether the antioxidant drug was effective in reducing oxidative stress or not). We found 66 articles published from the years 1991 to 2015 by studying just the titles of papers. Studying these abstracts reduced this number to 51 studies.

**VITAMINS**

Vitamin A was studied as a valuable antioxidant for pyelonephritis in 3 articles. The role of Vitamin A in preventing renal scaring after acute pyelonephritis (APN) in children was established. This clinical trial study was conducted in children with APN in Mofid Children Hospital (Tehran, Iran). The patients were randomly divided into 2 groups to receive ceftriaxone and Vitamin A or ceftriaxone only. Dimercaptosuccinic acid (DMSA) renal scintigraphy was performed before the start of the treatment and 6 months later. Results were compared for renal scaring between the groups. The second DMSA scan showed a significant change in the progression of kidney injury and scaring in favor of Vitamin A administration ($P < 0.001$).[7]

In a study on 50 children with APN, all subjects were given intravenous ceftriaxone for 10 days followed by oral cephalexin for 3 months. Cases, in addition, were given a single intramuscular dose of Vitamin A at the repeat DMSA scan after 3 months, 5 of 25 cases (20%) and 17 of 25 controls (68%) had abnormal findings ($P = 0.001$). In conclusion, administration of Vitamin A was associated with a significantly lower rate of permanent renal damage.[8]

The effects of oral Vitamin A or E supplementation in combination with antibiotics for the prevention of renal scarring in APN in children were the subject of another study. This simple nonblinded, randomized, clinical trial was conducted on 61 children aged 1 month–10 years. Each patient was evaluated twice by 99mTc-DMSA scintigraphy performed at least 6 months apart. A worsening of lesions, based on the second 99mTc-DMSA scan, was observed in 42.5%, 0%, and 23.3% of the control, Vitamin E, and Vitamin A patients, respectively ($P < 0.001$). Hence, Vitamin A or E supplements were effective in reducing renal scarring secondary to APN.[9] Vitamin E was administered as an antioxidant to prevent renal scarring in APN in 4 studies, 3 studies on rats, and 1 on humans (children with APN).

In the first study on rats, all rats in Groups 1–3 were given once-daily intraperitoneal injections of ceftriaxone for 5 consecutive days, beginning on the 3rd day after inoculation. The rats in Group 2 were given allopurinol co-treatment; whereas, in Group 3, Vitamin E co-treatment was started at fever onset. Both kidneys were excised 6 weeks later, for the evaluation of histopathologic changes, apoptotic damage, and concentrations of transforming growth factor-beta (TGF-beta). Only minimal changes were found in control samples. Pathologic scores of inflammation and fibrosis in Group 1 were higher than in the Vitamin E and allopurinol groups ($P < 0.05$). Apoptosis index was also decreased in Groups 2 and 3 compared to Group 1 ($P < 0.05$). There was no significant difference in average TGF-beta levels between the study groups.[10]

The effects of co-supplementation of Vitamins E and C for preventing renal scarring in APN in rats were investigated in another study. In this study, the group which received gentamicin only had moderate to severe scarring, but the 2 groups which received Vitamin C and Vitamin E showed no or mild renal...
scarring. The study showed that administration of antioxidants can protect scaring due to pyelonephritis with or without antibiotic administration.[11]

In another study, the effects of Vitamin E supplementation in combination with antibiotics for the treatment of girls with APN were investigated. In this double-blinded, randomized, controlled trial that was conducted on 152 girls aged 5–12 years with a first APN, the patients were randomized to receive a 14-day treatment with only antibiotics (control group; \( n = 76 \)) and 14-day treatment with supplements of Vitamin E (intervention group; \( n = 76 \)). Patients' clinical symptoms were monitored for 14 days, and urine culture was performed 3–4 days and 7–10 days after the start of the treatment and its completion, respectively. All of the girls once underwent DMSA scan 4–6 months after the treatment. During the follow-up days, the mean frequency of fever (\( P = 0.01 \)), urinary frequency (\( P = 0.001 \)), urgency (\( P = 0.003 \)), dribbling (\( P = 0.001 \)), and urinary incontinence (\( P = 0.006 \)) were significantly lower in the intervention group compared to the control group. There was no significant difference in the results of urine culture 3–4 days after starting the treatment (\( P = 0.16 \)) and 7–10 days after its termination (\( P = 0.37 \)). There was also no significant difference between the results of DMSA scan 4–6 months after starting the treatment (\( P = 0.31 \)).[12]

**CYTOFLAVIN**

It has been shown in a study that the antioxidant drug cytoflavin in combination with basic therapy reduces the intensity of lipid peroxidation processes with retention of the antioxidant status in patients with chronic pyelonephritis. The proposed treatment normalizes the ratio of blood plasma phospholipid fractions and erythrocytes membranes.[13]

**CAFFEIC ACID PHENETHYL ESTER**

Caffeic acid phenethyl ester (CAPE), an active component of propolis from honeybee hives, has antioxidant, anti-inflammatory, and antibacterial properties. The efficiency of CAPE administration in preventing oxidative damage in pyelonephritis caused by *Escherichia coli* in rats was investigated. CAPE administration reduced malondialdehyde (MDA) and nitric oxide (NO) levels, as well as xanthine oxidase activity although it increased superoxide dismutase (SOD) and glutathione peroxidase activities. Histopathological examination showed that CAPE reduced the inflammation grade-induced by *E. coli*.[14]

**MELATONIN**

Melatonin is a powerful antioxidant. In a study on rats, melatonin was given by intraperitoneal injection for 5 days alone or combined with the antibiotic ceftriaxone. Melatonin only and antibiotic plus melatonin treatment caused a marked reduction in the mean MDA values compared with no treatment and antibiotic-only treatment, with no significant difference compared with that of the control group. No significant differences were found in the renal scarring scores in rats receiving no treatment, and those treated only with antibiotic or melatonin. The authors concluded that when combined with antibiotics, melatonin prevents renal scar formation.[15]

For reviewing the results of another study that used melatonin, please refer to the “cranberry” section.[16]

**N-ACETYLCTYSTEINE**

N-acetylcysteine (NAC) is a potent antioxidant that has been shown in many studies to reduce oxidative stress in different conditions.[17–21] In an investigation, the contribution of free radicals to the development of APN induced by planktonic and biofilm cells of *Pseudomonas aeruginosa* was studied. Evaluation of the data revealed that excessive production of free radicals causes tissue damage, leading to bacterial persistence in the host’s tissues. Treatment of mice with NAC, a potent antioxidant, lead to significant amelioration of oxidative stress and subsequent decrease in bacterial titer, neutrophil influx, MDA as well as tissue pathology highlighting the important role of free radicals in *P. aeruginosa*-induced pyelonephritis.[4]

**OLEEUROPEIN**

Oleuropein, a novel immunomodulator derived from olive tree, was assessed *in vitro* and in experimental sepsis by *P. aeruginosa*. After addition in monocyte and neutrophil cultures, MDA, tumor necrosis factor-alpha (TNF-\( \alpha \)), interleukin (IL)-6, and bacterial counts were estimated in supernatants. APN was induced in 70 rabbits after inoculation of the pathogen in the renal pelvis. Intravenous oleuropein prolonged survival in experimental sepsis, probably by promoting phagocytosis or inhibiting biosynthesis of proinflammatory cytokines.[22]

**MONTELUKAST**

One study aimed to investigate the possible protective effect of montelukast, a selective antagonist of cysteinyl leukotriene receptor 1, against *E. coli*-induced oxidative injury and scarring in renal tissue.
Pyelonephritic rats were treated with either saline or montelukast immediately after surgery and at daily intervals. It seems likely that montelukast protects kidney tissue by inhibiting neutrophil infiltration, balancing oxidant-antioxidant status, and regulating the generation of inflammatory mediators.[23]

**OXYTOCIN**

The neurohypophyseal hormone oxytocin facilitates wound healing and is involved in the modulation of immune and inflammatory processes. Another study investigated the possible therapeutic effects of oxytocin against *E. coli*-induced pyelonephritis in rats both in the acute and chronic setting. All inflammatory parameters and elevation of lactate dehydrogenase in the late phase were reversed to normal levels by oxytocin treatment.[24]

**OZONE**

One study was conducted to evaluate the effect of ozone therapy (OT), as an immunomodulator and antioxidant, on the renal function, morphology, and biochemical parameters of oxidative stress in an experimental model of APN in rats. In the abstract of this article, it has not been mentioned how ozone was given to rats. Either antibiotherapy or OT markedly ameliorated renal dysfunction, the antioxidant status of the kidneys and histopathological injuries subjected to *E. coli*-induced APN. Interestingly, the combination of antibiotherapy and OT was much more effective than either of the treatment modalities alone.[25]

**PENTOXIFYLLINE**

One study designed to evaluate the efficiency of pentoxifylline (PTX), a methylxanthine derivative, in preventing renal scar formation after the induction of pyelonephritis in an experimental rat model with delayed antimicrobial therapy. In this study, delayed treatment with antibiotics had no effect on scarring compared with the untreated controls. However, the addition of PTX to the delayed antibiotic therapy significantly inhibited renal scarring compared with the untreated or antibiotic-only groups (*P* < 0.05).[26]

**TADALAFIL**

In order to evaluate the effects of tadalafil, a phosphodiesterase 5 enzyme inhibitor, on *E. coli*-induced renal damage in an APN rat model, another study designed. Tadalafil was administered between days 0 and 28 of bacterial inoculation. Inflammatory activity was significantly milder in rats treated with antibiotic + tadalafil versus no treatment group both in the early and late periods. In the late period, interstitial fibrosis or tubular atrophy was lower in the antibiotic + tadalafil group versus the no treatment and antibiotic groups, and in tadalafil versus antibiotic group. Tadalafil administration significantly reduced renal MDA and NO levels and enhanced SOD and catalase activities. In addition, circulating TNF-α, IL 1β was greatly reduced in tadalafil group versus the no treatment group.[27]

**BILIRUBIN**

Protective effects of bilirubin were investigated in an experimental rat model of pyelonephritis. Inflammatory activity was significantly lower in rats treated with antibiotic + bilirubin versus no treatment group both in the early and late periods. MDA levels were significantly lower in the antibiotic + bilirubin versus the no treatment group and SOD activity was significantly higher in the antibiotic and antibiotic + bilirubin groups versus the no treatment group. When used alone, bilirubin may also prevent inflammation (in the late period) and apoptosis.[28]

**CRANBERRY**

Cranberry as a known antioxidant was investigated in one of the studies. One study was done to evaluate the protective effects of cranberry fruit, on infection-induced oxidative renal damage in a rabbit model of vesico-ureteric reflux. This study shows that cranberries have an anti-inflammatory effect through their antioxidant function and might prevent infection-induced oxidative renal damage.[16]

**MELOXICAM AND L-CARNITINE**

One study designed to investigate the involvement of oxidative stress in the pathogenesis of APN and to evaluate the impact of meloxicam and/or L-carnitine in addition to conventional antibiotic treatment. Interstitial fibrosis (*P* = 0.06), chronic inflammation (*P* = 0.536), and tubular atrophy (*P* = 0.094) decreased in group (L-carnitine and meloxicam) compared with the other groups, but there was a statistically significant decrease only in acute inflammation (*P* = 0.015).[29]

**PERFLUORON**

Correlation between oxygen unbalance, development of cell membrane pathology and pyelo inflammatory affection of the kidneys was studied in 67 patients with acute obstructive pyelonephritis complicated by urosepsis. It was found that surgical manipulations are...
accompanied by development of reperfusion syndrome of the affected and contralateral kidney. Use of perfluoron in this situation promotes rapid compensation of gas transport disturbances, stabilization of the equilibrium in the system pro-oxidants-antioxidants, regress of pyelo inflammatory reactions, earlier recovery of functions of a more affected kidney, and anti-ischemic protection of the contralateral organ. Anti-ischemic and membrane-stabilizing actions of perfluoron make this drug adequate for use in patients with complicated renal infection.[30]

**METHYLPREDNISOLONE**

One study was designed to determine if adjunctive oral methylprednisolone (MPD) can prevent the renal scar formation after APN in pediatric patients. In this study, renal scarring was found in 33.3% of children treated with MPD and in 60.0% of those who received placebo ($P = 0.05$). The median cortical defect volumes on follow-up DMSA were 0.0 mL (range: 0–4.5 mL) and 1.5 mL (range: 0–14.8 mL) for the MPD and placebo groups, respectively ($P = 0.01$). Patients in the MPD group experienced faster defervescence after treatment than the placebo group.[31]

### Table 1: Summary of studies of using antioxidants in pyelonephritis

| Antioxidant                  | Type and number of subjects | Route of administration | Dosing                                                                 | Duration of treatment | Effective in reducing oxidative stress | Year of publication | Reference number |
|------------------------------|-----------------------------|-------------------------|-----------------------------------------------------------------------|-----------------------|----------------------------------------|---------------------|------------------|
| Vitamin A                    | Human (children) - 76       | IM                      | 25,000 IU → younger than 1-year-old 50,000 IU → 1 year or higher     | Once                  | Yes                                    | 2011                | [7]              |
| Vitamin A                    | Human (children) - 50       | IM                      | 25,000 IU → younger than 1-year-old 50,000 IU → 1 year or higher     | Once                  | Yes                                    | 2011                | [8]              |
| Vitamin A or Vitamin E       | Human (children) - 61       | PO                      | Vitamin A (1500 IU/kg/day); or Vitamin E (20 IU/day)                  | 10 days               | Yes                                    | 2012                | [9]              |
| Vitamin E or allopurinol     | Rat - 20                    |                         |                                                                       |                       |                                        |                     |                  |
| Vitamin E and Vitamin C      | Rat - 60                    | PO                      | 100 IU of oral Vitamin E on a daily basis, 1 tablet, daily            | 14 days               | No                                     | 2015                | [12]             |
| Cytoflavin                   | Human                       | PO                      |                                                                       |                       |                                        |                     |                  |
| Caffeic acid phenethyl ester | Human                       |                         |                                                                       |                       |                                        |                     |                  |
| Melatonin                    | Rat - 35                    | IP                      | 20 mg/kg, once daily                                                  | 5 days                | Yes                                    | 2006                | [15]             |
| Acetylcysteine               | Mouse                       |                         |                                                                       |                       |                                        |                     |                  |
| Oleuropein                   | Rabbit - 70                 | IV                      |                                                                       |                       |                                        |                     |                  |
| Montelukast                  | Rat - 24                    |                         |                                                                       |                       |                                        |                     |                  |
| Oxytocin                     | Rat - 24                    |                         |                                                                       |                       |                                        |                     |                  |
| Ozone                        | Rat - 40                    | IP                      | 50 mg/kg                                                              | 5 days                | Yes                                    | 2011                | [25]             |
| Pentoxifyllin                | Rat - 32                    | IP                      |                                                                       |                       | Yes                                    | 2003                | [26]             |
| Tadalafil                    | Rat - 32                    | IP                      |                                                                       |                       | Yes                                    | 2014                | [27]             |
| Bilirubin                    | Rat - 32                    | IP                      |                                                                       |                       | Yes                                    | 2012                | [28]             |
| Cranberry fruit or melatonin | Rabbit - 36                 | PO                      |                                                                       |                       | Yes                                    | 2007                | [16]             |
| Meloxicam or L-carnitine     | Rat - 48                    | IM                      | L-carnitine (500 mg/kg, IM)                                           |                       | Yes                                    | 2010                | [29]             |
| Perfluoran                   | Human - 67                  | PO                      | 1.6 mg/kg per day                                                     | 3 days                | Yes                                    | 2004                | [30]             |
| Methylprednisolone           | Human (children) - 84       | PO                      | 0.15 mg/kg, every 6 h                                                 | 3 days                | Yes                                    | 2012                | [31]             |
| Dexamethasone                | Human (children) - 54       | PO                      |                                                                       |                       |                                        | 2008                | [32]             |

IU=International unit, IM=Intramuscularly, IV=Intravenously, IP=Intraperitoneally, PO=Periorally
antibiotic therapy. UIL-6 and UIL-8 concentrations were determined by enzyme immunoassay in 34 children with pyelonephritis, who were treated with ceftriaxone and dexamethasone (case group), and in 20 patients with the same diagnosis treated with ceftriaxone alone (control group). Differences between cytokine/creatinine ratios in initial and follow-up urine samples were significant in the case group \((P < 0.001)\) but not for controls. In addition, combined antibiotic and dexamethasone significantly decreased UIL-6 and UIL-8 concentrations compared with antibiotic alone \((P < 0.05)\).\(^{[32]}\)

A summary of studies of using antioxidants in pyelonephritis is presented in Table 1.

**AUTHORS’ CONTRIBUTION**

Information gathering was done by Allameh, Z. Writing and editing the manuscript was done by Allameh, Z and Salamzadeh, J.

**Acknowledgments**

The authors would like to thank the Shahid Beheshti School of Pharmacy, Tehran, Iran, for valuable assistance in this research, which was a part of the clinical pharmacy specialty program of Dr. Z. Allameh.

**Financial support and sponsorship**

The research project was conducted and sponsored by Shahid Beheshti School of Pharmacy, Tehran, Iran.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Pavlova EL, Lilova MI, Savov VM. Oxidative stress in children with kidney disease. Pediatr Nephrol 2005;20:1599-604.
2. Plotnikov EY, Morosanova MA, Pevzner IB, Zorova LD, Mansikkh VN, Pulkova NV, et al. Protective effect of mitochondria-targeted antioxidants in an acute bacterial infection. Proc Natl Acad Sci U S A 2013;110:E3100-8.
3. Gupta R, Verma I, Sharma S, Ganguly NK. Prevention of tissue injury in an ascending mouse model of chronic pyelonephritis – Role of free radical scavengers. Comp Immunol Microbiol Infect Dis 2004;27:225-34.
4. Mittal R, Sharma S, Chhibber S, Harjai K. Contribution of free radicals to \(Pseudomonas aeruginosa\) induced acute pyelonephritis. Microb Pathog 2008;45:323-30.
5. Bychkovskikh VA, Dolgushin II, Korobeynikova EN. The comparative study of indicators of immunity and state of pro- and antioxidant systems in patients with chronic pyelonephritis of single kidney in active and latent stages of disease. Klin Lab Diagn 2012;5:43-6.
6. Neveus T. Can postpyelonephritic renal scarring be prevented? Pediatr Nephrol 2013;28:187-90.
7. Dalirani R, Yousefi Zoshk M, Sharifian M, Mohkam M, Karimi A, Fahimzad A, et al. Role of Vitamin A in preventing renal scarring after acute pyelonephritis. Iran J Kidney Dis 2011;5:320-3.
8. Ayzei P, Moshiri SA, Mahyar A, Moradi M. The effect of Vitamin A on renal damage following acute pyelonephritis in children. Eur J Pediatr 2011;170:347-50.
9. Sobouti B, Hooman N, Movahed M. The effect of Vitamin E or Vitamin A on the prevention of renal scarring in children with acute pyelonephritis. Pediatr Nephrol 2013;28:277-83.
10. Sadeghi Z, Kajbafzadeh AM, Tajik P, Monajemzadeh M, Payavbshav Elmi A. Vitamin E administration at the onset of fever prevents renal scarring in acute pyelonephritis. Pediatr Nephrol 2008;23:1503-10.
11. Emamghorashi F, Owji SM, Motamedifar M. Evaluation of effectiveness of Vitamins C and E on prevention of renal scar due to pyelonephritis in rat. Adv Urol 2011;2011:489496.
12. Yousefichaijan P, Kahbazi M, Rasti S, Rafeie M, Sharafkhamah M. Vitamin E as adjuvant treatment for urinary tract infection in girls with acute pyelonephritis. Iran J Kidney Dis 2015;9:97-104.
13. Gordiushina IV, Savchenko RP, Sukhanov DS, Petrov AI, Romanssov MG. Antioxidant and membranoprotector treatment of chronic pyelonephritis. Eksp Klin Farmakol 2011;74:27-30.
14. Celik S, Gorur S, Aslanotas O, Erdogan S, Ocak S, Hakverdi S. Caffeic acid phenethyl ester suppresses oxidative stress in \(Escherichia coli\)-induced pyelonephritis in rats. Mol Cell Biochem 2007;297:131-8.
15. Imamoglu M, Ay C, Cobanoglu U, Bahat E, Karahan C, Tosun I, et al. Effects of melatonin on suppression of renal scarring in experimental model of pyelonephritis. Urology 2006;67:1315-9.
16. Han CH, Kim SH, Kang SH, Shin OR, Lee HK, Kim HJ, et al. Protective effects of cranberries on infection-induced oxidative renal damage in a rabbit model of vesico-ureteric reflux. BJU Int 2007;100:1172-5.
17. Ucar F, Taslispinar MY, Alp BF, Aydin I, Aydin FN, Agilli M, et al. The effects of N-acetylcysteine and ozone therapy on oxidative stress and inflammation in acetaminophen-induced nephrotoxicity model. Ren Fail 2013;35:640-7.
18. Talasaz AH, Salamzadeh J, Khalili H, Eshraghi AH, Bahreman M. Evaluating the effect of intracoronary N-acetylcysteine on myocardial reperfusion markers following primary percutaneous coronary intervention in patients with STEMl. Eur Heart J 2013;34 Suppl I:610.
19. Csontos C, Rezman B, Foldi V, Bogar L, Drenkovics L, Röth E, et al. Effect of N-acetylcysteine treatment on oxidative stress and inflammation after severe burn. Burns 2012;38:428-37.
20. Ashworth A, Webb ST. Does the prophylactic administration of N-acetylcysteine prevent acute kidney injury following cardiac surgery? Interact Cardiovasc Thorac Surg 2010;11:303-8.
21. Millea PJ. N-acetylcysteine: Multiple clinical applications. Am Fam Physician 2009;80:265-9.
22. Giamarellos-Bourboulis EJ, Geladopoulos T, Chrisofos M, Koutoukas A, Vassiliadis J, Alexandrou I, et al. Immunomodulatory effects of melatonin in patients with chronic pyelonephritis. Int J Immunopharmacol 2006;26:410-6.
23. Tugtepe H, Sener G, Cetinel S, Velioglu-Ogünç A, Yegen BC. Oxidative renal damage in pyelonephritic rats is ameliorated by montelukast, a selective leukotriene CysLT1 receptor antagonist. Eur J Pharmacol 2007;557:69-75.
24. Biyikli NK, Tugtepe H, Sener G, Velioglu-Ogünç A, Cetinel S,
Midillioglu S, et al. Oxytocin alleviates oxidative renal injury in pyelonephritic rats via a neutrophil-dependent mechanism. Peptides 2006;27:2249-57.

25. Caliskan B, Guven A, Ozler M, Cayci T, Ozcan A, Bedir O, et al. Ozone therapy prevents renal inflammation and fibrosis in a rat model of acute pyelonephritis. Scand J Clin Lab Invest 2011;71:473-80.

26. Yagmurlu A, Boleken ME, Ertoy D, Ozsan M, Gokcora IH, Dindar H. Preventive effect of pentoxifylline on renal scarring in rat model of pyelonephritis. Urology 2003;61:1037-41.

27. Zhu CY, Liu M, Liu YZ, Li W, Zhai W, Che JP, et al. Preventive effect of phosphodiesterase 5 inhibitor tadalafil on experimental post-pyelonephritic renal injury in rats. J Surg Res 2014;186:253-61.

28. Kasap B, Soylu A, Ertoy Baydar D, Kiray M, Tugyay K, Kavukçu S. Protective effects of bilirubin in an experimental rat model of pyelonephritis. Urology 2012;80:1389.e17-22.

29. Gurocak S, Ure I, Cumaoglu A, Gonul II, Sen I, Tan O, et al. Renal tissue damage after experimental pyelonephritis: Role of antioxidants and selective cyclooxygenase-2 inhibitors. Urology 2010;76:508.e1-5.

30. Ushakova ND. Antiischemic efficacy of perfluoroorganic compounds in patients with renal inflammation. Urologia 2004;3:14-8.

31. Huang YY, Chen MJ, Chiu NT, Chou HH, Lin KY, Chiou YY. Adjunctive oral methylprednisolone in pediatric acute pyelonephritis alleviates renal scarring. Pediatrics 2011;128:e496-504.

32. Sharifian M, Anvaripour N, Karimi A, Fahimzad A, Mohkam M, Dalirani R, et al. The role of dexamethasone on decreasing urinary cytokines in children with acute pyelonephritis. Pediatr Nephrol 2008;23:1511-6.