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# Research Article
# Hepatic and Renal Impacts of Lesinurad on Experimental Hyperuricemia: Biochemical, Molecular and Pathological Investigations

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## Abstract

**Background and Objective:** Hyperuricemia is one of the most dangerous threats to human life. It is mainly associated with gout and inflammatory arthritis. Therefore, finding a safe medication that does not have severe side-effects is a goal shared by most physicians. The current study aimed to evaluate the effect of lesinurad (Zurampic; ZUR) and allopurinol (ALP), both alone or in combination, on the treatment of hyperuricemic mice at the biochemical, molecular and cellular levels. **Materials and Methods:** Lesinurad and allopurinol were orally administered to hyperuricemic and control mice for seven consecutive days, either alone or in combination. Levels of uric acid and xanthine oxidase activity, blood urea nitrogen, creatinine, ALT and AST were measured in the serum. The mRNA expression of mouse hepatic guanine deaminase (Gda), purine nucleotide phosphorylase (PNP), renal urate anion transporter-1 (URAT-1) and OAT-1 transporters were examined. The renal tissues were examined using H and E staining and the immunoreactivity technique. **Results:** Lesinurad and allopurinol administration resulted in a significant decrease in serum levels of uric acid, blood urea nitrogen and xanthine oxidase activity reported in hyperuricemic mice. Both partially reversed oxonate-induced alterations in renal mURAT-1 and mOAT-1 expressions, as well as alterations in the immunoreactivity of Bcl2. All showed an increase in renal uric acid secretion and excretion. ALP and ZUT significantly decreased the increase in Gda and PNP expression reported in hyperuricemic mice. The combined administration of ZUR and ALP restored and improved renal function histopathological changes reported in hyperuricemic mice. **Conclusion:** The hypouricemic impact of both lesinurad and allopurinol in the treatment of hyperuricemia in mice was confirmed following hyperuricemia treatment.

Key words: Hyperuricemia, molecular signalling, lesinurad, renal pathology

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Competing Interest: The author has declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

High uric acid (UA) is produced in the final stage of purine metabolism through exogenous and endogenous pools[1]. The exogenous pool comes from the diet[2], while the endogenous pool results from the production of uric acid by the liver, intestines, muscles and other tissues[3]. The exogenous pool of hyperuricemia (HU) is controlled by xanthine oxidase, which oxidizes xanthine into uric acid (UA)[4,5]. UA is mostly (65-75%) secreted through the kidneys by urine and, to a lesser extent (25-35%), through the gastrointestinal tract. UA is the strongest risk factor for cardiovascular disease and metabolic syndrome[4,6]. Hyperuricemia (HU) is known to increase the level of uric acid level in the blood[7], which can lead to gout[8].

HU is mainly associated with alcoholism, a fructose-rich diet, excessive consumption of seafood and meat, the use of diuretics and sometimes genetic factors[9,10]. Advanced gout is associated with the precipitation of monosodium urate crystals in joints and internal organs[11,12]. The precipitation of crystals is associated with neutrophil infiltration and severe gouty arthritis[13]. Until now, the treatment strategy for HU is based on xanthine oxidase inhibitors, including allopurinol (ALP), which remains the first line of gout therapy. ALP stimulates the renal secretion and excretion of UA[12]. Other anti-inflammatory non-steroidal drugs can be used to inhibit cyclooxygenase activity[14]. However, the side-effects and interactions of these medications are severe and can be harmfull to health[15]. Organic drugs with fewer side-effect may have a promising medicinal effect on renal diseases[16].

Hyperuricemia therapeutic strategies have been developed and updated over the last 10 years. Using dietary flavonoids as hypouricemic curative agents and as an alternative therapy, is needed for the safe management of hyperuricemia[17]. However, the use of such herbal hypouricemic agents is not particularly effective due to their cytotoxicity. A new therapeutic agent called Zurampic (ZUR; lesinurad) has therefore been approved as a therapeutic medication for hyperuricemia[18]. In addition, it is advised that ZUR and ALP be used in combination, as both have a beneficial effect on the urate-anion exchanger transporter (URAT1)[19]. URAT1 acts as a urate-specific and organic anion exchanger through trans-membrane proteins in the kidney[20]. It causes an increase in urate filtration and reabsorption in the proximal convoluted tubules[21]. The treatment of hyperuricemia is based on lowering uric acid in the serum through the inhibition of URAT1 and Organic Anion Transporters (OATs) and the enhancement of excretion of uric acid by the kidneys[22]. The current study aimed to examine the anti-hyperuricemic impact of Zurampic on experimental animal models of hyperuricemia, as well as possible interactions at the biochemical, molecular and histopathological levels.

## MATERIALS AND METHODS

**Animals and experimental design:** Animal studies and samples collection were performed in 2019 at the biology department, Turabah University college, Taif University, Saudi Arabia. Wistar albino mice were purchased from the College of Pharmacy, King Abdel-Aziz University, Jeddah, Saudi Arabia. A total of 42 male mice aged eight weeks (weight 30 g) were used for this experiment. Mice were handled manually for seven days before the onset of the experiment to minimize stress. The animals were kept on a 12/12-hrs dark cycle with free access to food and water Seven groups of mice (six mice/group) were used in this study. Group 1, the negative control (CNT), received free access to food and water. Group 2, the positive hyperuricemic group, had Potassium Oxonate (PO) intraperitoneally injected (250 mg $kg^{-1}$ b.wt., daily). The dosages of PO and timings were the same as for Group 1[23]. Group 3 was administered with an oral dose of allopurinol (ALP; 5 mg $kg^{-1}$ b.wt. daily one hour after PO administration) for seven days[18]. Group 4 received lesinurad (Zurampic; ZUR) in a dose of 80 mg $kg^{-1}$ orally based on a previous study[24]. Groups 5 and 6 were injected with PO at 8am, followed by ALP for Group 5 and ZUR for Group 6 one hour later (at 9 am) for seven consecutive days. Group 7 was injected first with PO at 8 am, followed by a combination of ALP and ZUR at 9 am for seven consecutive days. At the end of the experiment, mice were decapitated after overnight fasting and inhalation of dimethyl ether. Blood was taken for serum extraction and then stored at -20°C for biochemical measurements. The kidney and liver tissues were preserved in Qiazol for RNA extraction and gene expression and in 10% formalin for renal histo-pathological studies.

**Blood chemistry:** Kits to examine changes in liver and kidney biomarkers were purchased from the Biodiagnostic Company, Dokki, Giza, Egypt. ALT, AST, xanthine oxidase (XO), uric acid, creatinine and urea were measured colorimetrically, as explained in the instruction manual for each kit, using a Biorad Smart-Tech Spectrophotometer.

Table 1: Primers used for semi-quantitative PCR[23]

| Gene | Product size (bp) | Accession number | Direction | Sequence (5'-3') |
|---|---|---|---|---|
| mOAT-1 | 183 | NM_008766.3 | Sense | GACAGGGTCTCATCCCTAGC |
| (SLC22a6) | | | Antisense | GTCCCTGACACACTGACTGA |
| mOAT-3 | 153 | NM_001164635.1 | Sense | TACAGTTGTCCGTGTCTGCT |
| (SLC22a8) | | | Antisense | CTTCCTCCTTCTTGCCGTTG |
| mURAT-1 | 145 | NM_009203.3 | Sense | GATAGGTTTGGGCGCAGAAG |
| (SLC22A12) | | | Antisense | TCATCATGACACCTGCCACT |
| mGLUT-9 | 153 | NM_001102415.1 | Sense | TTCGGGTCCTCCTTCCTCTA |
| (SLC2a9) | | | Antisense | GGACACAGTCACAGACCAGA |
| mβ-actin | 143 | NM_007393.5 | Sense | CCAGCCTTCCTTCTTGGGTA |
| | | | Antisense | CAATGCCTGGGTACATGGTG |

**RNA extraction and semi-quantitative PCR (RT-PCR):** Total RNA was extracted from the kidney tissues as described earlier. RNA integrity was confirmed using denatured gel. A mixture of 2 µg total RNA and 0.5 ng oligo dT primer (Qiagen Valencia, CA, USA) was incubated in the Bio-Rad T100™ Thermal Cycle at 65°C for 10 min for denaturation. Reverse transcription was carried out using 2 µL of 10X RT-buffer, 2 µL of 10 mM dNTPs and 100 U of Moloney Murine Leukemia Virus (M-MuLV; SibEnzyme, Ak, Novosibirsk, Russia). The mixture was then re-incubated in the Bio-Rad T100™ Thermal Cycler at 37°C for one hour and then at 90°C for 10 min to inactivate the enzyme. PCR was carried out as described earlier[23]. Expression of beta actin mRNA was used as a reference. PCR products were run on 2% agarose (Bio Basic INC. Konrad Cres, Markham Ontario) gel in TE (Tris-EDTA) buffer. The primers used for RT-PCR were shown in Table 1. The gel was stained with ethidium bromide. PCR products were photographed under UV light. The intensities of the bands were quantified using the NIH image program (http://rsb.info.nih.gov/nih-image).

**Histopathology and immunohistochemistry of the kidney:** Histopathological specimens from renal tissue were fixed in 10% buffered neutral formalin, followed by dehydration in alcohols and clearing in xylene. This was followed by embedding and sectioning into 5 µm thickness. Finally, the slides were stained with hematoxylin and eosin (H and E). The slides were checked and photographed for histopathological evaluation using a Nikon Eclipse 80i microscope and a Canon SX620 H 20-megapixel digital camera. Immunohistochemical evaluation was implemented by deparaffinization, before soaking in 2% $H_2O_2$ for 15 m. The peroxidase activity was inhibited by PBS. Non-specific binding sites were blocked using 5% bovine serum albumin. Dilutions of 1:500 Bcl2 antibody (Catalog # sc-56015) were added to the slides and incubated at 4°C overnight. After three washes with PBS, the slides were treated with a biotin-conjugated secondary antibody (1:2000 dilution, cat# sc-2040). After reacting with 3,3-diaminobenzidine tetrahydrochloride, counter staining was done using hematoxylin and the number of positively stained cells was compared to the total number of cells to determine how many were immunoreactive for Bcl2[25]. Significance was determined using ANOVA for three different samples per each group.

**Statistical analysis:** The data are described as means with SEM. The SAS (Statistical Analysis System) was used to perform a one-way analysis of variance (ANOVA). Tukey's *post hoc* test was used to ascertain statistical differences between experimental groups. The *p<0.05 was set statistically significant.

## RESULTS

**Effect of zurampic on experimental hyperuricemia-induced mice:** The results listed in Hyperuricemia altered m levels of LT, ST, XOD, creatinine and urea was shown in Table 2. The administration of ALP or ZUR, either alone or in combination, showed an ameliorative effect on the altered levels.

**Ameliorative impacts of ZUR and/or ALP on the changes on hepatic genes associated with uric acid metabolism:** The induction of hyperuricemia induced an increase in the mRNA levels of guanidine deaminase (Gda) and purine nucleotide phosphorylase (PNP), as shown in Fig. 1 and 2. The administration of ALP or ZUR both alone or in combination showed a significant ameliorative effect and normalized the changes in the mRNA expression of both Gda and PNP genes.

Table 2: Effect of ALP and/or zurampic on hepatic and renal biomarkers altered during hyperuricemia in mice

| Items | ALT (U L$^{-1}$) | AST (U L$^{-1}$) | Uric acid (mg dL$^{-1}$) | XOD (U L$^{-1}$) | Creatinine (mg dL$^{-1}$) | Urea (mg dL$^{-1}$) |
|---|---|---|---|---|---|---|
| Control | 28.4±0.2 | 32.0±1.3 | 5.1±0.2 | 13.4±1.5 | 0.50±0.06 | 25.9±1.3 |
| Hyperuricemia (HU) | 52.0±1.6* | 59.6±3.1* | 13.2±0.9* | 47.0±2.9* | 1.30±0.09* | 39.0±2.4* |
| Allopurinol (ALP) | 35.0±2.3 | 31.0±2.1 | 6.5±0.3 | 12.9±1.2 | 0.40±0.04 | 22.0±1.1 |
| Zurampic (ZUR) | 31.4±1.5 | 33.2±1.5 | 6.1±0.21 | 15.8±2.1 | 0.60±0.1 | 24.0±1.3 |
| HU+ALP | 35.3±1.7$^{\#}$ | 37.0±2.9$^{\#}$ | 8.1±0.41$^{\#}$ | 18.3±1.54$^{\#}$ | 0.70±0.1$^{\#}$ | 26.0±1.8$^{\#}$ |
| HU+ZU | 34.5±1.6$^{\#}$ | 39.4±2.6$^{\#}$ | 6.9±0.21$^{\#}$ | 18.4±1.01$^{\#}$ | 0.81±0.14$^{\#}$ | 28.0±2.3$^{\#}$ |
| HU+ALP+ZU | 29.5±1.1$^{\$}$ | 31.4±2.6$^{\$}$ | 5.9±0.3$^{\$}$ | 14.4±1.2$^{\$}$ | 0.56±0.14$^{\$}$ | 24.0±2.3$^{\$}$ |

Values are Means±SE for six mice per each treatment. *p<0.05 vs. control, $^{\#}$p<0.05 vs. HU group, $^{\$}$p<0.05 vs all treated groups (HU, ALP, ZU and ZU groups)

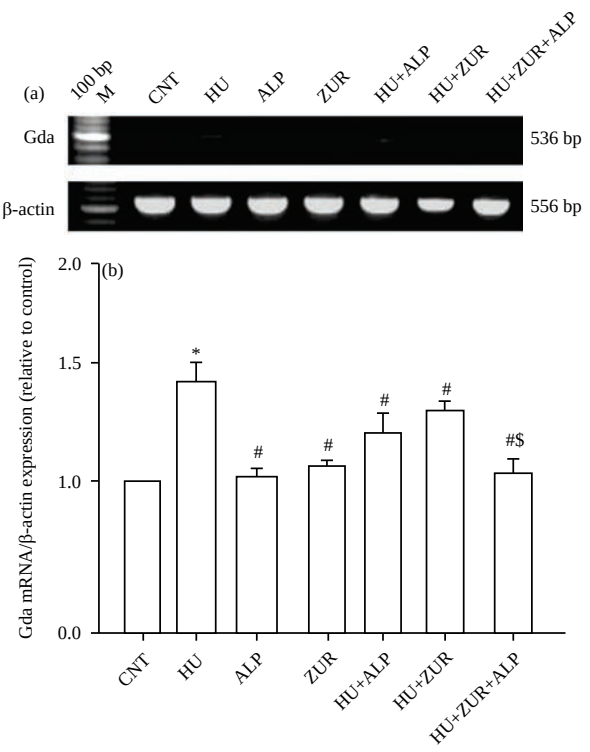


Fig. 1(a-b): Effect of ZUR on changes in hepatic Gda-1 expression in hyperuricemic mice

Total RNA was extracted from liver tissue and the expressions of Gda-1 were analyzed using semi-quantitative RT-PCR analysis. Values are Means±SE of 5 different mice (*p<0.05 vs. control group, $^{\#}$p<0.05 vs. HUR group and $^{\$}$p<0.05 vs. either HU+ALP or HU+ZUR groups). Upper panels (a) show the mRNA expression of examined genes. The lower columns (b) show the densitometric analysis of Gda-1 expression stated in the upper panels

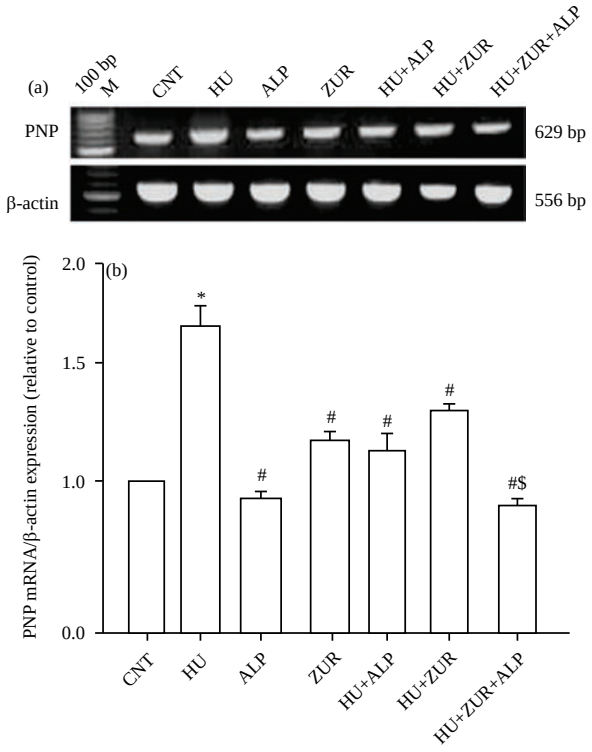


Fig. 2(a-b): Effect of ZUR on changes in hepatic PNP expression in hyperuricemic mice

Total RNA was extracted from liver tissues and the expressions of PNP were analyzed using semi-quantitative RT-PCR analysis. Values are Mean±SE of 5 different mice. *p<0.05 vs. control group, $^{\#}$p<0.05 vs. HUR group and $^{\$}$p<0.05 vs either HU+ALP or HU+ZUR groups. Upper panels (a) are mRNA expression of examined genes. Lower columns (b) are densitometric analysis of PNP-1 expression stated in the upper panels

**Ameliorative impacts of ZUR and or ALP on the changes on renal genes associated with uric acid transport:** Induction of hyperuricemia induced an increase in the mRNA levels of urate transporters (URAT-1), as shown in Fig. 3. The administration of ALP or ZUR, either alone or in combination, showed a significant ameliorative effect and normalized the changes in the mRNA expression URAT-1 gene. Unlike URAT-1, OAT-1 induced a decrease in its mRNA expression levels, as seen in Fig. 4. ALP or ZUR administration either alone or in combination showed a significant normalization effect and normalized the decrease in the mRNA expression of OAT-1.

**Histopathological examination:** Kidneys of the normal untreated group showed a normal histological appearance of the renal tissue, with normal cortical and medullary architecture (Fig. 5a). Kidneys of the potassium oxonate (PO)-administered group showed moderate periglomerular gene and peritubular round cell aggregations, with the

Table 3: Immunochemical scoring and intensity of Bcl2 in tissue sections of kidneys of the treated groups

| Immunohistochemical scoring of Bcl2 | CNT | PO | ALP | ZUR | PO+ALP | PO+ZUR | PO+ALP+ZUR |
|---|---|---|---|---|---|---|---|
| | 0 | 4 | 0 | 0 | 0 | 0 | 0 |
| Staining intensity | - | +++ | - | - | - | - | - |

Score 1: No expression, no positive stained cells for each of three high-power fields (HPF), at 40× magnification. Score 2: Weak, 1-10 positive stained cells/HPF), Score 3: Moderate, 11-20 positive stained cells/HPF), Score 4: Strong, >20 positive stained cells/HPF

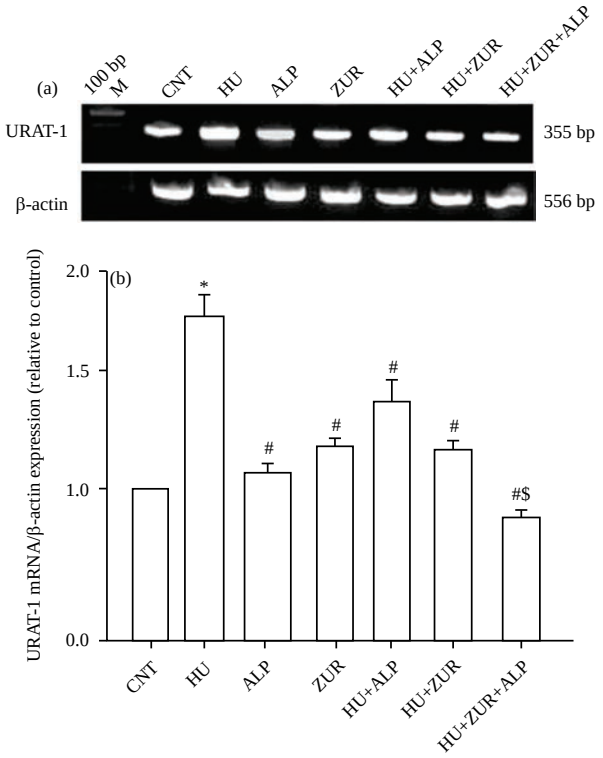


Fig. 3(a-b): Effect of ZUR on changes in renal URAT-1 expression in hyperuricemic mice

Total RNA was extracted from renal tissues and the expressions of URAT-1 were analyzed using semi-quantitative RT-PCR analysis. Values are Mean±SE of five different mice (*p<0.05 vs. control group, #p<0.05 vs. HUR group and $p<0.05 vs either HU+ALP or HU+ZUR groups). The upper panels (a) are the mRNA expression of examined genes. The lower columns (b) are the densitometric analysis of URAT-1 expression stated in the upper panels

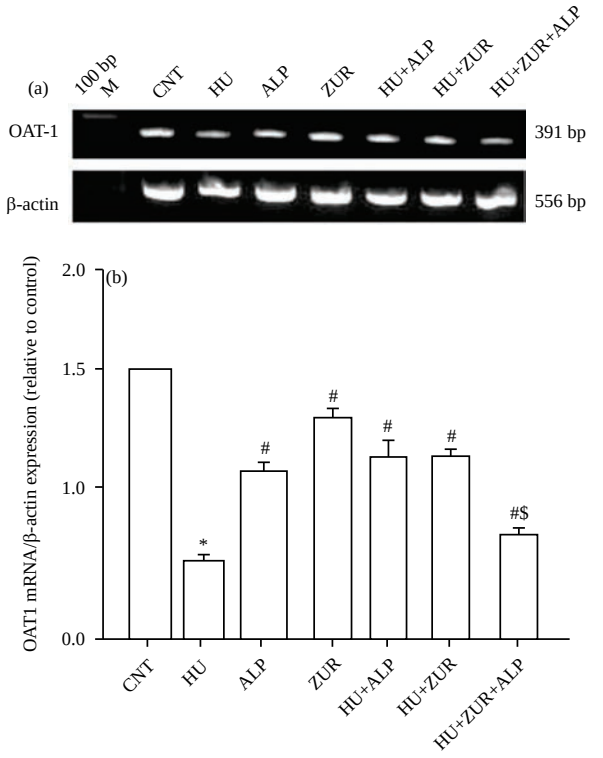


Fig. 4(a-b): Effect of ZUR on changes in renal OAT-1 expression in hyperuricemic mice

Total RNA was extracted from renal tissues and the expressions of OAT-1 were analyzed using semi-quantitative RT-PCR analysis. The values are Means±SE of five different mice (*p<0.05 vs. control group, #p<0.05 vs. HUR group and $p<0.05 vs. either HU+ALP or HU+ZUR groups). Upper panels (a) are mRNA expression of the examined genes. The lower columns (b) are the densitometric analysis of OAT-1 expression stated in the upper panels

presence of obstructive urate crystals inside the tubular lumina (Fig. 5b). Kidneys of the allopurinol group showed normal glomerular and tubular architecture (Fig. 5c). Kidneys of the Zurampic group showed only mild periglomerular round cell aggregation (Fig. 5d). Kidneys of the PO and allopurinol group showed a moderate improvement of the tubular lumina (Fig. 5e). Kidneys of the PO and zurampic group showed improvement of the tubular lumina with glomerular infiltration of round cells (Fig. 5f). Kidneys of the PO, Zurampic and allopurinol group showed restoration of normal tissue structure (Fig. 5g).

**Immunohistochemical examination of Bcl2:** Renal tissue of the control group showed no expression of Bcl2 in the renal cortex and medulla (Fig. 6a). Kidneys of the potassium oxonate group showed a marked expression of Bcl2 in the renal tubular tissue (Fig. 6b). Kidneys of the allopurinol group showed no obvious expression of Bcl2 in the renal tissue (Fig. 6c). Kidneys of the Zurampic-administered mice showed an absence of expression of Bcl2 in the renal tubular tissue (Fig. 6d). Kidneys of the PO and allopurinol group showed a lack of Bcl2 expression in tubular tissue (Fig. 6e). Kidneys of the PO group treated with zurampic alone showed no marked expression for Bcl2 in renal tissue (Fig. 6f). Kidneys of the PO group treated with both Zurampic and allopurinol showed restoration of normal architecture without Bcl2 reactivity in the renal tissue (Fig. 6g). Immunochemical scoring was recorded in Table 3.

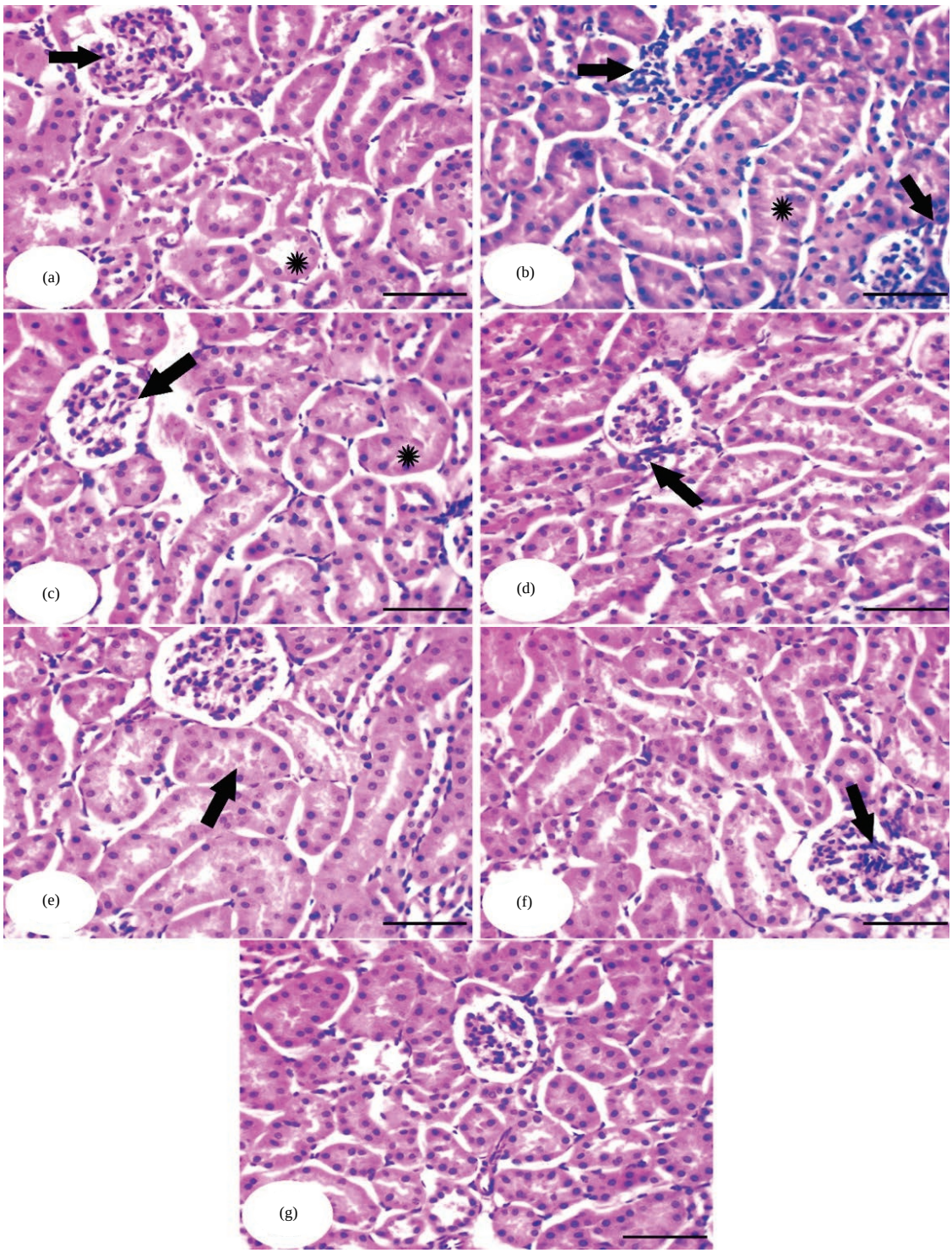


Fig. 5(a-g): Results of the histopathological examination

(a) A control group kidney showing normal glomeruli (arrow) and tubules (*). (b) A kidney from the PO group showing periglomerular round cell infiltration (arrow) with intraluminal urate crystals (*). (c) A kidney of the allopurinol group showing normal glomerular architecture (arrow) and tubular histology (*). (d) A kidney Zurampic group showing mild periglomerular infiltration of round cells (arrow). (e) Kidney of the PO and allopurinol group showing moderate intraluminal urate crystals (arrow). (f) Kidneys of the PO and Zurampic group showing increased infiltration of round cells in the renal glomeruli (arrow) and (g) Kidneys of the PO group treated with Zurampic and allopurinol showed restoration of glomerular and tubular tissue architecture. H and E. Scale bar = 50 μm

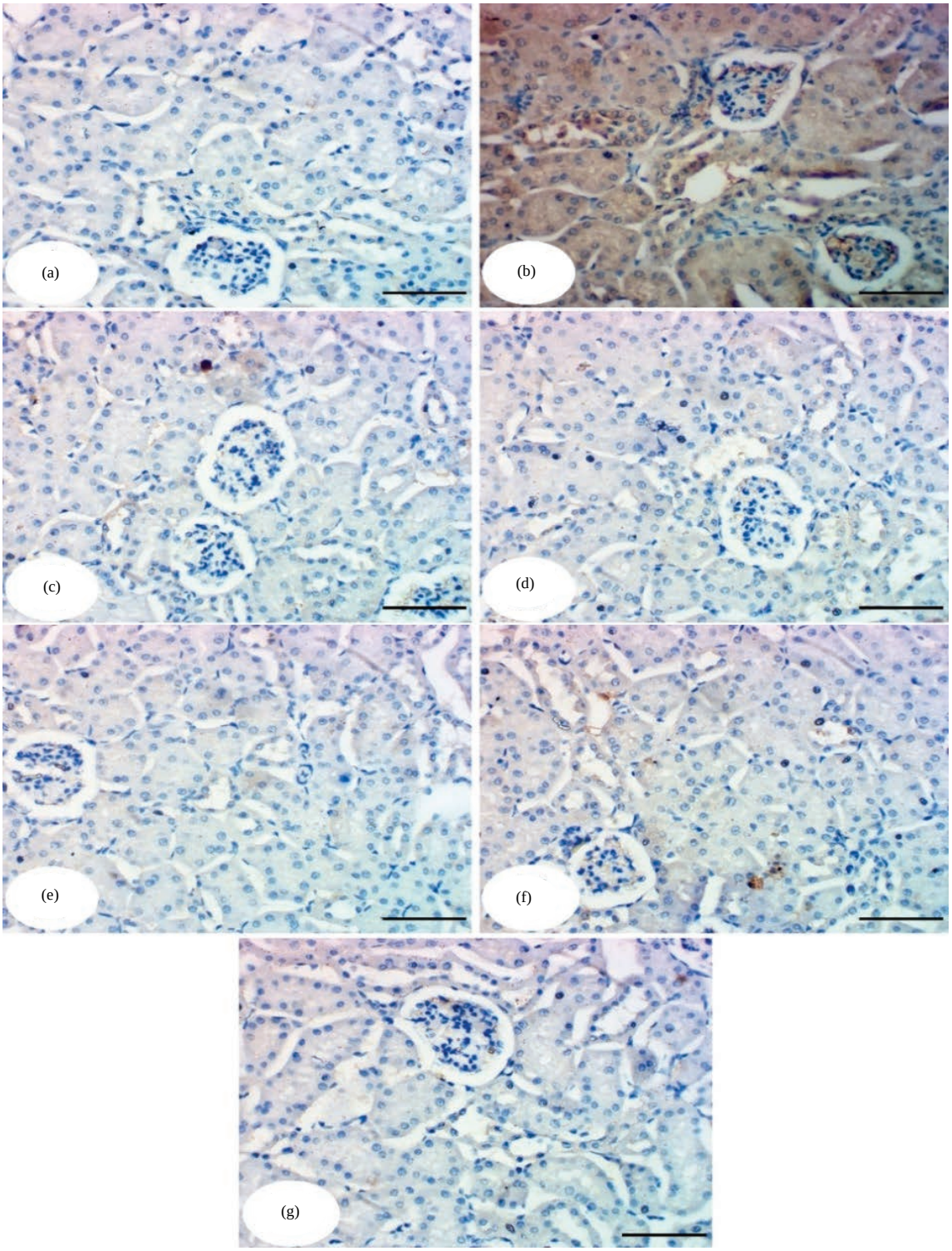


Fig. 6(a-g): Results of the immunohistochemical examination of Bcl2

(a) A kidney from the control group showing no expression of Bcl2 in the renal tissue, (b) A kidney from the PO group revealed a marked expression of Bcl2 in the renal tubular tissue, (c) A kidney of the allopurinol group showed a lack of expression of Bcl2 in the renal parenchyma, (d) A kidney of Zurampic group showed no obvious expression of Bcl2 in the renal tubular tissue, (e) Kidney of the PO and allopurinol group showed an absence of Bcl2 expression in the tubular tissue, (f) Kidney of the PO and zurampic group showed no detected reactivity for Bcl2 in renal tissue and (g) Kidney of the PO group treated with zurampic and allopurinol showed a lack of both glomerular and tubular Bcl2 expression. Scale bar = 50 µm

## DISCUSSION

The findings confirm that ZUR and ALP, either alone or in combination, have a hypouricemic effect on renal and hepatic tissues affected by PO. PO induced an alteration in liver and kidney biomarkers and an increase in serum uric acid, which was normalized by ZUR and ALP administration.

Hyperuricemia is associated with a general state of inflammation in soft tissues in both the kidney and liver[14]. It is noteworthy that this inflammation is controlled by ZUR and ALP administration; more effects were reported in the combination group that received both ZUR and ALP. These findings have also been confirmed in other studies using other models[26]. The use of xanthine oxidase inhibitors has some side-effects, such as skin rashes and gastrointestinal distress[26]. Therefore, finding a safe combined medication would have the benefit of reducing the incidence of such side-effects. This study used lesinurad, a promising hypouricemic medication that acts as an uricosuric drug. A recently published paperstated that uricosuric drugs, such as lesinurad, can be safely administered in association with xanthine oxidase inhibitors (ALP), offering promising options for the treatment of refractory hyperuricemia[27].

Several chronic conditions act as predisposing factors for hyperuricemia and consequently gout, namely cardiovascular disorders, chronic kidney disease, hypertension, diabetes, obesity and atherosclerosis[28]. Hyperuricemia is mostly associated with an increase in the production of free radicals, oxidative stress and up-regulation in the levels of some mediators[14,29]. This reflects the findings of the current study, in which oxidative stress was confirmed in the altered liver and kidney biomarkers. Therefore, ALP and ZUR inhibited the overproduction of uric acid levels and decreased hepatic and renal oxidative stress[30].

Kidney inflammation occurs due to the high level of uric acid in the blood[31]. This leads to precipitation in soft tissues such as the kidney, causing it to work improperly. This may cause renal failure and lead to changes in the levels of proinflammatory cytokines[32,33]. A recent study found that the use of ALP or ZUR alone failed to reduce levels of IL-1β and TNF-α in hyperuricemic mice, whilst the co-administration of ALP and ZUR exerted a potent anti-inflammatory effect to prevent the development of gout from HU[23].

Guanine deaminase (Gda) is an enzyme that converts adenine and guanine into hypoxanthine and xanthine. Gda plays an important role in the purine degradation pathway and lowers the purine content in a beverage[34]. In the current study, HU upregulated mRNA of Gda and the administration of ZUR and ALP had an ameliorative effect on controlling uric acid metabolism by inhibiting the synthesis of xanthine, with a decrease in Gda expression. Similarly, the inhibition of Purine Nucleoside Phosphorylase (PNP) represents a different strategy for lowering urate and plays a key role in the treatment of hyperuricemia[35]. The upstream reduction of purine catabolism and oxypurine production through the inhibition of PNP appears to be an appropriate approach for handling hyperuricemic patients.

There has previously been uncertainty about how the exact mechanism induced by lesinurad in the treatment of hyperuricemia works. It may interact with urate transporters, including URAT-1 and OAT-1. Transporters play an important role in the pharmacology of xenobiotics, such as purine metabolism. OAT proteins maintain kidney homeostasis by acting as urate efflux transporters and regulate urate secretion and excretion[36]. This study confirmed that lesinurad interacted through the regulation of OAT-1 and URAT-1 expression. Both proteins are the main transporters that control uric acid levels in the blood and urate secretions in the kidney. It should be noted that a synergistic effect was reported when both lesinurad and allopurinol were co-administered (Fig. 1-4).

## CONCLUSION

The current study confirmed that the co-administration of allopurinol and lesinurad had the potential to normalize serum uric acid levels; it showed a synergistic effect in decreasing xanthine oxidase activity and returning liver and kidney biomarkers to within normal levels. Furthermore, allopurinol and lesinurad co-administration synergistically down-regulated the mRNA expression of URAT1 and up-regulated OAT1 mRNA expression in an experimental model of hyperuricemia in mice. Both allopurinol and lesinurad synergistically improved kidney histology and reduced the Bcl2 immunoreactivity reported in renal tissues. In summary, it would be beneficial to receive a combined therapy of allopurinol and lesinurad for hyperuricemia treatment, as both have beneficial impacts on the liver and kidneys at the biochemical, molecular and cellular level.

## SIGNIFICANCE STATEMENT

This study is designed to assess the potential role of Lesinurad (Zurampic; ZUR) therapeutic which can normalize serum uric acid levels for patients with gout and inflammatory bowel diseases. These findings will help the researcher to uncover the critical areas of the regulation of genes associated with uric acid metabolism in liver and kidney. Thus, a new theory on controlling Hyperuricemia may developed.

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