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Tannic acid nanoparticles improve the renal histological structure and kidney function in arsenic trioxide-induced renal damage

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ABSTRACT

There has been a lot of interest in antioxidant chemicals, especially those that come from natural sources like tannins and polyphenols. In this regard, nanomedicine has helped to uncover novel ways to administer and protect antioxidants. This study looked at the potential benefits and processes of polyphenol-based nanoparticles, particularly tannic acid nanoparticles (TANPs), on oxidative stress brought on by arsenic trioxide (ASO), which has been connected to kidney injury in rats. Over the course of 30 days, rats were given intraperitoneal injections of TANPs and ASO (4 mg/kg body weight daily). Light microscopy was used to evaluate changes in renal morphology. Serum urea and creatinine concentrations were measured. The findings showed that exposure to ASO had a significant impact on these serum nephritic markers. On the other hand, these changes were lessened by TANP pretreatment. A histological evaluation also validated the biochemical results. Overall, the findings suggested that TANPs' ability to prevent ASO-induced nephrotoxicity may be related to their ability to lower ROS-mediated apoptosis. These findings may aid in the creation of novel treatment strategies aimed at stopping the progression of renal cell injury.

1. INTRODUCTION

One major environmental contaminant that has a negative impact on human health worldwide is arsenic, a naturally occurring metalloid. Numerous anthropogenic and natural mechanisms contribute to the ecological presence of arsenic. Numerous health problems, including diabetes, kidney cancer, skin disorders, and several other types of cancer, have been linked to arsenic exposure (Chen et al., 2012). Arsenic has been widely used since 400 B.C. to treat a variety of illnesses and has recently shown promise as a cancer treatment agent (Waxman et al., 2001). Trivalent arsenite and pentavalent arsenate are its two primary oxidative states. Studies have demonstrated that arsenic trioxide (ASO) exerts strong anticancer activity, particularly in acute promyelocytic leukemia (Soignet et al., 1998). However, it has also been reported to cause renal damage in both experimental models and patients (Sasaki et al., 2007; Shen et al., 2025). According to Jin et al. (2020), prolonged exposure to arsenic causes the body to produce large amounts of reactive oxygen species (ROS), which oxidatively damage DNA, induce several diseases, and finally cause cell death. Organic antioxidants have been recognized as potential therapeutic agents for oxidative stress-related disorders. Phytochemicals, in particular, have gained attention due to their beneficial effects on human health (Pandey & Rizvi, 2009; Lobo et al., 2010). However, despite evidence that antioxidant supplementation can alleviate oxidative stress-associated diseases, their clinical application remains limited by issues such as low bioavailability, poor solubility, and instability (Xiao & Högger, 2015; Szymańska et al., 2017). Novel approaches to antioxidant delivery have been made possible by recent developments in nanomedicine (Pucci et al., 2022). Many plants, fruits, grains, red wine, and green tea contain tannic acid (TA), a water-soluble polyphenolic compound (Fu et al., 2019; Abouelmagd et al., 2019). According to in vivo studies conducted on both humans and animals, the absorption rates of polyphenols such as tannic acid (TA) can vary significantly. This variability is likely attributed to differences in the chemical composition of polyphenolic compounds as well as the specific experimental conditions employed (Smith et al., 2021). About 85% of the TA that rats ingested disappeared from their intestines (Tak and Firestein, 2001), indicating that most of the TA was broken down in the large intestine and either absorbed as gallic acid or underwent further degradation (Jin et al., 2020).

TA has a variety of biological features, including antiapoptotic (Nie et al., 2016), antioxidant (Wu et al., 2019), antiinflammatory (Soyocak et al., 2019), and anticancer (Ren et al., 2019) effects. Additionally, it was discovered that tannic acid inhibits lipid oxidation by scavenging free radicals (Jin et al., 2020). Therefore, the present study aims to utilize the freshly synthesized tannic acid nanoparticles (TANPs) as a defense against ASO-induced nephrotoxicity.

The biochemical and pathological alterations will be assessed using an ASO-induced nephrotoxicity model to investigate the nephroprotective benefits of TANPs. Additionally, by evaluating the associated nephrotoxic effects, the possible mechanisms by which TANPs influence nephrotoxicity will be investigated.

2. MATERIAL AND METHODS

Ethical approval

The experimental setup and techniques were approved by the Shanghai Jiaotong University Institutional Animal Care and Use Committee and adhered to the National Institutes of

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Health Guide for the Care and Use of Laboratory Animals. The study was approved by the Ethical Committee of Research at Banha University of Egypt, Faculty of Veterinary Medicine (approval no: BUFVTM 23-11-23).

2.1. Chemicals

Arsenic trioxide was purchased from Beijing Shuanglu Pharmaceutical Co., Ltd., while tannic acid was acquired from Sigma Aldrich Trading Co., Ltd., Sigma Chemical Co. (St. Louis, MO, USA), the supplier of all other analytical-grade chemical reagents.

2.2. Synthesis of Tannic Acid Nanoparticles (TANPs)

Polyvinyl alcohol/tannic acid hydrogel nanoparticles were created by employing gamma radiation to promote the polymerization of tannic acid in an aqueous solution of polyvinyl alcohol (PVA) as a template polymer. γ-rays were applied to PVA/tannic acid mixtures of different compositions that were dissolved in deionized water. The irradiation process was carried out at 35° C in an air environment. According to Alkan et al. (2012), γ-radiated polymerization was used to create the polyvinyl alcohol-tannic acid (PVA-Tannic acid) nanogel. This polymerization occurs in an aqueous solution in a glass test tube when exposed to γ-rays from a 60Co source that has a temperature control mechanism inside. The suspensions of colloidal nanogel were ultracentrifuged (SORVALL® ULTRA 80, USA) at 20,000 rpm for 30 minutes at 4°C to determine the yield of nanoparticles. Aggregated nanogels and supernatants were collected and lyophilized in order to ascertain the weight of the polymers that created the nanogels. According to Lau and Mi (2002), the mass ratio of the polymers that formed the nanogel was divided by the mass ratio of the polymer and monomer to calculate the production yields.

2.3. Characterization of PVA-Tannic acid

2.3.1. Particle size analysis

The properties of PVA-Tannic acid (TANPs) nano dispersions were characterized by DLS to give the size of each preparation. DLS analysis displayed that the mean size of the nanoparticles was about 30.99 nm. Also, the polydispersity index (PDI) is 0.238, which confirms the uniform distribution of particles (Fig. 1A).

2.3.2. The surface zeta potential

The long-term stability of PVA-tannic acid and particle surface charge were assessed using a zeta potential analysis (Shabanzadeh et al., 2015). The optimized TANPs' zeta potential measurement, as shown in Fig. 1B, was −27.36 mV with a conductivity of 200µS. It has been observed that nanoparticles with zeta potentials of higher than >20 mV or less than −20 mV stay stable in solution, but those with zeta potentials of −10 and +10 mV are roughly neutral.

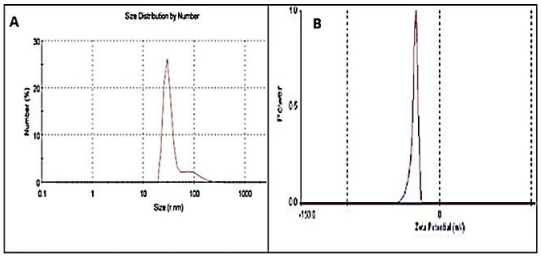

Fig. (1). Characterization of TANPs. (A): DLS analysis of TANPs' size distribution, (B) Zeta potential of TANPs.

2.4. Experimental design

The Nile Company provided male Wister rats weighing 120±10 g at four weeks of age for pharmaceutical use. Rats were housed in cages made of polypropylene and stainless steel, which provided proper ventilation, a 12-hour light/dark cycle, regulated temperatures (between 25 and 28 °C), and humidity levels below 55%. The rats were fed a pellet meal and had unrestricted access to water. rats were randomly allocated into four experimental groups (n = 10 per group), aiming to assess the nephroprotective effects of tannic acid (TA) against arsenic trioxide (ATO)-induced renal injury (Jin et al., 2020), as follows:

Control group: received oral normal saline, serving as a healthy baseline

TANPs group (TANPs): administered TANPs intraperitoneally (i.p.) three times a week for two weeks, in accordance with the dose LD50 (2 mg/kg).

ASO group (ASO): were given ASO i.p. daily for a month (4 mg/kg).

ASO + TANPs group (ASO+TANPs): received ASO (4 mg/kg) intraperitoneally (i.p.) every day for a month. After the third week of TANPs injection, the rats received ASO (2 mg/kg) intraperitoneally for two weeks.

The rats were put to sleep with urethane at the end of the experiment. Blood was collected from the abdominal aorta, centrifuged for 10 minutes to harvest the serum, that kept at -20 °C for further examinations.

2.5. Histopathological analysis

After being fixed in 10% formalin solution, kidney tissue specimens were cut off, dehydrated in increasing alcohol grades, and cleared in xylol. Following xylene clearing. The specimens were embedded in paraffin wax, and paraffin blocks were sectioned at a thickness of 4-6 µm. For histological evaluation, hematoxylin and eosin (H&E) staining was carried out according to Bancroft et al. (2013). Using a light digital microscope (Olympus XC30, Tokyo, Japan), prepared slide sections were inspected. A system of grading from 0 to 3 was employed, where 0 denoted normal histological structure, 1 indicated kidney injury in less than 25% of tissue, 2 indicated kidney damage in 25% to 50% of tissue, and 3 indicated kidney damage in ~50% of tissue. Pathological characteristics employed in this assessment included renal tubule degeneration and necrosis, glomerular congestion, glomerular hypercellularity, infiltration of interstitial inflammatory cells, interstitial oedema, and interstitial hemorrhage (Altınkaynak et al., 2018).

2.6. Biochemical Analysis

Urea and creatinine concentrations were spectro-photometrically determined following the procedures stated before (Kaplan, 1984; Schirmeister et al., 1984). They were measured by an automatic analyzer using a commercial kit supplied by Diamond Diagnostics, Cairo, Egypt.

2.7. Statistical analysis

The data were statistically analyzed using SPSS 20 software program (Analytical Software, USA) with one-way ANOVA and Bonferroni multiple comparison test. The significance level was set at $p<0.05$.

3. RESULTS

3.1. Effects of TANPs on serum Urea and Creatinine

To evaluate alterations in kidney function, serum levels of creatinine and urea were measured (Fig. 2). When compared to the control group, in the ASO group, urea and creatinine levels were significantly higher ($P < 0.01$), but in the TNPs + ASO group's serum urea and creatinine levels were significantly lower after TANP therapy ($P < 0.01$).

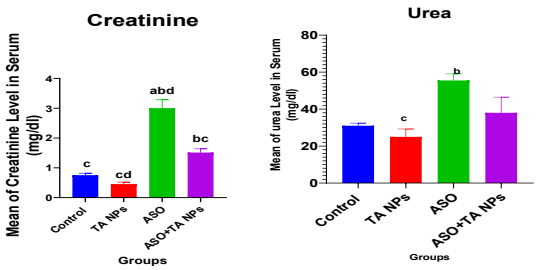

Fig. (2). Effects of TANPs on urea and creatinine levels in serum. Values are expressed as mean ± SE. [a] P < 0.01 compared to the control group; [b] P < 0.01 compared to the TANPs group; [c] P< 0.01 compared to the ASO group; [d] P<0.01 compared to the ASO+TANPs group.

3.2. Effect of TANPs on kidney histopathology

The histopathological scoring of kidney damage was assessed in different animal groups (Table 1). Kidney tissue sections of the normal control and TANPs groups showed normal histological structure characterized by glomeruli with normal structure of capillary tufts and Bowman's capsule. The renal tubules of both proximal and distal convoluted tubules revealed a normal arrangement and an intact epithelium without any signs of kidney injury (Fig. 2A & B). ASO kidney sections revealed tubular epithelial cell degeneration with tubular lumen blockage by eosinophilic albuminous deposits. Interstitial oedema, peri-tubular capillary congestion, and necrosis of tubular epithelial cells were seen. Numerous mononuclear cells, primarily macrophages and lymphocytes, were seen infiltrating the renal tissue. Capillary tuft congestion, glomerular Bowman's capsule thickening, and pericapsular leukocytic infiltration are found (Fig. 2C). Significant recovery was seen in the kidney tissue section of the ASO + TANPs group, with minor histological alterations evidenced by swelling of the tubular epithelium and a few intra-tubular eosinophilic albuminous casts without noticeable necrosis. Interstitial edema and mild glomerular tuft congestion with absence of inflammatory cell infiltration were seen (Fig. 2D).

Table 1 Histopathological scoring of the kidney tissue samples

Histopathological changes	Control	TANPs	ASO	ASO+TANPs
Glomerular congestion	0	0	2	1
Inflammatory cell infiltration	0	0	3	0
Interstitial edema	0	0	2	0
Tubular degeneration	0	0	3	1
Tubular necrosis	0	0	2	0
Tubular casts	0	0	2	1

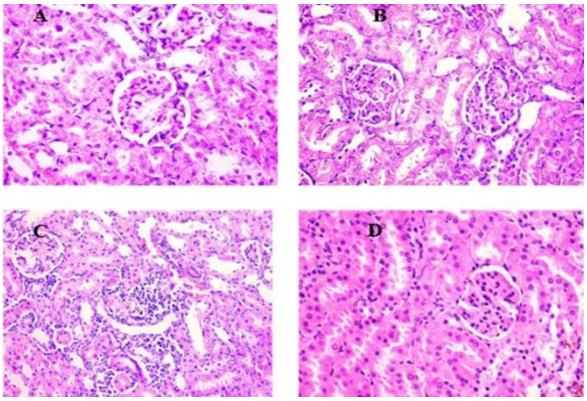

Fig. (3). The histopathological findings in (A) Control group, (B) TANPs group, (C) ASO group, (D) ASO + TANPs group. H&E stain X200. A & B- Kidney tissue sections of control and TANPs groups showing typical histological structure glomeruli with intact epithelial lining of proximal and distal convoluted tubules. C- ASO group showing degeneration of tubular epithelial cells, and congestion of peri-tubular capillaries with mononuclear cells infiltration. D- Kidney tissue section of the ASO +TANPs group revealing pronounced improvement, appearing as mild histological changes, swelling of the tubular epithelial lining with a few numbers of intra-tubular eosinophilic debris without significant necrosis or apoptosis.

4. DISCUSSION

Arsenic exposure—particularly through contaminated water and occupational sources—is a significant risk factor for kidney damage and chronic kidney disease (CKD). Its nephrotoxic effects are mediated via oxidative stress, mitochondrial dysfunction, inflammatory signaling, disrupted cellular energy metabolism, and epigenetic alterations. These discussion findings connecting arsenic to renal injury and highlight mechanistic insights with implications for disease progression and prevention

Arsenic trioxide (As_2O_3) is widely recognized for its therapeutic efficacy in acute promyelocytic leukemia; however, its clinical application is limited due to severe nephrotoxic effects. The nephrotoxicity of As_2O_3 is primarily mediated through oxidative stress, mitochondrial dysfunction, and the activation of inflammatory pathways such as NF-κB. Studies have demonstrated that arsenic exposure elevates reactive oxygen species (ROS) and decreases endogenous antioxidant defenses, leading to renal tubular epithelial injury, necrosis, and impaired kidney function (Flora, 2011; Shen et al., 2013). Moreover, As_2O_3 can promote apoptotic and autophagic cell death, further aggravating renal damage (Wang et al., 2021).

Tannic acid (TA), a naturally occurring polyphenol, has shown promising nephroprotective effects against As_2O_3-induced renal toxicity. Experimental evidence indicates that TA supplementation alleviates oxidative stress, reduces lipid peroxidation, and enhances antioxidant enzyme activity, thereby restoring cellular redox balance (Yadav et al., 2016; Rezaei et al., 2022). Additionally, TA modulates molecular signaling by suppressing NF-κB activation and upregulating the Nrf2/Keap1 pathway, resulting in decreased inflammation and improved renal histopathology (Khan et al., 2020; Guo et al., 2020). Furthermore, TA regulates apoptotic pathways by downregulating pro-apoptotic proteins such as Bax and p53 while enhancing anti-apoptotic markers like Bcl-2, ultimately protecting renal tubular cells from arsenic-induced apoptosis (Khan et al., 2020). Collectively, these findings suggest that tannic acid may serve as a potential therapeutic adjunct to mitigate arsenic-induced nephrotoxicity.

Oxidative stress has been implicated in the pathogenesis of various diseases, including kidney injury induced by arsenic trioxide (ASO). Consequently, antioxidant compounds have attracted considerable attention, particularly those derived from natural sources such as tannins and polyphenols (Yadav et al., 2016; Rezaei et al., 2022). However, the main limitations of conventional antioxidants lie in their susceptibility to oxidation, low bioavailability, and rapid enzymatic degradation in biological fluids (Boots et al., 2008; Chiva-Blanch & Badimon, 2014). To overcome these drawbacks, nanomedicine has offered novel strategies for improving the delivery and stability of antioxidants. The present study formulated tannic acid nanoparticles (TANPs), which exhibited an average nano size of 30.99 nm and a negative ζ-potential of −27.36 mV, ensuring colloidal stability and preventing particle destabilization or aggregation. A secondary objective of this work was to investigate the protective effect of TANPs against ASO-induced renal impairment. Although ASO is an effective anticancer agent, its clinical application is severely restricted due to hepatotoxicity, cardiotoxicity, and nephrotoxicity (Vineetha & Raghu, 2019).

Histopathological examination in the current study revealed that TANP administration alleviated ASO-induced renal damage, including necrosis, tubular epithelial edema, and inflammatory cell infiltration. These findings indicate that

TANPs may mitigate injury to renal tubular epithelial cells. Moreover, consistent with earlier reports, rats exposed to ASO demonstrated significant elevations in serum creatinine and urea levels (Gora et al., 2014; Zhang et al., 2014). Notably, TANP treatment significantly reduced these alterations, highlighting its potential role in attenuating ASO-induced nephrotoxicity.

5. CONCLUSIONS

In conclusion, the results of this investigation lend credence to the idea that TANPs may enhance kidney function and ameliorate the histological changes of renal injury brought on by ASO. However, more research on this topic is required before a therapeutic application is suggested.

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