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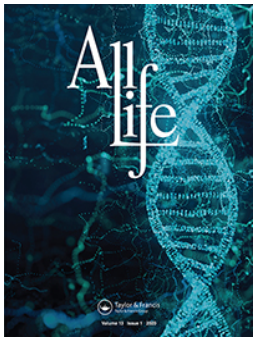
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N⁶-2-hydroxyethyl-adenosine ameliorate cisplatin induced acute kidney injury in mice

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ABSTRACT

N⁶-2-hydroxyethyl-adenosine (HEA) is one of the main bioactive components found in *Cordyceps cicadae* and it has been reported to display antioxidant and anti-inflammatory activities. Cisplatin (CP) is one of the most commonly used chemotherapeutic drug for treating various cancers and tumors, but the use is widely curtailed due to its toxicity of various organs including the kidney. This study was aimed at investigating the protective effect of HEA on cisplatin-induced kidney injury. Mice were pretreated with HEA for 7 days and administered with cisplatin. Kidney function index including blood urea nitrogen (BUN), creatinine, renal oxidative stress and pro-inflammatory indices such as malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), tumor necrosis factor (TNF- α), interleukin 1 beta (IL-1 β) and interleukin 6 (IL-6) were measured. Histopathological assessment of the kidney was also performed. The results indicated that HEA noticeably modulated the levels of BUN and creatinine as well as decreased the expression of MDA, TNF- α , IL-1 β and IL-6 in the kidney. In addition, HEA up regulated the activities of antioxidant enzymes SOD, CAT and GSH-Px. Therefore, we concluded that HEA could effectively alleviate cisplatin-induced nephrotoxicity by counteracting oxidative stress and inflammation.

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KEYWORDS



Cisplatin; inflammation; nephrotoxicity; n⁶-2-hydroxyethyl-adenosine; oxidative stress

Introduction

Cisplatin (CP) is an anticancer drug that is extensively used as the first line of treatment for various tumors and cancers including breast, bladder, lung, testicular, ovarian, head and neck cancers (Arany and Safirstein 2003; Dasari and Tchounwou 2014). The mechanism of action of cisplatin is thought to mediated through its interaction with purine bases in the DNA to form DNA–protein crosslink leading to apoptosis (Chválová et al. 2007; Dasari and Tchounwou 2014). Despite the effectiveness of cisplatin as a chemotherapeutic agent, the side effects and toxicities associated with the use has greatly limited its clinical application. Side effects such as nephrotoxicity, myelotoxicity, neurotoxicity, electrolyte disturbance, hemolytic anemia and ototoxicity have been widely reported (Fuertes et al. 2003; Florea and Busselberg 2011; Schanz et al. 2017; Zhang et al. 2020). Nephrotoxicity is one of the main side effects induced by cisplatin due to its accumulation in the renal proximal tubules and it has been

estimated that 25–30% of patients using cisplatin experience renal dysfunction (Ciarimboli et al. 2010; Crona et al. 2017; Sanchez-Gonzalez et al. 2017; Ning et al. 2018).

The pathogenesis involved in cisplatin-induced nephrotoxicity is complex, involving an interplay of inflammation, apoptosis, oxidative stress, production of high levels of reactive oxygen species (ROS) and deterioration of antioxidant enzyme levels (Manohar and Leung 2018; Sun et al. 2019; Yang et al. 2019). Furthermore, ROS and oxidative stress induced by cisplatin can activate several inflammatory mediators and pathways such as TNF- α and IL-1 β and nuclear factor- κ B (Sahu et al. 2014). As such, therapeutic agents that can effectively combat inflammatory response, oxidative stress and increase anti-oxidation could be beneficial in the treatment of cisplatin-induced nephrotoxicity. At present, there are no effective treatment for alleviating cisplatin-induced kidney injury.

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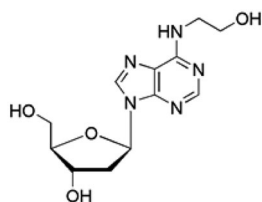


Figure 1. The chemical structure of HEA.

Natural products have been used in the treatment of several diseases due to their unique advantages attributed of their multiple effects, multi-active constituents and limited side effects. N⁶-2-hydroxyethyladenosine (HEA; Figure 1) is a bioactive nucleoside isolated from the medicinal mushroom *Cordyceps cicadae*. HEA has been demonstrated to manifest a host of pharmacological properties including antitumor, antioxidant, anti-inflammatory, antidiabetic, renal protective, neuroprotective, Ca²⁺ antagonist, radiation resistance and analgesic activities. For instance, HEA protected against H₂O₂ and LPS induced oxidative toxicity as well as renal interstitial fibrosis through its anti-oxidation and anti-inflammatory effect (Lu et al. 2015; Zheng et al. 2018; Wang et al. 2019; Zhang et al. 2019). However, the potential protective effect of HEA on cisplatin-induced nephrotoxicity have not been explored. In this study, we examined the protective effects of HEA on cisplatin-induced nephrotoxicity.

Materials and methods

Animals

Healthy specific pathogen free male ICR mice (20–22 g; 7 weeks old) were used for the experimental study. The experimental animal ethics committee of China–Japan Union Hospital of Jilin University approved the study protocol (ethics approval number 20190043) and the handling and care of the animals were in accordance with the requirement of the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978). All the mice were housed in a standard room with temperature and relative humidity of 22 ± 2°C and 55 ± 5%, respectively and a 12-h occulting cycle. The animals were allowed free access to standard diet and water *ad libitum* unless stated otherwise. After seven days of adaptation, the mice were randomly divided into five groups (eight mice in each

group). Group 1: healthy control group (HCG), group 2: cisplatin control group (CPG), group 3: CP + HEA (10 mg/kg), group 4: CP + HEA (20 mg/kg), group 5: CP + HEA (40 mg/kg). The mice in groups 3–5 were orally gavaged with HEA for seven consecutive days. On the 7th day, mice in groups 2–5 received a single injection of 20 mg/kg body weight of CP intraperitoneally. The mice designated as healthy control were given equal volume of normal saline. The mice were sacrificed three days after CP administration, blood and kidney tissues were collected for further experiments. Doses of HEA and CP used in this study were selected based on previous studies (Guo et al. 2018; Wang et al. 2019; Jin et al. 2020).

Histological analysis and determination of biochemical indicators

The kidneys were quickly excised and fixed in 10% neutral buffered formalin. The fixed tissues were further dehydrated, embedded in paraffin, cut into sections of 5 μm thickness and stained with hematoxylin and eosin (H&E). The stained slides were further visualized under light microscopy. The serum was obtained from the blood collected and used for determining the levels of creatinine and blood urea nitrogen (BUN).

Assessment of renal inflammatory cytokine levels

The levels of inflammatory cytokines including TNF-α, IL-1β and IL-6 in kidney tissue homogenates were detected using ELISA kits according to the manufacturer's protocols (Shanghai Enzyme-linked Biotechnology Co., Ltd., China).

Assessment of renal oxidative stress levels

The levels of renal antioxidant enzymes namely SOD, CAT, GSH-Px as well as MDA levels were estimated by using commercially available assay kits (Nanjing Jiancheng Bioengineering Institute, China) according to the manufacturer's instructions.

Statistical analysis

GraphPad Prism (version 7.0) was used for statistical analysis. Data were expressed as mean ± SD. Differences among groups were analyzed by one-way

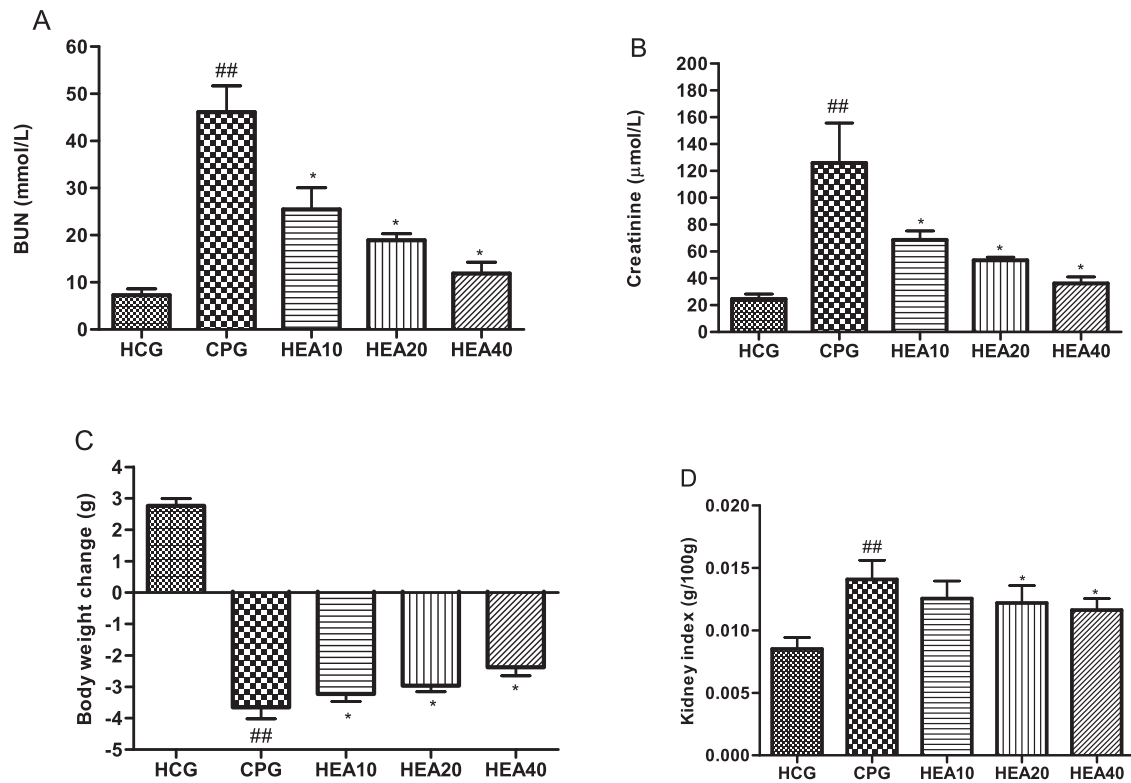


Figure 2. Effect of HEA on cisplatin-induced renal dysfunction (A) Blood urea nitrogen, (B) Serum creatinine, (C) Body weight changes, (D) Kidney index. ^{##} $P < .05$ versus normal control group, ^{*} $P < .05$ versus cisplatin treated group.

analysis of variance (ANOVA) and Tukey post hoc test. $P < .05$ was considered statistically significant.

Results

HEA attenuates cisplatin-induced renal dysfunction

We analyzed the effect of HEA on levels of the biomarkers of kidney function, including creatinine and BUN. As shown in Figure 2(A, B), cisplatin caused a dramatic increase in creatinine and BUN levels when compared to the levels observed in the healthy control mice ($P < .05$). In contrast, pretreatment with HEA led to a marked decrease in creatinine and BUN levels in a concentration dependent manner. Cisplatin also led to a significant weight loss when compared to the weight of mice in the healthy control group. Whereas, HEA considerably reduced this phenomenon (Figure 2(C)). Similarly, HEA improved kidney index in the treated mice when compared to the untreated cisplatin mice group (Figure 2(D)).

Effect of HEA on histological examination

As shown in Figure 3(A), the kidney tissues of the healthy control group showed normal kidney

architecture, with well and closely arranged renal tubule and epithelial cells. Whereas, the CP group showed gross renal tubules damage, congestion of renal capillaries, neutrophils infiltration, necrosis of renal cells, nucleus contraction and cellular vacuolation (Figure 3(B)). In the HEA pretreated groups, there were obvious signs of alleviated pathological changes at varying degrees (Figure 3(C)–(E)).

HEA alleviated cisplatin-induced renal oxidative stress

Oxidative stress is considered as a critical parameter in the pathogenesis of cisplatin-induced renal injury. As such, we investigated the effect of HEA on renal oxidative stress parameters. The results indicated that MDA levels in the kidneys of CP model group were significantly elevated compared to the healthy control group ($P < .05$). In addition, cisplatin caused a marked and evident reduction in antioxidant enzymes activities (CAT, SOD and GSH-Px) in the CP model group compared to the healthy control group. Whereas, compared to the CP model group, the levels of CAT, SOD and GSH-Px were significantly increased in the groups

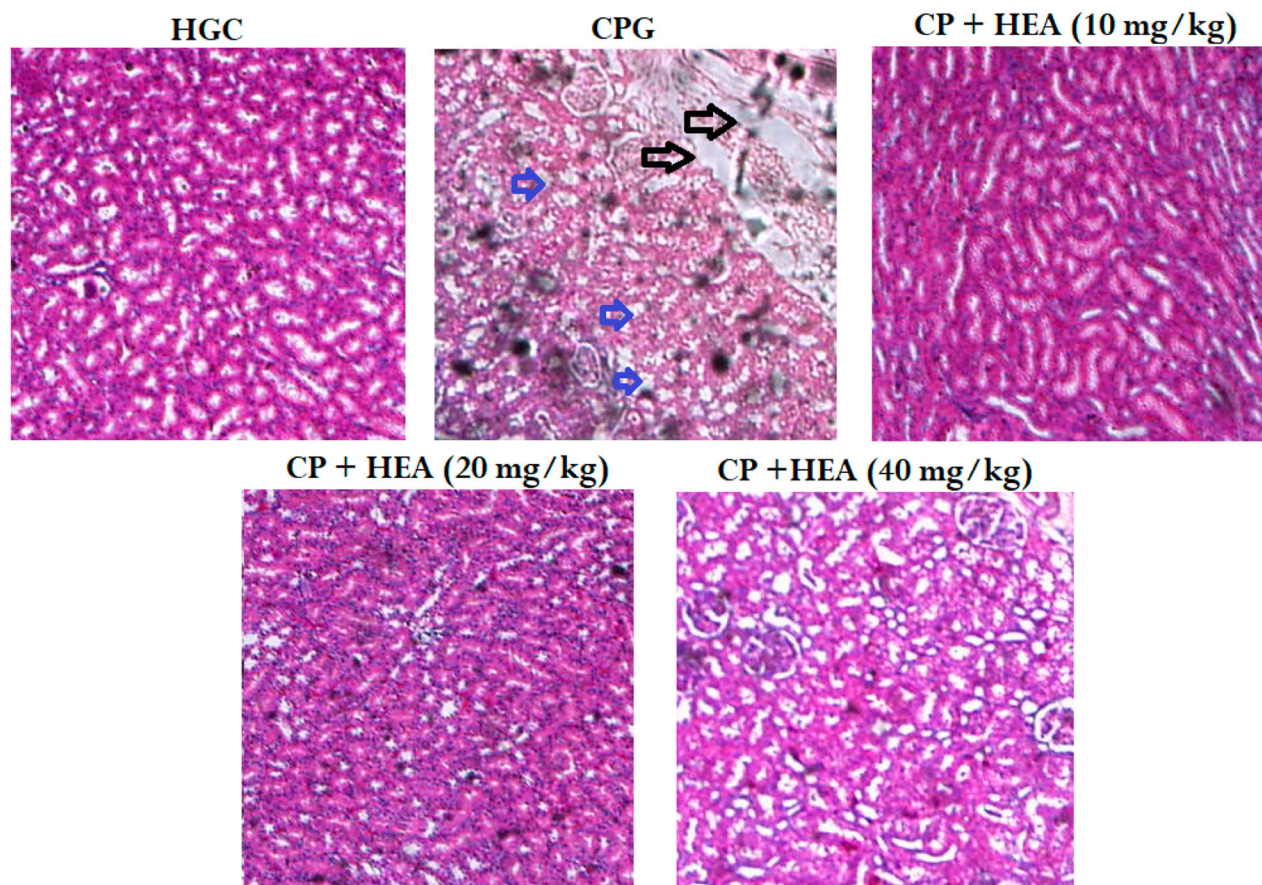


Figure 3. Effect of HEA on cisplatin-induced histopathological changes in kidney tissues (A) Normal control group, (B) Cisplatin group, (C) Cisplatin group + HEA (10 mg kg^{-1} body mass) group, (D) Cisplatin group + HEA (20 mg kg^{-1} body mass) group (D) Cisplatin group + HEA (40 mg kg^{-1} body mass) group.

that received HEA pretreatment, while MDA levels were noticeably reduced (Figure 4(A)–(D)).

HEA alleviated cisplatin-induced renal inflammation

As showed in Figure 5(A)–(C), $\text{TNF-}\alpha$, IL-6 and IL- 1β were obviously elevated in the kidney after the administration cisplatin in the CP model group compared with the healthy control group ($P < .05$). However, in groups that received pretreatment with HEA these inflammatory cytokines were significantly reduced by varying degrees, suggesting that HEA could alleviate kidney inflammation induced by cisplatin.

Discussion

Cisplatin is one of the most frequently used drugs in the treatment of a number of malignancies, cancers and solid tumors. However, its clinical application has been limited due to multiple toxicities and side effects accrued from its usage (Xing et al.

2019; Yucetas et al. 2019; Zhang et al. 2019). A lot of convincing evidences have implicated ROS generation, oxidative stress and inflammation as the main culprit responsible for cisplatin-evoked toxicity including nephrotoxicity (Arafa and Atteia 2019; Li et al. 2018). At present, amifostine, erythropoietin and dexamethasone are the most commonly used chemoprotective agent used for alleviating or preventing cisplatin-induced nephrotoxicity. However, unpleasant side effects have impeded their use (Tessoulin et al. 2017; Volarevic et al. 2019). Agents with antioxidant as well as anti-inflammatory activities have been considered as an alternative protective agent against cisplatin-induced nephrotoxicity (Ali and Al Moundhri 2006). As such, this study was designed to evaluate the therapeutic effect of HEA on cisplatin-induced acute kidney injury by exploring its antioxidant and inflammation effects. The results obtained in this study showed that the nephro-protective effect of HEA against cisplatin-induced toxicity is through the regulation

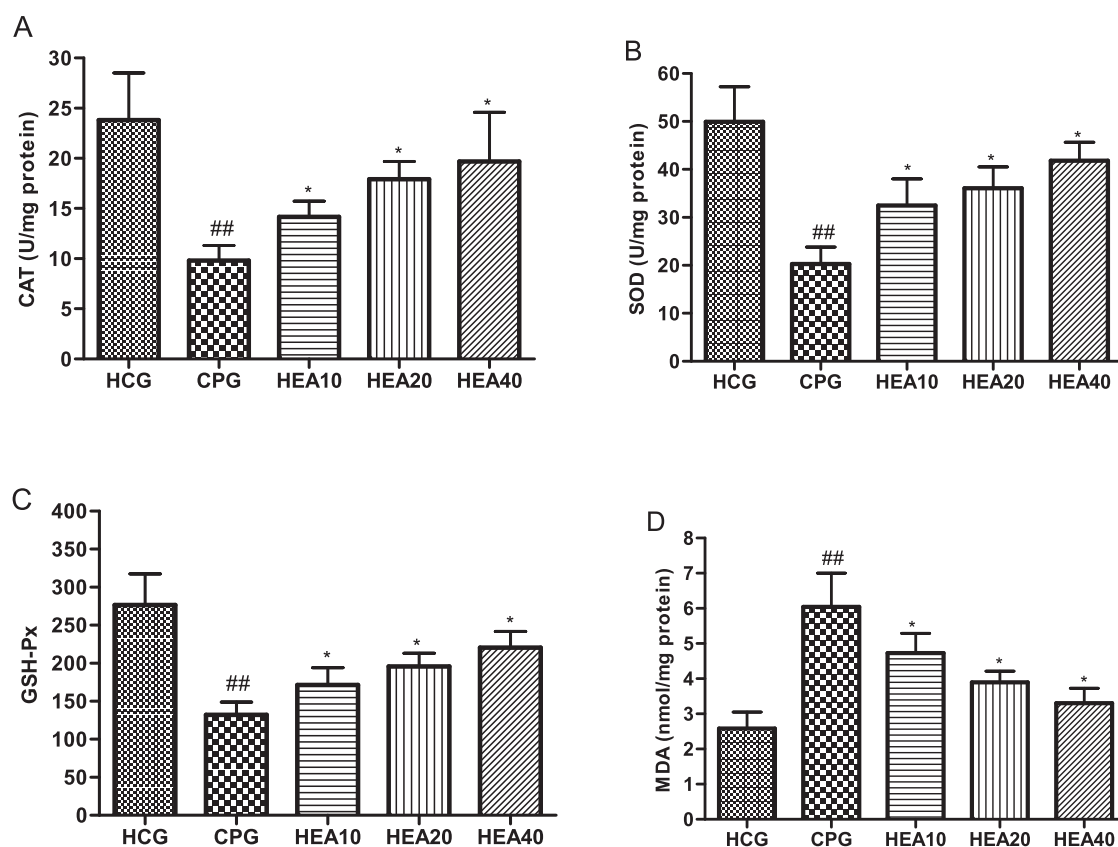


Figure 4. Effect of HEA on renal (A) SOD, (B) CAT, (C) GSH-Px, (D) MDA levels. ## $P < .05$ versus normal control group, * $P < .05$ versus cisplatin treated group.

of inflammation, oxidative stress and kidney function parameters.

Blood urea nitrogen (BUN) and creatinine are two key markers of kidney function that are obviously elevated in cisplatin-induced renal injury (Lee et al. 2013). BUN is an end product of protein metabolism and it is considered as a vital index of glomerular filtration function, while creatinine is a waste product that is excreted by the kidney as a result of muscle metabolism. High levels of serum creatinine and BUN is indicative of renal malfunctioning. Numerous studies have linked cisplatin-induced toxicity to a decrease in glomerular filtration rate and subsequently increased serum BUN and creatinine levels (Malik et al. 2016; Boroja et al. 2018). Our findings are consistent with previous studies showing CP-induced significant elevation of serum creatinine and BUN levels (Qin et al. 2019; Sioud et al. 2020). Our study also revealed an increase in serum BUN and creatinine levels in the CP model group suggesting kidney damage and HEA effectively attenuated cisplatin-induced

kidney damages by reducing serum BUN and creatinine levels.

The impact of ROS and oxidative stress in cisplatin-induced nephrotoxicity has been extensively documented. Cisplatin can evoke the generation of ROS and mitochondrial dysfunction, which inevitably leads to increase in the levels of lipid peroxidation by product (MDA) (Xiao et al. 2003; Berndtsson et al. 2007). Oxidative stress is one of the main mechanisms associated with cisplatin-induced organ damages and it is a common pathway involved in cognitive dysfunction, kidney, liver and testicular injuries caused by cisplatin (Afsar et al. 2017; Lomeli et al. 2017; Adeoye et al. 2019; Jing et al. 2019). In addition, numerous reports have clearly portrayed that cellular antioxidant enzyme activities are impeded during ROS and oxidative stress induced damages. SOD, CAT and GSH-Px antioxidant enzymes offers protection against oxidative insults in the cells and the reduction in their activities makes the target cells and organs vulnerable to oxidative damages (Hassan et al. 2017; Meng et al. 2017). Our results

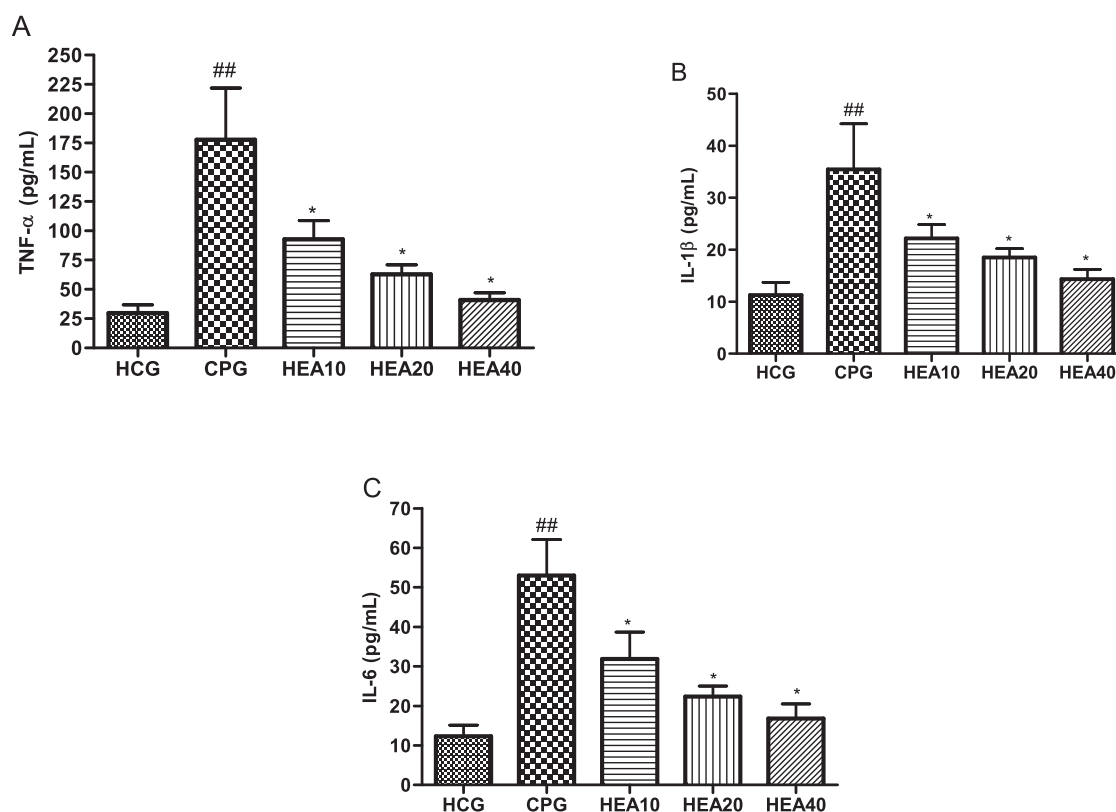


Figure 5. Effects of HEA on renal (A) TNF- α , (B) IL-1 β , (C) IL-6 levels. $##P < .05$ versus normal control group, $*P < .05$ versus cisplatin treated group.

indicated that cisplatin impaired the activities of SOD, CAT and GSH-Px and increased the content of MDA in the kidney which was consistent with results from other studies (Adeoye et al. 2019; Kandemir et al. 2019; Qin et al. 2019). Treatment with HEA improved the activities of CAT, SOD and GSH-Px in the kidney. This suggests that HEA can reduce cisplatin-induced oxidative stress in the kidney by upregulating the activities of antioxidant enzymes.

Aside the direct effect on oxidative damage, ROS and oxidative stress can also significantly trigger several other avalanches of inflammatory related reactions. The interplay between ROS, oxidative stress and inflammation has been well illustrated in cisplatin-induced acute kidney injury (Kang et al. 2009; Jing et al. 2019). Cisplatin-induced kidney damage can activate macrophages triggered inflammation resulting in the production of an array of inflammatory related cytokines, including TNF- α , IL-1 β and IL-6 (Hagar et al. 2015). The results from this study are in accordance and consistent with the previous studies indicating the toxicity of CP in renal tissues by increasing the levels of pro-inflammatory cytokines

(Hagar et al. 2015; Al Fayi et al. 2020). In agreement with previous studies, our results indicated that CP administration caused significant increase in pro-inflammatory cytokines suggesting the initiation of inflammation. HEA attenuated cisplatin-evoked release of pro-inflammatory cytokines, suggesting the anti-inflammatory ability of HEA.

Conclusion

In conclusion, this study illustrated the protective effect of HEA against cisplatin-induced kidney injury. HEA pretreatment protected against oxidative stress and inflammation by elevating the renal antioxidant enzymes as well as inhibiting the release of inflammatory related cytokines in the kidney. These results may provide useful hints in the utilization of HEA for the treatment of cisplatin-induced nephrotoxicity.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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