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Protective Role of Hesperetin against γ-rays Induced Nephrotoxicity in Mice

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HESPERETIN (HPT) is a natural flavonoid utilizing pharmacological activities such as anti-oxidation and anti-inflammation activities. Its effect on nephrotoxicity induced by γ-rays and its precise mechanism remains unclear. This study aims to explore the potential renoprotective efficacy of HPT on nephrotoxicity triggered by γ-rays-exposure in mice. Thirty-two male mice were randomly divided into four groups. The control group (vehicle), HPT group (orally, 60 mg/ kg daily over 14 days), irradiated (IRR) group received vehicle+ γ-rays (6Gy), and HPT+ γ-rays group (mice treated with HPT before exposure to γ-rays). Serum urea and creatinine, renal malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), as well as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) levels were determined. Damage to the proximal and distal tubules was observed using histopathological examination. The results showed that HPT significantly elevated renal GSH, SOD, CAT and GPx and decreased the MDA, urea, creatinine levels, and inflammatory markers. In the irradiated group, the histopathological findings showed glomerulus atrophy and dilated renal tubules including enlarged capsular space, degenerating variations and hyaloid casts. Aggregation of leukocytes in renal tubules may be shown in some cases. Exposing mice to γ-rays exacer bated oxidative stress, malondialdehyde, and kidney tissue injury. Mice can be protected against gamma hazards by giving HPT. This is an important feature in protecting or treating acute kidney illnesses.

Keywords: Hesperitin, kidney, Radio protector, γ-rays, Mice.

Introduction

Chronic nephrology disease is a prevalent public health problem worldwide (Liu et al., 2024). Oxidant stress is an important contributor to renal dysfunction (Wang et al., 2024). Radiation induced normal tissue complications such as kidney fibrosis and vascular damage (Carpenter et al., 2024) due to the ability of flavonoids to suppress oxidation and counteract free radicals. Currently, interest in flavonoids' potential health benefits has been increased (Olędzki and Harasyn, 2024). Gamma rays are concerned with the production of free radicals that cause serious damage to living cells in the biological system. These free radicals cause liver and kidney cells damaged in rats (Singh et al., 2024). A recent consistent study has shown that feeding of plant-derived foods rich in bioactive phytochemicals has a protective effect against pro-inflammatory cytokines and oxidative stress in animal or laboratory cell-line experiments (Venturini et al., 2024).

The HPT, an aglycone of the flavanone glycoside hesperidin, exhibited biological and pharmacological activities, such as anti-inflammatory, anti-carcinogenic and antioxidant activities (Hassan et al., 2023). In addition, results indicate that HPT protects against

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ionizing-radiation induced ill effects and organ dysfunctions (Park and Yu, 2024) and treats symptoms of radiation sickness (Raghu et al., 2023). Yu et al. (2016) concluded that HPT may be used as apotent radio protector against in vitro DNA break induced by γ-rays.

The present study aims to reveal the possible effect of HPT in mice with nephropathy induced by γ-rays.

Materials and Methods

Animals and HPT agent

All chemicals and agents were obtained from Sigma-Aldrich; Merck KGaA. Thirty-two male mice were purchased from the Laboratory Animal House of Institute of Ophthalmology, Giza, Egypt. The animals were 8-9 weeks and weighed 20-21g. All animals were maintained under controlled temperature, humidity, and a 12-h light/dark cycle and had free access to food and water in NCRRT Laboratory Animal Unit. All experiments were conformed to the procedure and guides for the care and use of laboratory animals published earlier, National Institutes of Health, No. 85–23, revised 1996. HPT was administered orally by gavages at 60 mg/ kg/ day from 7 days prior to treatment to 7 days post-treatment in 0.4 ml of 0.5% carboxymethyl cellulose (CMC) as a vehicle (Wang et al., 2017).

Radiation facility

The source of radiation was a gamma cell-40 for biological irradiation (^{137}Cesium) installed at the NCRRT, Nasr City, Cairo, Egypt. The radiation dose was whole body single dose of 6Gy γ-rays at an exposure rate of 0.38Gy/ minutes. Animals were lightly anesthetized (87mg ketamine/kg and 13mg xylazine/kg of body weight) before irradiation.

Intervention method

Thirty-two male mice were randomly divided into 4 groups: Control group, treated orally with daily 0.4 ml of vehicle over 14 days. HPT group, treated with their respective HPT doses of 60 mg/ kg/ day over 14 days. Irradiated (IRR) group, treated orally with 0.4 ml of vehicle/ day for 7days before exposure to 6 Gy γ-rays and to another 7 days post-irradiation. HPT+IRR group, treated with their respective HPT doses for 7 days before being exposed to 6 Gy γ-rays and to 7 days post-irradiation.

The mice were killed by cervical dislocation 24 hours after the end of the experiment and kidney tissue samples were taken. Blood samples were drawn from the heart and immediately centrifuged at 13000xg for 5 min at 4℃. Sera were then collected and stored at -20℃.

Evaluations of lipid-peroxidation and renal antioxidant indices

Serum urea and creatinine levels were conducted using a commercial kit (Biodiagnostic kits, Egypt). The GSH and MDA levels (Cigala et al., 2012; Ohkawa et al., 1979) and the enzyme activities of GPx,CAT and SOD were estimated in the renal homogenates (Lawrence&Burk, 2012; Titov & Osipov, 2017; Kakkar et al., 1984). Detection of serum TNF-α, IL-6 and IL-1β was performed by ELISA technique (Technology Biotech Company Kits, China) according to the manufacturer's instructions.

Histopathological examination

Renal tissues were placed in 10% buffered formalin for 24 hours, embedded in paraffin, and sliced into 4-µm thick sections. The sections were stained with haematoxylin-eosin (H&E) for 5 minutes, and then visualized by light microscopy to assess the extent of renal injury as previously described (Lin et al., 2005).

Statistical analysis

Data are represented as mean± standard error (S. E.). The values were tested with the statistical analysis-ANOVA "One way variance" followed by a post-hoc Fisher's PLSD-test. A value of $p<0.05$ was approved as statistically significant (Snedecor and Cochran, 1994).

Results

As presented in Tables 1 and 2, animal groups treated with HPT showed non-significant changes in the levels of all estimated renal function, inflammatory, oxidant and antioxidant parameters of the current study.

In IRR-group, serum urea, creatinine, TNF-α, IL-6, IL-1β and renal MDA levels were significantly augmented comparing with their respective averages in the control group (Tables 1 and 2) but significant decline were recorded in total GSH, SOD, CAT andGPx levels when compared with their levels in the control group (Tables 1, 2). Whereas, significant reduction in serum TNF-α, IL-6, IL-1β and renal MDA levels were recorded in the HPT+ IRR group when compared with their levels in the IRR-group but their levels still significantly changed compared to the control and resveratrol rat groups (Tables 1 and 2.

TABLE 1. The effects of HPT on renal function, oxidant and antioxidant parameters in γ-rays-induced nephrotoxicity in mice.

Groups	Control	HPT	IRR	HPT+ IRR
Urea (mg/ dl)	4.3± 0.21	4.1± 0.20	15.3± 0.31[a,b]	7.5± 0.13[a,b,c]
Creatinine (mg/ dl)	0.5± 0.01	0.5± 0.02	2.19± 0.11[a,b]	1.1± 0.21[a,b,c]
MDA (nmol/ g tissue)	2.17± 0.044	2.14± 0.041	4.09± 0.078[a,b]	3.17± 0.063[c]
GSH (nmol/ g tissue)	4.21± 0.082	4.24± 0.085	2.72± 0.081[a,b]	3.95± 0.119[c]
SOD (U/ g protein)	33.2± 0.66	33.1± 0.62	14.4± 0.29[a,b]	23.6± 0.47[a,b,c]
CAT (U/ g protein)	58.3± 1.75	57.8± 1.64	36.9± 0.74[a,b]	50.3± 1.01[a,b,c]
GPx (U/ g protein)	38.2± 1.15	37.4± 1.12	25.4± 0.51[a,b]	33.9± 0.68[a,b,c]

Data presented as mean ± S. E. obtained from 8-mice per group.
HPT= Hesperetin. IRR= irradiation. HPT+ IRR= Hesperetin+ irradiation.
a. Significantly different versus control group.
b. Significantly different versus HPT group.
c. Significantly different versus IRR-group.

TABLE 2. Effect of HPT on renal inflammatory markers in γ-rays-induced nephrotoxicity in mice.

Groups	Control	HPT	IRR	HPT+ IRR
TNF-α (pg/ ml)	62.1± 1.83	60.8± 1.71	151.1± 3.04[a,b]	82.7± 1.65[a,b,c]
IL-1β (ng/ ml)	42.2± 1.26	42.3± 1.25	81.1± 2.49[a,b]	59.2± 1.18[a,b,c]
IL-6 (ng/ ml)	79.4± 1.58	80.6±1.61	168.2± 3.37[a,b]	118.1± 2.36[a,b,c]

The legends as in Table 1.

In addition, HPT+ IRR group showed significant enhancements in content of total GSH and activities of the SOD, CAT and GPx enzymes were recorded when compared to their values in the IRR-group but their levels still significantly changed compared to the control and resveratrol rat groups,Table 1. The usage of the HPT clarified that its administration led to nearly normalization of the alteration in MDA and GSH levels (Table 1).

Histopathological findings

The control and HPT groups reveal normal histological appearance (Fig. 1&2).

Histological examination of the mouse kidney in the IRR-group, the renal tubules showed clear glomerular atrophy, capsular size extension (Fig. 3), increased tubules enlargement, degenerative changes, and hyaloid casts with loss of brush boundaries (Fig. 4).

Also, aggregations of leukocytes in the dilated tubules are shown (Fig 5). In HPT+IRR group, in many cases, renal tissues seem to be typical when compared with the γ-rays-exposed group. In afew cases, hyaline casts were present (Fig. 6).

Discussion

The HPT is a bioflavonoid, available in the fruits and vegetables diet. It is rapidly absorbed and its concentration observed 20 minutes after dosing and reaches a peak in 4 hoursin human subjects (Yuan et al., 2020). Free radicals' production following ionizing-radiation exposure injures vital organs resulting in oxidative stress that is strongly related with nephrotoxicity in experimental animals (Soliman et al., 2019). Oxidative stress elevated intracellular reactive oxygen species levels that significantly contributed to γ-rays induced nephrotoxicity (Abdel-Magied and Elkady, 2019).

In the present study, HPT exerted protective effects against total body 6Gy γ-rays' irradiation by reducing kidney injury, interstitial nephritis, haemorrhage and inflammation as shown by histopathologic findings, and also maintaining kidney functions and oxidants/ antioxidants status in irradiated mice.

It was found that HPT could be used to counter diabetic nephropathy through antioxidant and anti-inflammatory mechanisms (Abdou and Abd Elkader, 2022). It significantly decreased

urea, creatinine with a notable reduction in MDA, TNF-α and IL-6, as well as significant rise in total antioxidant capacity, GSH and CAT levels in HPT+IRR group compared to the IRR rats (Abdou aaaaaaaa and Abd Elkader, 2022). The HPT relieves the oxidative stress that causes severe kidney injury induced by cisplatin toxicity. It could significantly attenuate kidney toxicity and blood urea and creatinine. Furthermore, it clarified oxidative stress and reduced MDA level and increased SOD and GSH levels (Chen et al., 2019).

The molecular and biochemicalmechanisms of HP Tagainst cisplatin chemotherapy may limit the major mortal side effect of cisplatin (Kumaret al., 2017). In mice HPT has been demonstrated to ameliorate histological abnormalities, lipid and DNA oxidation, and kidney dysfunction in lipopolysaccharide-induced renal injury (Yang et al., 2023). Also, it protects septic mice from histopathological damage induced by lipopoly saccharidesthroughconquering oxidative stress, and inflammation mechanisms (Chen et al., 2023).

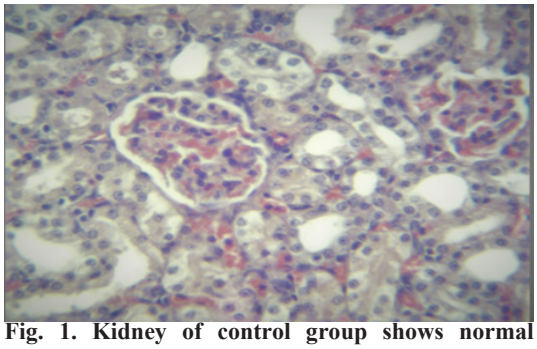

Fig. 1. Kidney of control group shows normal structure (H&E 400 x).

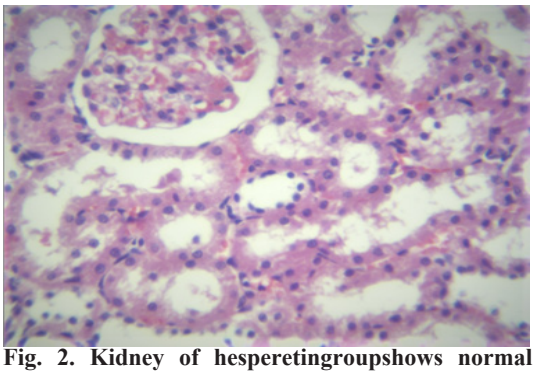

Fig. 2. Kidney of hesperetingroupshows normal renal tissues (H&E 400 x).

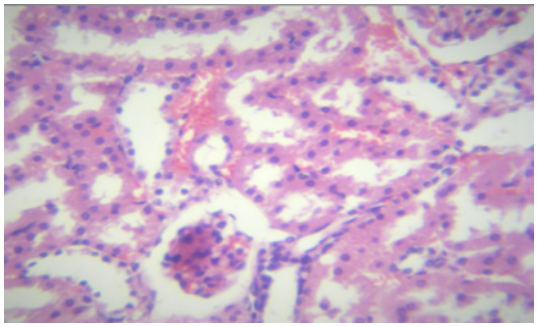

Fig. 3. Kidney of irradiated group shows atrophy of glomeruli with increasing Bowman's capsular space and dilated tubular blood vessels (H&E 400 x).

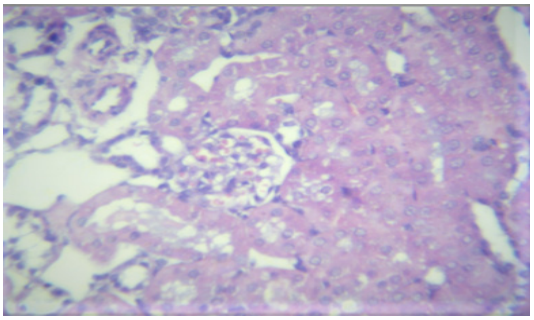

Fig. 4. Kidney of irradiated group shows degenerative changes of tubular epithelium (H&E 400 x).

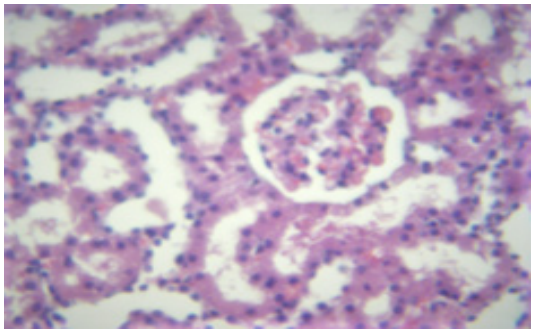

Fig. 5. Kidney of hesperetin + irradiation group showing normal renal tissues with expanded tubules, associated with albuminous droplets (H&E 400 x).

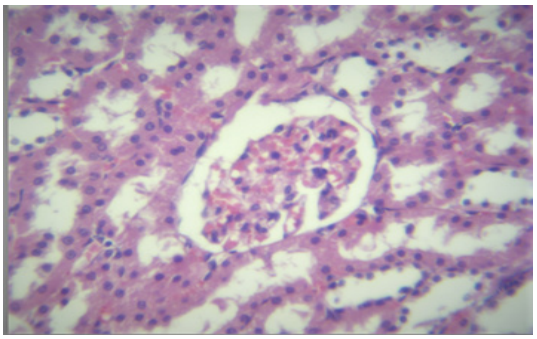

Fig. 6. Kidney of hesperetin+ irradiation group showing normal renal (H&E 400 x).

Whole body gamma-irradiation dosage of 6Gy significantly increased the serum urea and creatinine levels, as demonstrated by the biochemical analyses, suggesting that this dose led to renal dysfunction in mice. Hormati et al.(2020) have reported that ionising-radiation increased the serum urea and creatinine levels in the mice. The administration of HPT protects kidney function from γ-rays' intoxication as indicated by significant restoration of serum urea and creatinine. Similarly, HPT ameliorated the renal morphological changes of diabetic rats reflected by the decreased urea and serum creatinine levels in rats (Chen et al., 2019).

The increased permeability in the tubular epithelial cell membrane as well as swelling and lysis in the tubular epithelial cell and radiolysis of water is suggested to influence the pathogenesis of γ-rays-induced nephrotoxicity (Hasan et al., 2021). In the current review, γ-rays' exposure at a dose of 6Gy in the IRR group led to oxidative stress, as shown by the increased renal MDA level and decreased SOD, CAT, and GPx activities and GSH content. This revealed that γ-rays-induced kidney damage in mice could be accompanied by oxidative stress, consistent with other studies (El Bakary et al., 2021; Mahmoud Moustafa et al., 2021). Several studies have demonstrated that various antioxidant plant, algae, and agents, such as orange peels and Chlorella vulgaris (Abdelrahman er al., 2023), Trans-resveratrol (El Bakary et al., 2022), propolis and bee venom (El Adham et al., 2022), Ajwa date (Abulnaja et al., 2022), Diosmin (Mahmoud Moustafa et al., 2021), Fucoxanthin (El Bakary et al., 2021) prevented γ-rays-induced kidney destructiveness in rats andmice. The treatment with HPT antioxidant agent in the IRR+ HPT group significantly alleviated the γ-rays-induced renal oxidative stress, as demonstrated by the decreased MDA levels and increased SOD, CAT, and GPx activities and GSH levels. This suggests that HPT antioxidants could significantly decrease the free radicals that cause cellular injury resulting from γ-rays nephrotoxicity. Chen et al. (2019) demonstrated that HPT mechanism acts via activating Nrf2 andattenuating the MAPK signaling pathways against inflammation to protect kidney against acute kidney damage by mitigating oxidative stress, inflammation and apoptosis.The current trial showed that γ-rays caused inflammation in rat kidneys, as revealed by the increased TNF-α, IL-6 and IL-1β levels in γ-rays-induced nephrotoxicity. Similarly, Oxidative stress activates pro-inflammatory cytokines released in renal cells (Hu et al., 2024). Carpenter et al. (2024) have suggested that the inflammation process plays a central role in γ-rays-induced kidney damage. Elkady and Ibrahim (2016) have reported that inflammatory cells infiltration, and pro-inflammatory cytokines release occurs in γ-rays-induced nephrotoxicity and that erdosteine polyphenolic antioxidant agent attenuates the pro-inflammatory cytokines expression.

Likewise, the HPT attenuates the pro-inflammatory cytokines release. HPT has been shown to reduce the inflammatory cytokine; TNF-α, IL-6 and IL-1β levels through prevention and/or suppressing oxidative stress in mice (Jing et al., 2023). HSP plays a protectingmechanism by modulating oxidative stress, inflammation, and apoptosis via pro-inflammatory cytokines pathways activation (Liu et al., 2021). In this study, similarly, HPT significantly alleviated γ-rays-induced renal inflammation via their anti-inflammatory mechanism by significantly decreasing the TNF-α, IL-6 and IL-1β levels and by ameliorating interstitial nephritis, as shown by the histopathological examination in the IRR+ HPT group.

The HPT treated rat diabetic nephropathy through attenuation of oxidative stress, inflammation and proinflammatory cytokines (Abdou and Abd Elkader, 2021). Also, HPT saved the patchy alterations in the basement membrane of glomeruli and aberrations of the mesangial areas. Moreover, HPT repaired the function of the podocyte by increasing renal nephron expression and decreasing renal alpha-smooth muscle actin expression (Zhang et al., 2018). In addition, from the findings of the kidney histopathological slices, HPT mechanismslessened the cisplatin-induced nephrotoxicity (Chen et al., 2019).

The current study revealed that HPT at a dose of 60 mg/ kg daily over 14 days, orally administered to mice exposed to acute single dose of 6Gy, attenuated the increase in renal kidney functions and MDA and enhanced the renal antioxidant parameters. It also improved the histopathological findings in renal tissues.

Conclusion

HPT could attenuate γ-rays-induced nephrotoxicity by decreasing oxidative stress and inflammation and increasing antioxidants. This study supports the hypothesis that HPT antioxidants is a potential therapeutic compound that can be used for the alleviation of γ-rays-induced nephrotoxicity.

Recommendation

Adding HPT to the radiation therapy protocol may benefit patients to prevent nephrotoxicity caused by γ-rays.

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الدور الوقائي للهسبيريتين في التصدي لتسمم الكلى التي تحدثه أشعة جاما في الفئران البيضاءالصغيرة

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الهسبيريتين عبارة عن فلافونويد طبيعي يستخدم كمضاد للأكسدة والالتهاب. ونظرا لعدم وضوح تأثيره وآلية عمله بدقة في التصدي للسمية الكلوية الناتجة عن ضغط التأكسد. تم دراسة واستكشاف الفعالية المحتملة للهسبيريتين في حماية الكلى من السمية الناتجة عن تعريض الفئران البيضاء لأشعة جاما. تم تقسيم 32 من ذكور الفئران بشكل عشوائي إلى أربع مجموعات. تجرعت المجموعة الضابطة (المذيب)، ومجموعة الهسبيريتين (60 ملليجرام/كجم يوميا لمدة 14يوم)، كما تم تعريض فئران المجموعة الثالثة لجرعة6 جراي من أشعة جاما، والمجموعة الأخيرة تم تجريع الفئران عقار الهسبيريتين كما تم تعريضها لأشعة جاما.تم تقدير مستوى كل من اليوريا والكرياتينين في مصل الدم، ومستوى المالونداي ألدهيد (MDA)، ومستوى الجلوتاثيون (GSH)، ونشاط إنزيمات السوبر أوكسيد ديسميوتيز (SOD)، والكتاليز (CAT)، والجلوتاثيون بيروأكسديز (GPx) في نسيج الكلى، بالإضافة إلى تحديدمستوى كل من: عامل نخر الورم (TNF−α) والإنترلوكين6− (IL−6) وانترلوكين−1ابيتا (IL−1β). وقد تبين تلف خلايا الكلى في المجموعة التي تعرضت لأشعة جاما. كما تم تحديد التغييرات في تركيب نسيج الكلى الدقيق باستخدام الفحص المجهري. وقد تبين وجود إلتهاب بالكلى مع وجود كريات دم بيضاء داخل نسيج الكلى وضمور في الكبيبات الكلوية (glomeruli) مع تمدد في القنوات البولية ووجود حصوات هيلينية.أظهرتالنتائجأن استخدام الهسبيريتين زاد بشكل ملحوظ مقدار الجلوتاثيون، ونشاط إنزيمات السوبر أكسيد ديسميوتيز، والكتاليز، والجلوتاثيون بيروأكسديز في نسيج الكلى، وانخفضت معدلاتالمالونداي ألدهيد، واليوريا، والكرياتينين ووسمات الالتهاب. تشير النتائج إلى أن تعرض الفئران للإجهاد التأكسدي الناجم عن تعريضها لأشعة جاما يسبب إصابة الكلى بالتسمم واختلال وظائفها. يمكن وقاية الفئران بتجريعهم عقار الهسبيريتين الذي يخفف من سمية أشعة جاما، وهي خاصية يمكن أن تسهم وتفيد في التصدي وعلاج أمراض الكلى الحادة.