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The protective effects of rutin and stem cells against the kidney function changes induced by paracetamol in rats.

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A B S T R A C T

The aim of study was the evaluation of proficiency of rutin and stem cells on the kidney function changes induced by paracetamol in rats. 70 male rats were divided into two main studies. Primary study was used twenty young rats used as a source of bone marrow-derived MSCs. Secondary study were used fifty adult male rats which divided into 5 groups: Group (1) control group; group (2) were administrated of PCM (750 mg/kg b.w./every 72h) orally for 21 days, then left for 30 and 60 days without treatment, group (3) were administrated of PCM for 21 days then, treated with rutin (25mg/kg b.w/d) for 30 and 60 days, group (4) were administrated of PCM for 21 days then, the rats were injected by BM-MSCs (1.5x 106 cells in 0.5 PBS) in the tail vein for 30 and 60 days, and group (5) were administrated of PCM for 21 days then, the rats were injected by BM-MSCs in the tail vein, then treated with rutin for 30 and 60 days. PCM administration significantly increased the creatinine, urea levels with decreasing the albumin level when compared with normal rats at 30 and 60 days. While, rats treated with Q-3-R and MSCs showed a significant decrease in the creatinine, urea levels with increasing the albumin level when compared with PCM rats at 30 and 60 days. The rutin and BM-MSCs have the effects of the antioxidant activities, anti-inflammation and tissue regeneration on the PCM-induced kidney toxicity in rats.

1 Introduction

Paracetamol (PCM) is an extensively used as analgesic and antipyretic manager which is harmless when occupied in medical doses (Bessems and Vermeulen, 2001 and Abdallah *et al.*, 2016). However, it can produce acute toxicity in liver and kidney in both human and animals' model when administrated in unnecessary high doses (Abdallah *et al.*, 2016 and Abdalally *et al.*, 2021). Moreover, PCM toxicity is caused by excessive use or overdose of analgesic drugs. Also, toxicity of PCM is from the metabolites of N-acetyl-p-benzoquinoneimine (NAPQ), where it reasons reduction of glutathione (GSH) in liver cells as NAPQI react quickly with GSH, which promote oxidation stress in conjunction with mitochondrial dysfunction, that lead to massive hepatocyte necrosis, liver failure or death (Michael *et al.*, 2012 and Alshailabi *et al.*, 2021).

Flavonoids are a great group of polyphenolic complexes which performance an imperative role in detoxification of free radicals and are obviously create in fruits, vegetables and medicinal plants (Sattanathan *et al.*, 2011 and Alkhamees., 2013). Glycosidic flavonoids as rutin are greatly extra readily engrossed than aglycones. Where, rutin (quercetin-3-rutinoside) (Q-3-R) has antioxidant properties and act antitumor, anti-inflammatory, and antimutagenic potential, besides myocardial protection, and immunomodulating activities (Khan *et al.*, 2012 and Ganeshpurkar and Saluja, 2017). Moreover, Q-3-R also has an inhibitory effect counter to membrane lipid peroxidation and generation of reactive oxygen species (ROS) (Lopez-Revuelta *et al.*, 2006 and Yang *et al.*, 2012).

Mesenchymal stem cells (MSCs) are the greatest commonly used stem cells due to their easy availability in tissues, such as bone marrow aspirate and fat tissue (Lee *et al.*, 2004) and to their large capacity for ex vivo development (Giordano *et al.*, 2007). Their immunosuppressive properties are allowing them to be used in allogenic transplantation (Le Blanc and Pittenger, 2005). They have a greatly elastic differentiation likely that embrace not only adipogenesis, osteogenesis and chondrogenesis (Bruder

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et al., 1998), but also endothelial, cardiovascular (Gojo *et al.,* 2003), neurogenic (Sanchez-Ramos *et al.,* 2000) and neovascular development (Kobayashi *et al.,* 2000).

Consequently, there is an increasing essential for exogenous materials of antioxidants such as Q-3-R that have numerous biological actions. So, the present study examined the evaluation of proficiency of Q-3-R and stem cells on the kidney function changes induced by paracetamol in male rats.

2 Materials and Methods

2.1. Chemicals:

•Paracetamol ($C_8H_9NO_2$). It was purchased from Sigma chemical Company (USA) (Anbarasu *et al.,* 2011).

•Rutin ($C_{27}H_{30}O_{16}$) the natural antioxidant. It was purchased from Sigma chemical Company (USA) (Shenbagam and Nalini., 2011).

• Mesenchymal stem cells (MSCs), have been isolated and cultured in Medical Research Center, Aleibbasiuh, Ain shams University.

2.2. Experimental animals:

The present study was conducted using 70 male albino rats of the strain (*Rattus norvegicus*). They were divided into two main studies. In the first, twenty young male albino rats (weight 100 g) were used as a source of bone marrow-derived MSCs, and second, fifty adult male albino rats were divided into five groups (weight of 150-160g) for the experimental work. Male healthy rats were taken from Animal House of El-Salam Farm, Giza-Cairo, Egypt and were adapted to the laboratory environments for 14 days previous to the start the experimental deign. Animals were kept in cages at a room temperature (24-27 ℃), 12 hours dark/ light cycle and given standard food and water ad-libitum with new daily foods. The experimental procedures complied with guidelines of the Committee on Care and use of Experimental Animal Resources, Ain Shams University, Cairo, Egypt.

2.3. Assessment of the bone marrow-derived mesenchymal stem cells (MSCs):

Twenty young male albino rats (weight 100 g at 6 weeks old) were used as a source of bone marrow-derived MSCs (Nagaya *et al.,* 2004). Young rats were injected by BM-MSCs (1.5x 106 cells in 0.5 PBS) (Oskouei et al., 2012) in the tail vein (Jiang *et al.,* 2006). The cultured BM-MSCs were characterized by using NAVIOS flow cytometer by BECKMAN COULTER in Medical Research Center of Ain Shams University (Krishan *et al.,* 2011 and El-Nahrawy *et al.,* 2017).

2.4. Experimental groups:

Fifty adult male rats were randomized divided into 5 groups (10 rats) in each:

Group (1): Control group (NC), rats were left as control rats, and given food and water ad lib.

Group (2): Paracetamol treated group (PCM), animals were orally administrated with a dose of PCM (750 mg/kg b.w.) every 72h for 21 days, then left for 30 and 60 days without any treatment.

Group (3): Paracetamol with rutin group (PCM+Q-3-R), animals were received oral doses of PCM (750 mg/kg b.w.) every 72h for 21 days. Then, orally treated with Q-3-R at a dose of (25mg/kg b.w/d) for 30 and 60 days.

Group (4): Paracetamol with stem cells group (PCM+MSCs), animals were received oral doses of PCM (750 mg/kg b.w.) every 72h for 21 days. Then, the rats were injected by BM-MSCs (1.5x 106 cells in 0.5 PBS) in the tail vein for 30 and 60 days.

Group (5): Paracetamol with stem cells and rutin group (PCM+MSCs+Q-3-R), animals were received oral doses of PCM (750 mg/kg b.w.) every 72h for 21 days. Then, the rats were injected by BM-MSCs (1.5x 106 cells in 0.5 PBS) in the tail vein, with orally treated with rutin at a dose of (25mg/kg b.w/d) for 30 and 60 days.

At the end of the experimental work, the rats were overnight fasted after the last dose and blood samples were collected.

2.5. Serum biochemical analysis:

Blood samples were occupied into clean and dry centrifuge tubes and centrifuged at 3000rpm for 15 minutes in order to separate clear serum samples. They were then stored at -20ºC until used for evaluation of different biochemical parameters. Sera were used for the evaluation of biochemical examination of kidney of the control and the experimental animals [creatinine (Cre), urea (Ur), and albumin (Alb)], by using commercial kit which taken from Randox, U.K. according to the method of Newman and Price (1999) and Thomas (1998).

2.6. Statistical analysis:

Statistical procedures were performed with (version 17 for Windows), and the data were analyzed by applying a one-way ANOVA method to test the mean differences observed among the all groups. Aso, using Tukey's test at $P < 0.05$ for separated means.

3 Results

3.1. Evaluation of the creatinine level (Cre): -

The Cre levels from all rats were assumed in Table (1), it is showed an important increase ($P < 0.05$) in the mean value of the Cre level after 30 days in the PCM (1.500±0.031) group as compared to the NC (0.5400±0.024) group. Whereas, there was a significant decrease ($P < 0.05$) between the PCM+Q-3-R

(1.3400±0.024), PCM+MSCs (1.040±0.024), and PCM+MSCs+Q-3-R (0.8200±0.037) groups as compared to the PCM group. Also, the mean values of the Cre level after 60 days showed, a significant increase in treated group with the PCM (1.800±0.031) when compared with the NC (0.5000±0.020). Moreover, the other treated groups showed, a significant decrease (1.4400±0.024 "PCM+Q-3-R"), (1.2600±0.024 "PCM+MSCs"), and (0.9600±0.081 "PCM+MSCs+Q-3-R") when compared with PCM group, and no significant found between the PCM+Q-3-R and PCM+MSCs groups.

3.2. Evaluation of the urea (Ur) level: -

Statistically, a highly important increase ($P < 0.05$) found in the mean value of the Ur level in Table (1) after 30 days in the PCM (69.20±3.031) rats as compared to the NC (25.20±1.358) rats. While, there was a significant reduction ($P < 0.05$) in the PCM+Q-3-R (53.00±2.497), PCM+MSCs (42.80±1.502), and PCM+MSCs+Q-3-R (36.00±1.228) rats as compared to the PCM rats, and no important changes were detected on the mean value of the Ur level between the PCM+MSCs and PCM+Q-3-R+MSCs rats. In addition, the mean values of the Ur level after 60 days showed, a highly significant increase in the PCM (91.60±3.825) as compared to the NC (25.00±1.36) rats. Furthermore, the mean value of Ur level between the PCM+Q-3-R (67.20±16.59), PCM+MSCs (53.40±1.811), and PCM+MSCs+Q-3-R (39.600±0.814) rats showed, a significant decrease as compared to the PCM group.

3.3. Evaluation of the albumin (Alb) level: -

In the Table (1), showed a significant decrease ($P < 0.05$) in the mean value of the Alb level in the PCM group after 30 days (2.9600±0.040) group as compared to the NC (4.100±0.122) group. Moreover, there was no notable effects between the mean value of the Alb level in the PCM group and the PCM+Q-3-R (3.2200±0.20) group, while the PCM+MSCs (3.3800± 0.0375) group, and the PCM+MSCs+Q-3-R (3.5800±0.0476) group showed, a significant increase ($P < 0.05$) in the mean value of the Alb level as compared to the PCM group. Although, the mean values of the Alb level after 60 days showed, a significant decrease in the PCM (1.940±0.103) as compared to the NC (4.000±0.123) group. Additionally, the mean value of Alb level showed, a significant increase in the PCM+Q-3-R (2.6800±0.066), PCM+MSCs (3.100±0.070), and PCM+MSCs+Q-3-R (3.2600±0.068) groups when compared with PCM group.

Table 1: The creatinine, urea and albumin levels in normal and experimental animals for 30 and 60 days of treatment (Mean ±Standard Error of mean, at $P< 0.05$).

Duration	Parameter	NC	PCM	PCM + Q-3-R	PCM + MSCs	PCM+ MSCs+ Q-3-R
30 days	Cer (mg/dl)	0.5400± 0.024^{E}	1.500± 0.031^{A}	1.3400± 0.024^{B}	1.040± 0.024^{C}	0.8200 ± 0.037^{D}
	Ur (mg/dl)	25.20± 1.358^{D}	69.20± 3.031^{A}	53.00± 2.497^{B}	42.80± 1.502^{C}	36.00± 1.228^{C}
	Alb (g/dl)	4.100± 0.122^{A}	2.9600± 0.040^{D}	3.2200± 0.20^{CD}	3.3800± 0.0375^{BC}	3.5800± 0.0476^{B}
60 days	Cer (mg/dl)	0.5000± 0.020^{D}	1.800± 0.031^{A}	1.4400± 0.024^{B}	1.2600± 0.024^{B}	0.9600± 0.081^{C}
	Ur (mg/dl)	25.00± 1.36^{E}	91.60± 3.825^{A}	67.20± 16.59^{B}	53.40± 1.811^{C}	39.600± 0.814^{D}
	Alb (g/dl)	4.000± 0.123^{A}	1.940± 0.103^{D}	2.6800± 0.066^{C}	3.100± 0.070^{B}	3.2600± 0.068^{B}

* NC= control group, PCM= Paracetamol group, PCM+Q-3-R= Paracetamol with rutin group, PCM + MSCs= Paracetamol with stem cells group, and PCM+MSCs+Q-3-R = Paracetamol with stem cells and rutin group.

4 Discussion

In the present study, PCM produced a significant increase ($P < 0.05$) were found in the Cer and Ur levels in treated rats that given PCM as compared to NC group. These results were supported by Sabiu *et al.* (2016); Al-Asmari *et al.* (2020) and Abdalally *et al.* (2021), who found that the administration of PCM showed an important rise in the Cer and Ur levels in the treated group.

Serum concentrations of the Cer and Ur grant signs to the functional ability of the nephrons at the glomerular and tubular levels. The Cer and Ur levels in the renal dysfunction, are passed down into the bloodstream and caused an increase their concentration. Also, increasing the serum concentrations of Cer and Ur may duo to revealing of kidney tissues damage and cell necrosis resulting from the forming of NAPQI by PCM administration (Sabiu *et al.,* 2016). Furthermore, Yakubu *et al.* (2003) found that the important rise of the Ur levels may duo to accredited to injury of the urea cycle. Thus, an increase in the Ur levels flaws in urea synthesis that may affect in ammonia intoxication. Additionally, Benhelima *et al.* (2016) suggested that the increasing in the serum level of Cer and Ur levels in rats were caused by several deleterious renal histopathological changes and lesions.

On the other hand, the levels of Alb level were detected to reduction meaningly ($P < 0.05$) in the treated rats by PCM when compared with NC group. These are similar results with the Iyanda and Adeniyi (2011); Mohamed *et al.* (2014) and Saleh *et al.* (2018) who recommended that the PCM produces decreasing of the Alb levels. These reductions in the Alb levels may be due to liver injury in the paracetamol administered rats, where most

of the plasma proteins are synthesized by the hepatocytes, and the abnormality of which resulted in decreased synthesis it which resulted Alb in lower serum level (Iyanda and Adeniyi, 2011). Moreover, Saleh *et al*. (2018) suggested that the decrease of serum proteins may be due to decrease number of functional hepatocytes or due to renal toxicity which mains to leak of Alb in urine with declining of serum Alb concentration.

Moreover, this study presented a significant decline in the mean values of Cer and Ur with a significant increase in the mean value of Alb level in the PCM+Q-3-R, PCM+MSCs, and PCM+MSCs+Q-3-R groups as compared to the PCM group. This is accompanied with El-Ridi and Rahmy, (2000). These effects may duo to the antioxidant activities, anti-inflammatory effects, phenolic compounds and flavonoid glycosides of Q-3-R (Lee and Jeune, 2013). However, Rahmani *et al.* (2023) stated that the Q-3-R can induce important protective properties against synthetic elements and toxins with diverse mechanisms of toxicities. Moreover, Q-3-R has been reported to exhibition multiple pharmacologic activities including anti-inflammatory, vasoactive and membrane lipid peroxidation inhibitory properties (Park *et al.*, 2002). Rutin provides protection against nephrotoxicity and has also showed the heling of the histological structures and ameliorating straight bilirubin, creatinine, and blood urea nitrogen levels (Ali *et al.*, 2023). On the other hand, Ayala-Cuellar *et al.* (2019) said that the MSCs have capability to migrate to damage positions through chemoattractant gradients in the stromal extracellular matrix and peripheral blood. Also, incentives all indorse to the formation of abundant growth factors by MSCs that join together to augment tissue regeneration (Rhee et al., 2015), and tissue healing (Liu *et al.*, 2014).

5 Conclusions

The Q-3-R and BM-MSCs have the effects of the antioxidant activities, anti-inflammation and tissue heling and regeneration on the PCM-induced kidney toxicity in rats.

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