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Protective Effect of Chromium Picolinate on Methotrexate Induced Nephrotoxicity in a Rat Model

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Abstract

Methotrexate, a folic acid antagonist, is a chemotherapeutic agent frequently employed in treating certain forms of cancer. Nephrotoxicity caused by high-dose Methotrexate is a medical emergency due to the delayed renal excretion of Methotrexate. Chromium is a trace element found in certain foods and the environment. The primary function of chromium is to regulate glucose levels, which is used as a supplement by people with type 2 diabetes Mellitus. The current study aims to evaluate the renal therapeutic effect of chromium against Methotrexate-induced Nephrotoxicity in rats. Thirty-two Wistar rats were allocated into four groups and treated as Group-1 (Control group): The rat was administered distilled water orally as a vehicle for eight consecutive days. Group-2 (Induction group): Methotrexate was injected in rats at a single dose of 20 mg/kg intraperitoneally on the first day. On the following days, the rats received distilled water for seven days. Group-3 (Chromium 2mg): methotrexate injected Rats at a dose of 20 mg/kg intraperitoneally, as a single dose on the first day. On the following days, the rats received Chromium picolinate at a dose (2mg/kg) orally by oral gavage for seven days. Group-4 (Chromium 4mg): Methotrexate injected in rats at a dose of 20 mg/kg intraperitoneally, as a single dose on the first day. On the following days, the rats receive Chromium picolinate at a dose (4mg/kg) orally by oral gavage for seven days. The levels of creatinine, blood urea nitrogen (BUN), and malondialdehyde (MDA) were evaluated with the assessment of gene expression of superoxide dismutase-1 (SOD-1) enzyme for all studied groups. The results indicated that injection (20mg/kg) of Methotrexate caused a significant increase in creatinine, BUN, and MDA, with a significant reduction in the expression of SOD-1. Interestingly, treatment with chromium picolinate (2mg/kg) and (4mg/kg) showed significant drops in creatinine, BUN, and MDA with a significant elevation in SOD-1 expression compared to Methotrexate-treated rats. The current investigation revealed that the administration of chromium to rats has a beneficial impact on reducing Nephrotoxicity generated by Methotrexate. This is achieved by enhancing the antioxidant defenses of the kidneys.

Keywords: Antioxidants, Nephrotoxicity, Chromium picolinate, Methotrexate, Creatinine.

Introduction

Acute kidney injury (AKI) is defined by a sudden rise in blood creatinine levels, a reduction in urine output, or perhaps both [1,2]. AKI is observed in approximately 10-15% of hospitalized patients. Renal dysfunction or damage may develop over an extended period or as a consequence of traumatic renal injury on a continuum of acute and chronic kidney disease [2]. Acute kidney injury (AKI) is a complication that is becoming more prevalent among patients who are hospitalized for an acute illness [3]. Nephrotoxicity is the third most prevalent cause of acute kidney disease (AKD), and it has become increasingly severe in recent decades as a result of the increased use of drugs that have the potential to cause kidney injury. Studies have demonstrated that critical patients are exposed to nephrotoxic drugs at a rate of up to 20% [4]. Many medicines have been documented to cause acute kidney injury (AKI), which reduces the therapeutic utility of these treatments [5]. Among these agents, methotrexate (MTX), has been effectively employed for over sixty years, administered in large doses to treat different forms of cancer and at lower doses to manage autoimmune disorders. MTX, when used at high doses, can lead to significant acute renal damage in around 12% of individuals [6]. Nephrotoxicity caused by high-dose Methotrexate (HDMTX) is a medical emergency due to the delayed renal excretion of MTX. The protracted exposure to high concentrations of the drug can result in severe and life-threatening toxicity [7]. Methotrexate -induced nephrotoxicity is thought to happen in two main ways. MTX and its byproducts build up in the kidney tubules, which leads to crystal nephritis. Nephropathy is initially characterized by elevated blood creatinine levels that do not produce any identifiable symptoms, and it subsequently progresses to tubular necrosis.

The second mechanism is attributed to the oxidative stress (OS) that produced by MTX which has a nephrotoxic effect on renal tubules, which is a consequence of the increase in reactive oxygen species (ROS) which lead to cellular damage in renal tissues [8] which is also considered as the primary cause of MTX nephrotoxicity [9]. The two proposed mechanisms of MTX nephrotoxicity differ in that the first mechanism causes a crystal nepritis due to accumulation of MTX and its metabolite within the kidney tubules whereas the second mechanism causes a cellular damge as a consequence of ROS production. Although MTX has side effects, it is a potent chemotherapeutic drug. Therefore, research should focus on avoiding and treating its adverse consequences [10]. Trivalent chromium (Cr (III)) is a crucial trace mineral that has gotten much attention lately [11]. Concerns that people may not get enough Cr have led to research into the possible positive effects of supplementing with Cr on the health and function of animals and people because it performs a proactive function in the metabolic processes of carbohydrates, lipids, and proteins [11]. There are several types of chromium, the most common being trivalent and hexavalent. On one hand, industrial exposure to chromium can be hazardous and cause bronchitis and asthma due to the hexavalent form, which is known to be toxic [12]. Conversely, chromium picolinate (CrPic) is a trivalent chromium compound with a high bioavailability that is frequently prescribed to those who have issues with their metabolism of carbohydrates, such as insulin resistance and type 2 diabetes mellitus (DM2) [13]. Chromium plays a crucial role in the metabolism of proteins, lipids, and carbohydrates by enhancing the effectiveness of insulin [14]. The primary function of chromium is to activate apochromodulin to chromodulin which is capable of binding to the insulin receptor thereby resulting in amplification of insulin signaling which in turn regulates glucose levels. In addition to the physiological changes, such as changes in body composition and enhanced training performance, CrPic also shows beneficial effects on cardiovascular diseases, cholesterol levels, antioxidant capacity, and anti-inflammatory capacity. It also regulates behavioral patterns like anxiety and depression [13].

Since chromium has these benefits, it should be considered a possible renoprotective addition to the standard MTX treatment. Understanding these factors led to the current study, which looked at whether chromium could help protect rat kidneys from damage caused by MTX, indicating that it might be able to lower OS.

The current investigation aimed to assess the therapeutic effect of chromium picolinate against methotrexate-induced Nephrotoxicity in a rat model.

Materials and Methods

Materials

Methotrexate (50mg/5ml) was supplied from Pfizer, USA and Chromium was supplied from Source Natural, USA.

Animal

In this investigation, 32 adult male rats with a weighing range between (150-200g) were maintained in cages under controlled conditions of humidity, temperature, and light periodicity (12-hour cycle of light and dark) at the Animal Experimental and Scientific House in the College of Pharmacy, Baghdad University. They were provided with commercial food and potable water as needed throughout the experiment.

Experimental protocol

The study received approval from the Scientific and Ethical Committees of the Baghdad University - College of Pharmacy. A total of thirty-two adult waster rats were divided into four groups, with each group consisting of eight rats. Each group was assigned specific treatments as follows:

1. Group 1 (Control group): The rat was administered distilled water orally as a vehicle for eight consecutive days.
2. Group 2 (Induction group): MTX injected Rats at the dose of 20 mg/kg intraperitoneally, as a single dose. On the first day as demonstrated by the previous study which stated that this dose produced a significant induction of nephrotoxicity [15]. On the following day, the rats received distilled water for seven days.
3. Group 3 (Chromium $(pic)_3$ 2mg+MTX20mg): MTX injected Rats at a dose of 20 mg/kg intraperitoneally, a single dose on the first day. On the following day, the rats received Chromium picolinate at a dose (2mg/kg body weight) orally by oral gavage for seven days which is proposed in a previous research with significant results [16].
4. Group 4 (Chromium $(pic)_3$ 4mg+MTX20mg): MTX injected Rats at a dose of 20 mg/kg intraperitoneally, a single dose on the first day. On the following day, the rats received Chromium picolinate at a dose (4mg/kg body weight) orally by oral gavage for seven days [16].

Collection of samples and preparation of kidney tissue homogenate

Twenty-four hours after the last drug administration, All the rats were euthanized by dislocating their necks while they were under the effects of diethyl ether anesthesia. After euthanization, the samples of blood (7-8 ml) were obtained from the jugular vein (near the Throat or neck) under diethyl ether anesthesia [17]. The blood sample was transferred into a Serum separator tube and stored at room temperature (25℃) for 30 minutes to clot. Then, it was centrifuged at 3000 rpm /15 min to obtain serum. The supernatant was then

transferred as 250 µl aliquots into appropriately labeled microcentrifuge tubes and kept at −20°C [18]. The preserved serum samples were used to quantify the concentrations of creatinine and blood urea nitrogen (BUN).

The kidney was quickly removed, thoroughly washed with extremely cold phosphate buffer saline (PBS) to remove any extra blood, and then weighed and cut into little pieces. The kidney tissue was then homogenized by adding 0.9 mL of PBS (pH 7.4) to a tube containing 0.1 g of kidney tissue. Following homogenization using a homogenizer, the materials were centrifuged for 10 minutes at 10000 rpm in a cool centrifuge 4°C. The fluid supernatant was then collected and stored at -20°C till analysis. The supernatant was used to evaluate malondialdehyde (MDA) using MDA ELISA kit. The principle of this assay is based on the quantitative sandwich ELISA technique. The microplate provided with this kit had been precoated with purified antibodies specific for rat MDA and the detecting antibody was a polyclonal antibody labelled with biotin levels according to manufacturers' procedures (MyBioSource) [19]. Another part of the supernatant was used for the estimation of (SOD) by (RT-qPCR) method [20].

Gene expression analysis

The gene expression study of SOD was conducted by quantifying mRNA levels in kidney tissue using a common method termed quantitative reverse transcription-polymerase chain reaction (qRT-PCR) [21].The TransZol up plus RNA Kit (TransGen, biotech) was used to separate total RNA from kidney lysates that had been mixed with TRIzol. Following that, the EasyScript® one-step gDNA removal and cDNA synthesis (TransGen, biotech) technique was used to synthesize complementary DNA (cDNA) [22]. Whole gene expression procedure performed with the use of RNase free water that included in the kit contents.

GAPDH was used as a control gene in SYBR Green Supermix (TransGen, biotech) to measure the amounts of mRNA expression. The sequence of the primers used in this study is in "Table 1".

Table 1. Genes for the primers

Primer	Sequence 5′→3′ direction
GAPDH Forward GAPDH Reverse	CCATCAACGACCCCTTCATT CACGACATACTCAGCACCAGC
SOD Forward SOD Reverse	AGGGCGTCATTCACTTCGAG CTCTCTTCATCCGCTGGACC

Biochemical analysis

Serum levels of kidney function indicators, such as blood urea nitrogen (BUN) and creatinine (sCr), were quantified using ELISA kits. The kits were utilized in strict accordance with the instructions provided by their producers. To assess the balance between oxidants and antioxidants in the tissue, the levels of MDA were quantified in the kidney tissue homogenate using the sandwich ELISA technique, following the instructions provided by the kit's manufacturer [23]. The gene expression study of SOD was conducted using a standard quantitative reverse transcription-polymerase chain reaction (qRT-PCR) method to quantify the mRNA levels in kidney tissue [21].

Statistical analysis

The statistical analysis results performed with SPSS software version 25 were shown as Mean± Standard Deviation (SD). A one-way ANOVA with Tukey's post hoc test was used to compare data from different groups as we compared four groups and Tukey post hoc test used to assess the significance of differences between pairs of group means. Statistical significance was determined at a level of $P<0.05$ across all groups.

Results

Effects of chromium on serum levels of creatinine

"Table 2" and "Figure. 1" show that the administration of rats with Methotrexate at a dose of (20mg/kg) led to a significant elevation in the serum levels of creatinine in the MTX group II as compared to the control group I ($P<0.05$). At the same time, after chromium treatment, a significant decrease is observed when comparing group III(chromium 2mg+mtx20mg) and group IV(chromium4mg+mtx20mg) with the MTX group ($P<0.05$). Moreover, there was no significant difference between groups III (chromium 2mg+mtx20mg) and IV (chromium4mg+mtx20mg) ($p>0.05$).

Effects of chromium on the serum levels of blood urea nitrogen (BUN)

"Table 2" and "Figure. 2" show that injection rats with Methotrexate at a dose of (20mg/kg) led to a significant increase in the levels of BUN in the MTX Group II as compared to the control group I ($P<0.05$). At the same time, a significant decrease is observed when comparing group III (chromium 2mg+mtx20mg) and group IV (chromium4mg+mtx20mg) with the MTX group ($P<0.05$). Moreover, there was a significant difference between treated groups Group III and Group IV ($P<0.05$).

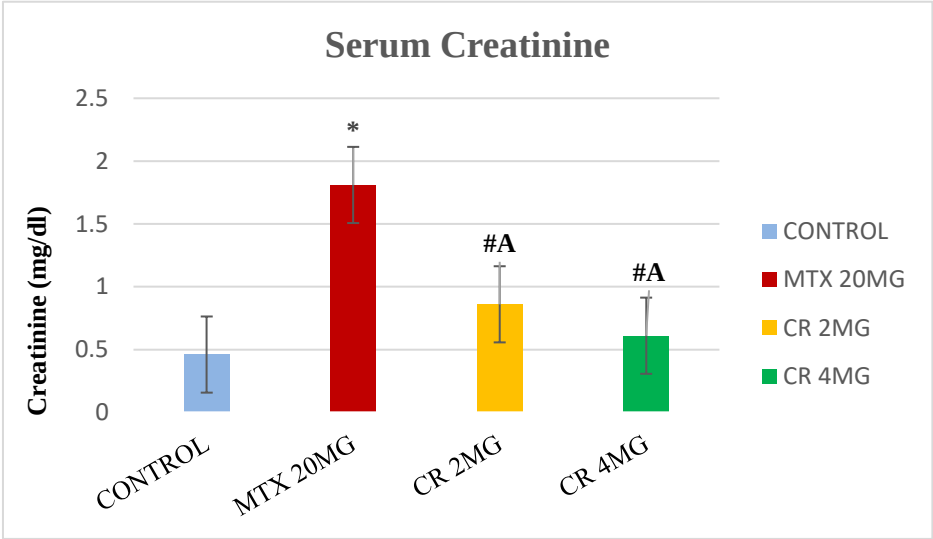

Figure 1. Effects of chromium on serum creatinine levels against methotrexate-induced Nephrotoxicity in male rats.

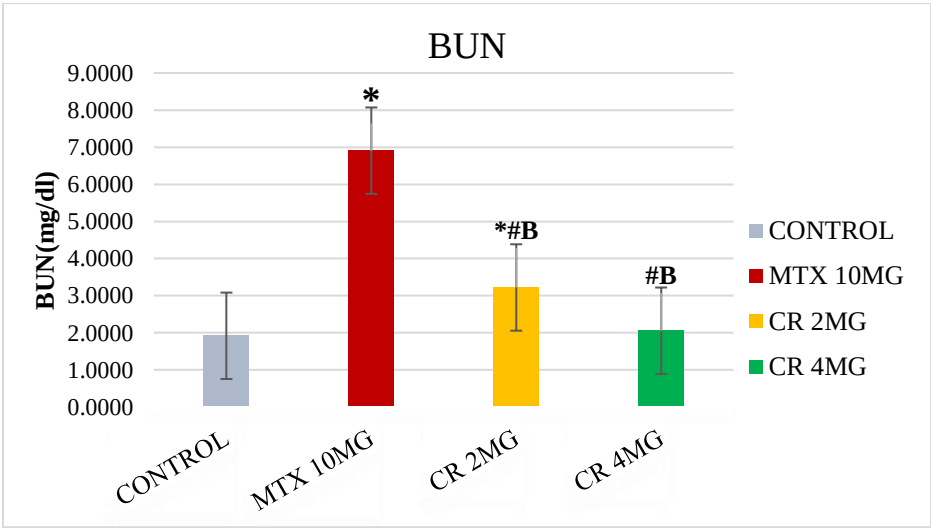

Figure 2. Effects of chromium on blood urea nitrogen (BUN) levels against methotrexate-induced Nephrotoxicity in male rats.

Table 2. The effect of chromium on the serum level of creatinine and BUN

Groups	Creatinine (mg/dl)	BUN(mg/dl)
Group I Negative control group	0.46±0.31	1.91±0.90
Group II MTX group	1.81±0.43*	6.90±0.35*
Group III Chromium 2mg +MTX	0.86±0.13 $^{\#A}$	3.22±0.12 $^{*\#B}$
Group IV Chromium 4mg +MTX	0.61±0.19 $^{\#A}$	2.05±0.15 $^{\#B}$

In this table, Data are expressed as Mean ± STD, the number of rats in each group =8.
Superscript (*) indicates a significant difference when compared to group I (control) (P<0.05).
Superscript (#) indicates a significant difference when compared to group II (MTX group) (P<0.05).
Identical capital letter (A) indicated there are no significant differences between test groups (p>0.05)
Identical capital letter (B) indicated there are significant differences between test groups (p<0.05)

Effects of chromium on the serum levels of malondialdehyde (MDA)

"Table 3" and "Figure. 3" show that there is a significant elevation in the levels of MDA in the MTX group as compared to the control group (P<0.05). At the same time, a significant decrease is observed comparing group III(chromium 2mg+mtx20mg) and group IV (chromium4mg

+mtx20mg) with the MTX group (P<0.05). Moreover, there was a significant difference between group III and group IV (p<0.05).

Effects of chromium on the expression of superoxide dismutase-1 (SOD-1)

In "Table 3" and "Figure. 4" shows that there is a significant decrease in the levels of SOD expression in the group II MTX group as compared to the group I control group (P<0.05). At the same time, no significant difference was observed when comparing group III(chromium 2mg+mtx20mg) with the MTX group (P>0.05). Interestingly, in the same table, there was a significant difference when the expression of SOD in group IV(chromium 4mg+mtx20mg) when compared to the MTX group (P<0.05). Moreover, there was no significant difference between groups III and IV (P>0.05).

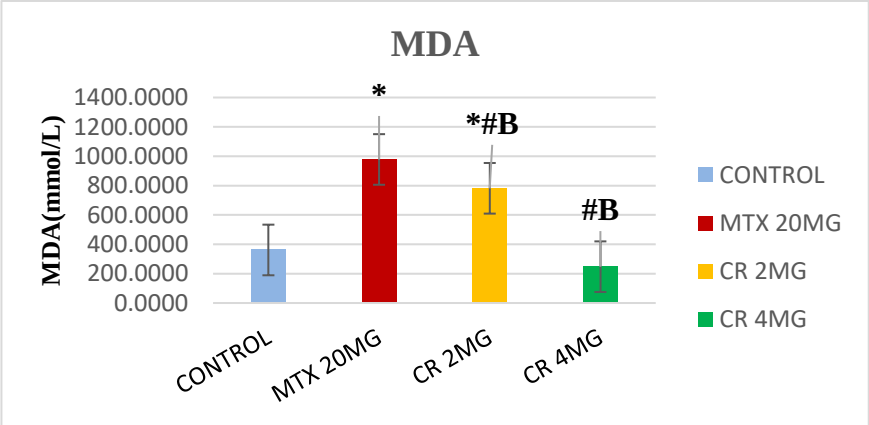

Figure 3. The effect of treatment with chromium on MDA levels against methotrexate-induced Nephrotoxicity in male rats.

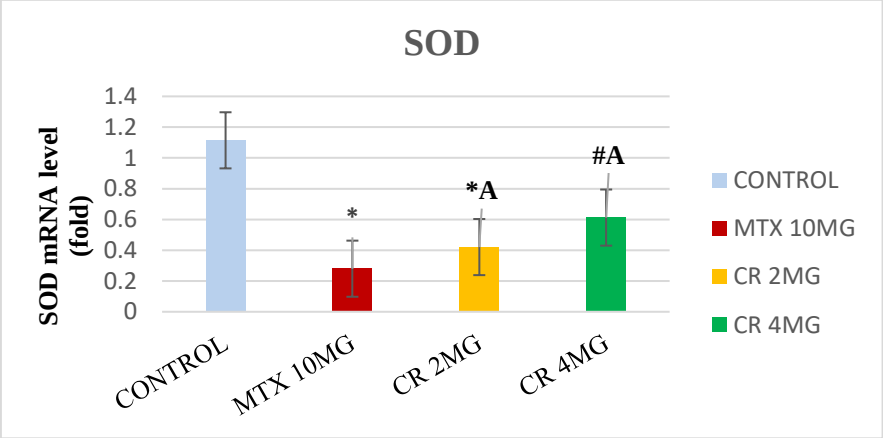

Figure 4. Effects of chromium on superoxide dismutase (SOD) expression against methotrexate-induced Nephrotoxicity in male rats.

Table 3. The effect of treatment with chromium on the levels of malondialdehyde (MDA) and superoxide dismutase (SOD-1) mRNA expression against methotrexate-induced Nephrotoxicity in male rats.

Groups	MDA (mmol/L)	SOD mRNA (folds)
Group I Negative control group	361.40±174.58	1.11±0.50
Group II MTX group	978.03±25.87 *	0.27±0.11 *
Group III Chromium 2mg +MTX	781.48± 82.59 $^{*\#B}$	0.42±0.23 ^{*A}
Group IV Chromium 4mg +MTX	247.52±40.14 $^{\#B}$	0.61±0.21 $^{\#A}$

In this Table, Data are expressed as Mean ± STD, the number of rats in each group =8.
Superscript (*) indicates a significant difference when compared to group I (control) (P<0.05).
Superscript (#) indicates a significant difference when compared to group II (MTX group) (P<0.05).
Identical capital letter (A) indicated there are no significant differences between test groups (p>0.05)
Identical capital letter (B) indicated there are significant differences between test groups (p<0.05)

Discussion

Acute kidney injury (AKI) is a significant medical condition that can lead to end-stage renal disease (ESRD) with potentially fatal outcomes if not correctly identified and managed [24]. The primary cause of AKI is nephrotoxic medications, which are medicinal substances that have adverse side effects and impair renal function [25]. Research has demonstrated that large dosages of MTX can result in uremia, hematuria, elevated blood creatinine levels, and acute renal failure. After MTX treatment, renal impairment is the most prevalent adverse effect [26]. The typical presentation includes non-oliguric renal failure, defined by a sudden increase in serum creatinine levels during or immediately after MTX infusion. There may also be symptoms such as bone marrow suppression, liver fibrosis, pneumonitis, homoeopathy, baldness, nausea, vomiting, and Diarrhea [27]. It is still unclear how MTX causes Nephrotoxicity. However, they discovered that the main reason for tissue destruction caused by MTX is oxidative damage, which can produce free radicals. It is known how oxidative stress (OS) contributes to MTX-induced Nephrotoxicity [28]. Furthermore, researchers demonstrated that MTX boosted the formation of reactive oxygen species by overpowering homocysteine remethylation, NADPH depletion, neutrophil stimulation, NADPH oxidase activation, and mitochondrial dysfunction [29]. Results of the present research revealed that the administration of chromium following MTX treatment effectively mitigated kidney damage by reducing OS. Urea and creatinine are good markers of appropriate kidney function and increases of them in the serum are symptoms of renal impairment [30, 31]. Blood urea nitrogen (BUN) and serum creatinine levels were significantly higher in the MTX induction group than in the control group which indicated that there may be a slight blockage in excreting urea in kidney disease patients and an impairment of renal function caused by a decrease in GFR or an obstruction that interferes with urine excretion. This study demonstrates that the administration of CrPic for seven days resulted in a substantial reduction in serum creatinine, BUN levels in the CrPic group compared to the MTX group which is compatible with a result obtained previously which demonstrated that after eight weeks of CrPic administration, serum creatinine, BUN, and urinary albumin all significantly decreased in the CrPic-treated group, compared to the diabetic nephropathy group [32]. Additionally, another study conducted on diabetic male mice demonstrated that high doses of CrPic causes moderate reduction in albuminuria with a slight improvement in the creatinine clearance [33]. The present study proposes that CrPic restore renal function in rats by reducing the adverse reactions induced by MTX. Oxidative stress is common in people with AKI and is thought to be an essential inflammatory process. Oxidative stress happens when the production of free radicals is out of balance, often caused by mitochondria dysfunction [34]. MDA is a substance that is produced as a result of the breakdown of fats (lipid peroxidation) in the body. Therefore, evaluating the concentration of MDA in the kidneys can provide information on the level of damage to the kidney cells. It is commonly known that OS plays a significant role in the pathophysiology of renal damage caused by MTX [35]. The results of this study confirm that the kidney of the MTX group exhibited a decrease in SOD expression and an increase in MDA. These findings may indicate that the kidney is undergoing a disrupted redox balance, a formation of reactive oxygen species (ROS), and an increase in lipid peroxidation in rats. Following seven days of CrPic therapy, MDA levels stabilized, and SOD activity went back to normal. This implies that CrPic reduces the oxidative stress and serve as restoring agent against Nephrotoxicity. The present study found that a high dose of chromium (4 mg/kg) significantly reduced MDA, SOD, BUN, and creatinine levels. Conversely, a lower chromium 2mg/kg dose was less effective in achieving these outcomes. The explanation of the role of CrPic in restoring renal functions assumed to be the result of its anti-oxidant activity that comfirmed by the results of the present study which showed significant reduction in the MDA levels with a significant increase in the expression of SOD-1 enzyme which is considered as strong evidence that support the previously demonstrated results. Previous studies demonstrated that the administration of CrPic showed an antioxidant and anti-inflammatory effect which is reflected in the histological improvement of the renal tissues and support the renal performance [32,33].

Conclusion

It was concluded that the administration of CrPic can improve the kidney function parameters that include creatinine and BUN and reduces the oxidative stress and serve as restoring agent against Nephrotoxicity as it causes a decrease in the levels of creatinine, BUN, and MDA with an increase in the levels of SOD expression which may indicate that chromium in a trivalent form can be used as promising protective agent against MTX-induced nephrotoxicity.

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Conflicts of Interest

The author affirms the absence of any conflict of interest.

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Ethics Statements

The study received approval from the scientific and ethical committees of the College of Pharmacy at the University of Baghdad. Approval Number: RECAUBCP211222023K in 2023/12/21.

Author Contribution

The authors confirm contribution to the paper as follows: Jehan Najm Aldeen Farhan made contributions to the study in the areas of data collection, analysis, practical (follow the process), and written components for the research. Ali Faris Hassan provided his ultimate consent and acceptance for all areas of the study, including those pertaining to monitoring, review, and rearrangement.

References

1. Rashed AR, Mohamed AS, Soliman AM. Ameliorative Effect of Galium Verum (Rubiaceae Family) Methanolic Extract on Folic Acid-induced Acute Kidney Injury in Male Rats. Iraqi J Pharm Sci. 2023; 32(3):14–24.
2. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019; 394(10212):1949–1964.
3. Rewa O, Bagshaw SM. Acute kidney injury-epidemiology, outcomes and economics. Nat Rev Nephrol. 2014;10(4):193-207.
4. Sales GTM, Foresto RD. Drug-induced nephrotoxicity. Rev Assoc Med Bras (1992). 2020;66Suppl 1(Suppl 1):s82-s90.
5. Soares S, Souza LCR, Cronin MT, Waaga-Gasser AM , Grossi MF, Franco GR, Tagliati CA. Biomarkers and in vitro strategies for nephrotoxicity and renal disease assessment. J Nephrol Renal Dis. 2020; 5:1-14 ISSN 2399-908X.
6. Morsy MA, El-Sheikh AAK, Ibrahim ARN, El-Daly M. Protection of hesperidin against Methotrexate-Induced Nephrotoxicity may be Mediated by Nrf2/HO-1 Pathway. Indian J Pharm Educ Res. 2021; 55(4):1066–73
7. Ramsey LB, Balis FM, O'Brien MM, Schmiegelow K, Pauley JL, Bleyer A, Widemann BC, Askenazi D, Bergeron S, Shirali A, Schwartz S, Vinks AA, Heldrup J. Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance. Oncologist. 2018;23(1):52-61.
8. Mohammed Zakri NM, Al-Shawi NN. Possible protective effects of two different doses of Cyanocobalamin against Methotrexate Nephrotoxicity Model in Rats. Iraqi J Pharm Sci. 2022; 31(2):211–7.
9. Mahmoud AM , Hussein OE , Abd El-Twab SM , Hozayen WG . Ferulic acid protects against methotrexate nephrotoxicity via activation of Nrf2/ARE/HO-1 signaling and PPARγ, and suppression of NF-κB/NLRP3 inflammasome axis. Food Funct. 2019;10(8):4593-4607.
10. Abdel-Daim MM, Khalifa HA, Abushouk AI, Dkhil MA, Al-Quraishy SA. Diosmin Attenuates Methotrexate-Induced Hepatic, Renal, and Cardiac Injury: A Biochemical and Histopathological Study in Mice. Oxid Med Cell Longev. 2017; 2017:1–10.
11. Stępniowska A, Juśkiewicz J, Tutaj K, Fotschki J, Fotschki B, Ognik K. Effect of chromium picolinate and chromium nanoparticles added to low-or high-fat diets on chromium biodistribution and the blood level of selected minerals in rats. Pol J Food Nutr Sci. 2022; 72(3): 229-238.
12. Prasad S, Yadav KK, Kumar S, Gupta N, Cabral-Pinto MMS, Rezania S, Radwan N, Alam J. Chromium contamination and effect on environmental health and its remediation: A sustainable approaches. J Environ Manage. 2021;285:112174.
13. MARMETT B, NUNES RB. Effects of chromium picolinate supplementation on control of metabolic variables: A Systematic Review. J Food Nutr Res. 2016; 4(10): 633-639.
14. Kooshki F, Tutunchi H, Vajdi M, Karimi A, Niazkar HR, Shoorei H, Pourghassem Gargari B. A Comprehensive insight into the effect of chromium supplementation on oxidative stress indices in diabetes mellitus: A systematic review. Clin Exp Pharmacol Physiol. 2021 Mar;48(3):291-309.
15. Morsy MA, El-Sheikh AAK, Abdel-Hafez SMN, Kandeel M, Abdel-Gaber SA. Paeonol Protects Against Methotrexate-Induced Nephrotoxicity *via* Upregulation of P-gp Expression and Inhibition of TLR4/NF-κB Pathway. Front Pharmacol. 2022 Feb 4;13:774387.
16. Liu Y, Wang D. Administration of Chromium (III) and manganese (II) as a potential protective approach against Daunorubicin-Induced Cardiotoxicity: in vitro and in vivo Experimental Evidence. Biol. Trace Elem. Res. 2013; 156(1–3):253–61.
17. Aledani AHE, Khudhair NA, Alrafas HR. Effect of different methods of anesthesia on physiobiochemical parameters in laboratory male rats. Basra J Vet Res. 2020; 19(1): 206-214.
18. Greenfield EA. Sampling and Preparation of Mouse and Rat Serum. Cold Spring Harb Protoc. 2017S;2017(11):pdb.prot100271.
19. Voller A, Bartlett A, Bidwell DE. Enzyme immunoassays with special reference to ELISA techniques. J Clin Pathol. 1978;31(6):507-20.
20. Mahmood SH, Hassan AF. The Protective Effect of Omega-7 on Cisplatin-Induced Nephrotoxicity in Rat Model. Iraqi J Pharm Sci. 2023; 32(2):128–33.

21. Robinson N, Ganesan R, Hegedűs C, Kovács K, Kufer TA, Virág L. Programmed necrotic cell death of macrophages: Focus on pyroptosis, necroptosis, and parthanatos. Redox Biol. 2019;26:101239.

22. Mahmood YS, Kadhim SH. Protective Effects of Citronellol Against Rhabdomyolysis-Induced Acute Kidney Injury in Mice by Inhibiting NF-κB and IL-1β Signaling Pathway. Iraqi J Pharm Sci. 2023; 32:85–90.

23. ALDOSSARY SA. Protective effect of hesperidin against methotrexate-induced nephrotoxicity in rats. Life Science Journal. 2019; 16(2): 18-22.

24. Yeh HC, Ting IW, Huang HC, Chiang HY, Kuo CC.Acute kidney injury in the outpatient setting associates with risk of end-stage renal disease and death in patients with CKD. Sci Rep. 2019; 9(1): 17658.

25. Finlay S, Bray B, Lewington AJ, Hunter-Rowe CT, Banerjee A, Atkinson JM, Jones MC. Identification of risk factors associated with acute kidney injury in patients admitted to acute medical units. Clin Med (Lond). 2013;13(3):233-8.

26. Amitai I, Rozovski U, El-Saleh R, Shimony S, Shepshelovich D, Rozen-Zvi B, Raanani P, Gafter-Gvili A, Gurion R. Risk factors for high-dose methotrexate associated acute kidney injury in patients with hematological malignancies. Hematol Oncol. 2020;38(4):584-588.

27. Hamed KM, Dighriri IM, Baomar AF, Alharthy BT, Alenazi FE, Alali GH, Alenazy RH, Alhumaidi NT, Alhulayfi DH, Alotaibi YB, Alhumaidan SS, Alhaddad ZA, Humadi AA, Alzahrani SA, Alobaid RH. Overview of Methotrexate Toxicity: A Comprehensive Literature Review. Cureus. 2022;14(9):e29518.

28. Wasfey EF, Shaaban M, Essam M, Ayman Y, Kamar S, Mohasseb T, Rozik R, Khaled H, Eladly M, Elissawi M, Bassem A, Elshora SZ, Radwan SM. Infliximab Ameliorates Methotrexate-Induced Nephrotoxicity in Experimental Rat Model: Impact on Oxidative Stress, Mitochondrial Biogenesis, Apoptotic and Autophagic Machineries. Cell Biochem Biophys. 2023;81(4):717-726.

29. Mahmoud AM, Germoush MO, Al-Anazi KM, Mahmoud AH, Farah MA, Allam AA. Commiphora molmol protects against methotrexate-induced nephrotoxicity by up-regulating Nrf2/ARE/HO-1 signaling. Biomed Pharmacother. 2018;106:499-509.

30. Yano M, Nishino M, Ukita K, Kawamura A, Nakamura H, Matsuhiro Y, Yasumoto K, Tsuda M, Okamoto N, Matsunaga-Lee Y, Egami Y, Tanouchi J, Yamada T, Yasumura Y, Tamaki S, Hayashi T, Nakagawa A, Nakagawa Y, Sotomi Y, Nakatani D, Hikoso S, Sakata Y; Osaka CardioVascular Conference (OCVC)-Heart Failure Investigators. Clinical impact of blood urea nitrogen, regardless of renal function, in heart failure with preserved ejection fraction. Int J Cardiol. 2022;363:94-101.

31. MAHDI EM. The Influences of Aminophylline and Indomethacin in Glycerol-Induced Acute Renal Failure in Rats. Al-Kindy Col Med J. 2010; 6(1): 62-70.

32. Qi SS, Zheng HX, Jiang H, Yuan LP, Dong LC. Protective Effects of Chromium Picolinate Against Diabetic-Induced Renal Dysfunction and Renal Fibrosis in Streptozotocin-Induced Diabetic Rats. Biomolecules. 2020;10(3):398.

33. Mozaffari MS, Baban B, Abdelsayed R, Liu JY, Wimborne H, Rodriguez N, Abebe W. Renal and glycemic effects of high-dose chromium picolinate in db/db mice: assessment of DNA damage. J Nutr Biochem. 2012;23(8):977-985.

34. Piko N, Bevc S, Hojs R, Ekart R. The role of oxidative stress in kidney injury. Antioxidants. 2023; 12(9) :1772.

35. Abd MR, Hassan AF. The Ameliorative Effect of Fimasartan against Methotrexate-Induced Nephrotoxicity in Rats. Iraqi J Pharm Sci. 2022; 31(1):87–94.

التأثير الوقائي لبيكولينات الكروم في التسمم الكلوي المحدث بالميثوتريكسيت في نموذج الجرذان

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الخلاصة

الميثوتريكسات، وهو أحد مضادات حمض الفوليك، هو علاج كيميائي يستخدم بشكل متكرر في علاج أشكال معينة من السرطان. السمية الكلوية الناجمة عن جرعة عالية من الميثوتريكسيت هي حالة طبية طارئة بسبب تأخر إفراز الميثوتريكسيت عن طريق الكلى. الكروم هو عنصر نادر موجود في بعض الأطعمة والبيئة المحيطة ووظيفته العلاجية الرئيسية هي تنظيم مستويات الجلوكوز حيث يستخدم كمكمل من قبل الأشخاص المصابين بداء السكري من النوع ٢. هدفت هذه الدراسة إلى تقييم التأثير العلاجي للكروم ضد التسمم الكلوي الناجم عن الميثوتريكسيت في الجرذان. شملت هذه الدراسة اثنين وثلاثين جرذ من نوع ويستار تم تقسيمهم إلى أربع مجموعات كالتالي: المجموعة الضابطة (السيطرة) حيث تم إعطاء الجرذ الماء المقطر عن طريق الفم لمدة ثمانية أيام متتالية، المجموعة المُحَفَزَة حيث تم حقن الميثوتريكسيت في الصفاق بجرعة وحيدة قدرها ٢٠ ملغم/كغم من وزن الجرذ في اليوم الأول. وفي لأيام التالية، تلقت الجرذان الماء المقطر لمدة سبعة أيام، المجموعة الثالثة (كروم ٢ ملغ/كغم من وزن الجرذ) شملت جرذان تم حقنهم بالميثوتريكسات بجرعة ٢٠ ملغم/كغم داخل الصفاق، جرعة واحدة في اليوم الأول و في الأيام التالية ، تلقت الجرذان بيكولينات الكروم بجرعة (٢ ملغم/كغم من وزن الجرذ) عن طريق الفم باستخدام الأنبوب الفموي لمدة سبعة أيام، المجموعة الرابعة (الكروم ٤ ملغ/كغم): شملت جرذان تم حقنهم الميثوتريكسات بجرعة ٢٠ ملغم/كغم داخل الصفاق بجرعة واحدة في اليوم الأول و في الأيام التالية ، تلقت الجرذان

بيكولينات الكروم بجرعة (٤ ملغم/كغم) عن طريق الفم باستخدام الأنبوب الفموي لمدة سبعة أيام. وتم قياس معدلات الكرياتينين ونيتروجين يوريا الدم والمالونديالدهيد مع تقييم نسب التعبير الجيني لانزيم فوق أكسيد ديسموتاز-لكل المجموعات التي شملتها الدراسة. أشارت نتائج هذه الدراسة إلى أن حقن الميثوتريكسات (٢٠ ملغم/كغم) أدى إلى زيادة معنوية في الكرياتينين ونيتروجين يوريا الدم والمالونديالدهيد وانخفاض معنوي في التعبير الجيني لانزيم فوق أكسيد ديسموتاز-١. ومن المثير للاهتمام أن المعاملة ببيكولينات الكروم (٢ ملغم/كغم) و (٤ ملغم/كغم) أظهرت انخفاضًا معنويًا في الكرياتينين ونيتروجين يوريا الدم والمالونديالدهيد وزيادة معنوية في التعبير الجيني لانزيم سوبر أكسيد ديسموتاز –١ مقارنة بالجرذان المعالجة بالميثوتريكسات. أظهر البحث الحالي أن إعطاء الكروم للجرذان له تأثير مفيد على تقليل السمية الكلوية الناتجة عن الميثوتريكسيت. ويتحقق ذلك من خلال تعزيز الدفاعات المضادة للأكسدة في الكلى.

الكلمات المفتاحية: مضادات الأكسدة، السمية الكلوية، بيكولينات الكروم، الميثوتريكسيت، كرياتينين.