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The Anti-Inflammatory Effect of Chromium Picolinate in Doxorubicin Induced Cardiotoxicity in Rats

Asmaa Muhammad Khalifa [*,1] and Ali Faris Hassan[2]

[1]Ministry of Health, Baghdad Al-Karkh Health Directorate, Baghdad, Iraq.
[2]Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
***Corresponding author**
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Abstract

Doxorubicin is a potent antineoplastic drug used to treat many types of human tumor that causes cardiomyopathy as a long-term adverse effect as a result of the extensive production of reactive oxygen species which relates to several events related to nucleic acid metabolism and the activation of the immune system. Chromium is an essential trace element mostly used to regulate glucose levels and enhance the response to insulin, especially in diabetes. The current study aims to evaluate the anti-inflammatory effect of chromium picolinate in doxorubicin-induced cardiotoxicity of rats. Twenty-eight Wister male rats were used in this study and divided into 4 groups (7 animals in each group). Group I (Control): Rats received distilled water orally for 8 days. Group II: Rats administered distilled water orally for 7 days, followed by a single dose of doxorubicin (25 mg/kg) IP. Group III: Rats received 2 mg /kg chromium picolinate orally for 7 days, followed by a single dose of doxorubicin (25 mg/kg) IP. Group IV: Rats received 4 mg /kg chromium picolinate orally for 7 days, followed by a single dose of doxorubicin (25 mg/kg) IP. All animals have been euthanized on the ninth day and the levels of lactate dehydrogenase, creatine kinase MB and Interleukin1β were assessed in the sera of all groups by ELISA technique while the cardiac homogenate used to assess Tumor necrosis factor α expression by RT-qPCR method. The outcome of this study indicated that single IP dose of doxorubicin (25mg/kg) caused a significant elevation in cardiac creatine kinase MB, lactate dehydrogenase, and inflammatory cytokines (Interleukin1β and Tumor necrosis factor α) in group 2 compared to group 1 ($P<0.05$). Interestingly, co-administration of 2 or 4mg/kg chromium picolinate caused a significant decrease in cardiac biomarkers and inflammatory cytokines in groups 3 and 4 compared to group 2 ($P<0.05$). Larger dose of chromium (4mg/kg) was more effective than the lower dose (2mg/kg) at reducing doxorubicin induced cardiotoxicity which indicated that chromium picolinate may have a potential role in reducing cardiac injury and inflammation in patients treated with doxorubicin. Recommendation for future studies may use chromium picolinate with other anticancer drugs.

Keywords: Cardiotoxicity, Chromium picolinate, Creatine kinase MB, Lactate dehydrogenase, Tumor necrosis factor alpha.

Introduction

Doxorubicin (DOX) is a potent anthracycline antibiotic used in treatment of many types of human neoplasms. However, research has identified a significant cardiotoxic effect following an acute, as well as cumulative DOX dosage, which reduces the clinical value of medication [(1)]. The long-term adverse effects of DOX are permanent such as cardiomyopathy that can result in congestive heart failure [(2)].There are many theories explaining cardiotoxic effects of doxorubicin [(3)]. Cardiotoxicity is primarily caused by the extensive production of reactive oxygen species (ROS), resulting in several events related to nucleic acid metabolism, mitochondrial damage and the activation of the immune system [(4)] .

Apoptosis has recently been submitted as a prevalent mechanism for acute and chronic damage of cardiomyocytes [(3,4)].

Doxorubicin has been indicated as one of the most potent agents in inducing apoptosis in many different types of cells [(4)]. Treatment with DOX caused structural alteration in the mitochondria, resulting in the depletion of ATP generation. The interaction between DOX and a membrane phospholipid, cardiolipin that presents in the inner membrane of mitochondria in cardiomyocytes, appears to be affected by DOX induced cardiotoxicity. The anionic charge of cardiolipin binds irreversibly with the cationic charge of DOX, resulting in the formation of Doxorubicin cardiolipin complex causing the mitochondrial dysfunction.

The DOX cardiolipin complex affects the role of cardiolipin in the chain of electron transport, with the consequent inhibition of many enzymes, such as cytochrome c oxidase and cytochrome c oxidoreductase [5].

No particular treatments exist to prevent or cure DOX-induced cardiotoxicity, and only a limited number of cardioprotective agents are being tested in patients, primarily restricted to normal heart failure medications. The sole medicine approved by the FDA specifically for DIC is dexrazoxane. Dexrazoxane is an iron-chelating compound that addresses oxidative stress. Research has demonstrated that certain pharmacological agents, including antioxidants, iron chelators, calcium antagonists, hypoglycemic agents, redox modulators, and specific receptor antagonists, can mitigate DOX-induced cardiotoxicity [6].

Chromium (Cr) is an essential trace element mostly indicated to regulate glucose levels and enhance the response of body to insulin, particularly in diabetes. This mineral has two different forms: a toxic hexavalent form and an organic trivalent form. Chromium supplements often contain Chromium in its trivalent state, coupled with ligands such as picolinic acid, to form a compound known as chromium picolinate [7]. Chromium (Cr+3) is mostly known for its potential role in regulating glucose levels by the activation of apochromodulin to chromodulin which is important for amplifying the insulin signaling effect [8]. Additionally, chromium picolinate has been found to have valuable effects on cardiovascular diseases by lowering cholesterol levels and blood pressure, as well as antioxidant and anti-inflammatory ability. It also has the ability to modulate behavioral patterns such as depression and anxiety, and to cause physical changes such as improved body composition and training performance [9,10].

The current study aims to evaluate the cardio protective of chromium picolinate impact in doxorubicin-induced cardiotoxicity and inflammation in a rat model.

Materials and Methods

Materials

In this current study, Doxorubicin HCL and Chromium picolinate were used. Doxorubicin HCL was acquired from Pfizer laboratories in USA, whereas chromium picolinate was obtained from Source Naturals in the United States.

Experimental design

Twenty-eight Wister rats weighing (160-200) gm were brought and kept in animal house of Pharmacy college/ Baghdad University, at standard temperatures, humidity, and light/ dark cycles, ethical approval were taken from the scientific and ethical committees with approval number: RECAUBCP221122023K in 21/12/2023. Rats used in the study were divided randomly into 4 groups:

1. Group I (Control group): Rats received distilled water orally for eight days. The rats were euthanized on the ninth day.
2. Group II (DOX group): Rats that received distilled water orally for seven days. On the eighth day, rats were injected with doxorubicin as a single dose (25 mg/kg) IP. The rats were euthanized on the ninth day.
3. Group III (Chromium 2 mg): Rats that received Chromium picolinate at a dose (2 mg /kg) orally for seven days. On the eighth day, rats were injected with doxorubicin in a single dose (25 mg/kg) IP. The rats were euthanized on the ninth day.
4. Group IV (Chromium 4 mg): Rats that received Chromium picolinate at a dose (4 mg /kg) orally for seven days. On the eighth day, rats were injected with doxorubicin in a single dose (25 mg/kg) IP. The rats were euthanized on the ninth day.

After 24 hours from DOX administration, whole blood was collected from the jugular vein under diethyl ether anesthesia. Then, the animals were euthanized by cervical dislocation under diethyl ether anesthesia. Then, cardiac tissues were separated for examination. Experimental design and procedure were done with small modification according to [11-13].

Preparation of serum samples

Animals' blood was drawn from the jugular vein under diethyl ether anesthesia [14,15]. Whole blood was collected in a serum separator tube at room temperature for 30 minutes for clotting. Then, centrifuging for 15 minutes at 3000 rpm to obtain serum. The supernatant was then transferred as 250µl aliquots into appropriately labelled micro-centrifuge tubes and maintained at −20°C until use for the estimation of LDH, CK-MB and IL-1β by ELISA technique [16,17].

Gene Expression analysis

"The Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)" method was utilized to estimate gene expression level of TNFα relative to the housekeeping gene GAPDH as a reference gene in cardiac tissue homogenate samples. The assay briefly involved total RNA extraction and purification, cDNA preparation, measurement of gene expression, and data analysis [18,19]. The sequence of the primers used for GAPDH and TNFα showed in Table1.

Table 1. The sequence of the primers used in this study

Primer	Sequence 5′→3′ direction
GAPDH F	CCATCAACGACCCCTTCATT
GAPDH R	CACGACATACTCAGCACCAGC
TNFα F	ATCCGAGATGTGGAACTGGC
TNFα R	ACTGATGAGAGGGAGCCCAT

Statistical analysis

The numeric data presented in this study were expressed as "mean ± standard deviation (STD)". The statistical analysis was done using "the Statistical Package for Social Sciences software (SPSS)" version 25. The differences between the mean values were determined by ANOVA. The significance threshold of $P<0.05$ was employed to detect statistical significance. If the estimated P-value is less than 0.05, it indicates statistical significance.

Results

Effect of Chromium picolinate on serum Lactate dehydrogenase (LDH) levels

The data analysis in Table 2 indicated a significant elevation in the serum LDH levels in group II and group III comparing to group I ($P<0.05$). At the same time, there is a significant decrease in LDH can be observed when comparing both group III (2mg/kg) and group VI (4mg/kg) with group II ($P<0.05$). Moreover, there was a significant difference when group III was compared to group IV ($P<0.05$).

Table 2. The Effect of Chromium picolinate on serum levels of LDH induced by doxorubicin in rats

GROUPS		LDH (pg/ml)
I.	Negative control group	27.99 ± 4.25
II.	DOX group	91.78 ± 1.37*
III.	Chromium 2mg/Kg+ DOX	76.95 ± 2.95*#a
IV.	Chromium 4mg/Kg + DOX	29.41 ± 4.15#b

- Data was expressed as Mean± STD.
- Superscript (*) indicates a significant difference when compared to group I (negative control) ($P<0.05$).
- Superscript (#) indicates a significant difference when compared to group II (positive control) ($P<0.05$).
- Values with small letter superscripts (a, b) between group III and group IV are considered significantly different ($P<0.05$).

Effect of Chromium picolinate on the serum levels of Creatine Kinase (CK-MB)

The data analysis in Table 3 indicated a significant elevation in the serum CK-MB levels in group II and group III comparing to group I ($P<0.05$). At the same time, there is a significant decrease in CK-MB can be observed when comparing both group III (2mg/kg) and group VI (4mg/kg) with group II ($P<0.05$). Moreover, there was a significant difference when group III was compared to group IV ($P<0.05$).

Table 3. The Effect of Chromium picolinate on serum levels of CK-MB Induced by doxorubicin in rats.

GROUPS		CK-MB (pg/ml)
I.	Negative control group	4.66 ± 0.19
II.	DOX group	17.81 ± 0.17*
III.	Chromium 2mg/Kg+ DOX	11.34 ± 1.14*#a
IV.	Chromium 4mg/Kg + DOX	4.31 ± 0.32#b

- Data was expressed as Mean± STD.
- Superscript (*) indicates a significant difference when compared to group I (negative control) ($P<0.05$).
- Superscript (#) indicates a significant difference when compared to group II (positive control) ($P<0.05$).
- Values with small letter superscripts (a, b) between group III and group IV are considered significantly different ($P<0.05$).

Effect of Chromium picolinate on the serum levels of IL-1β

The data analysis in Table 4 indicated a significant elevation in the serum levels of IL-1β in group II and group III as compared to group I (P<0.05). At the same time, there is a significant decrease in IL-1β can be observed when comparing both group III (2mg/kg) and group VI (4mg/kg) with group II (P<0.05). Moreover, there was a significant difference when group III was compared to group IV (P<0.05).

Table 4. The Effect of Chromium picolinate on serum levels of IL-1β induced by doxorubicin in rats

GROUPS		IL-1B (pg/ml)
I.	Negative control group	62.77 ± 14.02
II.	DOX group	584.45 ± 10.29*
III.	Chromium 2mg/Kg+ DOX	169.52 ± 8.94*#a
IV.	Chromium 4mg/Kg + DOX	65.53 ± 0.32#b

- Data was expressed as Mean± STD.
- Superscript (*) indicates a significant difference when compared to group I (negative control) (P<0.05).
- Superscript (#) indicates a significant difference when compared to group II (positive control) (P<0.05).
- Values with small letter superscripts (a, b) between group III and group IV are considered significantly different (P<0.05).

Effect of Chromium picolinate on TNFα m RNA expression

The data analysis in Table 5 indicated a significant elevation in the gene expression levels of TNFα in group II only as compared to group I (P<0.05). Interestingly, there is a significant decrease in gene expression levels of TNFα can be observed when comparing both group III (2mg/kg) and group VI (4mg/kg) with group II (P<0.05). Moreover, there was no significant difference when group III was compared to group IV (P>0.05).

Table 5. The Effect of Chromium Picolinate on TNFα m RNA Expression Induced by doxorubicin in Rats.

GROUPS		TNF α (folds)
I.	Negative control group	1.12 ± 0.62
II.	DOX group	3.21 ± 1.24*
III.	Chromium 2mg/Kg+ DOX	1.60 ± 0.21#
IV.	Chromium 4mg/Kg + DOX	1.41 ± 0.84#

- Data was expressed as Mean± STD.
- Superscript (*) indicates a significant difference when compared to group I (negative control) (P<0.05).
- Superscript (#) indicates a significant difference when compared to group II (positive control) (P<0.05).
- Values with small letter superscripts (a, b) between group III and group IV are considered significantly different (P<0.05).

Discussion

The predominant occurrence of cardiac failure and cardiomyopathy is the primary adverse effect associated with the administration of doxorubicin [20]. Chronic exposure to doxorubicin can lead to structural changes in the cardiac tissue, including fibrosis and hypertrophy, which compromise cardiac function [21].To evaluate cellular damage and membrane leakage, the integrity of the plasma membrane is often assessed by monitoring the activities of cytoplasmic enzymes such as LDH and CK-MB in the blood [22]. Lactate dehydrogenase is an enzyme that facilitates the conversion of lactate to pyruvate intracellularly, hence playing a vital part in cellular respiration and the generation of energy [22]. There is a potential association between LDH and doxorubicin in cancer treatment [23]. In this current study, DOX administration to rats in group II led to a significant elevation of LDH levels due to cardiac tissue damage in comparison to group I (control group). These results were similar to those of other previous studies and showed the occurrence of cardiac injury after doxorubicin treatment [24-26]. Furthermore, pre-treatment with chromium picolinate in groups III and IV significantly reduced LDH levels compared to DOX group II. Creatine kinase (Creatine phosphokinase) is mostly found in the heart and skeletal muscle, less in the brain, and in trace amounts in the liver, red blood cells, and smooth muscle, where it catalyzes the phosphorylation of creatine [27].

Creatine kinase MB (CK-MB) is one of three isoenzymes of creatine kinase, with the other two being CK-BB (found in the brain) and CK-MM (found in skeletal muscle). When the cardiac tissue is damaged, CK-MB is released into the bloodstream, making its levels an important

indicator of cardiac injury [27].In this current study, DOX administration to rats in group II led to a significant elevation of CK-MB levels due to cardiac tissue damage in comparison to group I (control group). These results were similar to those of other studies which showed the precipitation of cardiac injury after doxorubicin treatment [28,29]. Furthermore, pre-treatment with chromium picolinate in groups III and IV significantly reduced CK-MB levels compared to DOX group II.

Doxorubicin promotes inflammation in cardiomyocytes by complex mechanisms that involve many pathways [30]. Doxorubicin induces oxidative stress and mitochondrial damage, leading to the activation of "the nuclear factor-kappa B (NF-κB) pathway". This system regulates the generation of many inflammatory cytokines, such as interleukins (IL-1β), tumor necrosis factor-alpha (TNF α), and others [31]. These cytokines exacerbate inflammation and further damage cardiomyocytes [31]. In this current study, DOX administration to rats in group II led to the activation of inflammatory cytokine response by the significant increase of cardiac TNF-α and IL-1β levels in comparison to group I (control group). These results were similar to those of other previous study conducted by Roberta Vitale in 2024 that has shown the crucial role of oxidative stress in the progression of cardiac injury following doxorubicin treatment [32]. Furthermore, pre-treatment with chromium picolinate in groups III and IV significantly reduced cardiac TNF-α and IL-1β levels comparing to DOX group II.

Conclusion

In conclusion, the results of this current study indicated that chromium picolinate has a cardio protective effect against cardiotoxicity induced by doxorubicin. Chromium picolinate has been found to play a significant role as a potential anti-inflammatory agent in chemotherapy. It could be used as a cytoprotective agent in patients treated with doxorubicin. Recommendation for future studies may use chromium picolinate with other anticancer drugs or studying the antioxidant effects of chromium picolinate in comparison with other known antioxidants like vitamin E.

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Conflicts of Interest

The authors have no conflict of interests.

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Ethics Statements

The study was approved by the scientific and ethical committees of the College of Pharmacy University of Baghdad. Approval Number: RECAUBCP221122023K in 21/12/2023.

Author Contribution

The authors confirm their contribution to the paper as follows: Khalifa AM did the practical work and result analysis; Hassan AF supervised the whole work.

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التأثيرات المضاد الالتهابي لمكملات الكروم ضد السمية القلبية الناتجة عن الدوكسوروبيسين في نموذج الجرذان

اسماء محمد خليفة [١] و علي فارس حسن [٢]

[١] وزارة الصحة دائرة صحة بغداد، الكرخ، بغداد، العراق.

[٢] فرع الادوية والسموم، كلية الصيدلة، جامعة بغداد، بغداد، العراق.

الخلاصة

دوكسوروبيسين هو مضاد حيوي قوي من نوع انثراسيكلين يستخدم لعلاج العديد من الأورام البشرية. الاستخدام طويل الامد له تأثير السلبي و هو اعتلال عضلة القلب ، والذي يحدث بسبب الانتاج المكثف لأنواع الأوكسجين التفاعلية ،والذي يرتبط بالعديد من الأحداث المتعلقة باستقلاب الحمض النووي والجهاز المناعي .الكروم هو عنصر نادر يستخدم في الغالب لتنظيم مستويات الجلوكوز وتعزيز استجابة الجسم للأنسولين وخاصة في الأفراد المصابين بداء السكري. تهدف الدراسة الحالية الى تحديد ما اذا كانت بيكولينات الكروم قد يكون لها تأثير وقائي للقلب في نموذج الجرذان لتسمم القلب والالتهاب الناجم عن الدوكسوروبيسين. تم تقسيم ثمانية وعشرون من ذكور الجرذان ويستر الى أربع مجموعات (سبعة جرذان في كل مجموعة).المجموعة الأولى : تلقت الجرذان الماء المقطر عن طريق الفم لمدة ثمانية ايام. المجموعة الثانية : الجرذان التي تلقت الماء المقطر عن طريق الفم لمدة سبعة ايام . في اليوم الثامن تم حقن الجرذان بالدوكسوروبيسين كجرعة واحدة (٢٥ مجم / كجم). المجموعة الثالثة : الجرذان التي اعطيت بيكولينات الكروم بجرعة (٢مجم / كجم) عن طريق الفم لمدة سبع ايام. في اليوم الثامن تم حقن الجرذان بالدوكسوروبيسين بجرعة واحدة (٢٥ مجم / كجم. المجموعة الرابعة : الجرذان التي اعطيت بيكولينات الكروم بجرعة (٤مجم / كجم) عن طريق الفم ولمدة سبعة ايام . في اليوم الثامن تم حقن الجرذان بالدوكسوروبيسين بجرعة واحدة (٢٥ مجم / كجم). وتم التضحية بجميع الحيوانات في اليوم التاسع وتم قياس مستويات انزيم هيدروجين اللاكتات والكرياتين كيناز و الانترلوكين ١ بيتا في مصل الجرذان بينما تم قياس مستوى التعبير الجيني لعامل نخر الورم الفا في في متجانسة الأنسجة حيث اضهرت النتائج ان حقن دوكسوروبيسين تسبب في ارتفاع كبير في مستوى انزيم هيدروجين اللاكتات والكرياتين كيناز والستوكينات المؤيدة للالتهاب في المجموعة الثانية مقارنة بالمجموعة لاولى . في الوقت نفسه ادت المعالجة المسبقة ببيكولينات الكروم الى انخفاض كبير في المؤشرات الحيوية للقلب والسيتوكينات المؤيدة للالتهابات في المجموعتين الثالثة والرابعة مقارنة بالمجموعة الثانية. كانت الجرعة الاكبر من الكروم اكثر فعالية من الجرعة الاقل في تقليل سمية القلب الناتجة عن الدوكسوروبسين. واشارت هذه الدراسة الى ان بيكولينات الكروم لها دور محتمل في تقليل اصابات القلب والالتهابات لدى المرضى الذين عالجوا بالدوكسوروبسين. ومن الموصى به للدراسات المستقبلية استخدام بيكولينات الكروم مع أدوية أخرى مضادة للسرطان

الكلمات المفتاحية: سمية القلب, بيكولينات الكروم, كرياتين كيناز, انزيم نازع هيدروجين اللاكتات, عامل نخر الورم.