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Lycopene Supplement Restores the Oxidation/Antioxidation Balance Through Efficient Antioxidant Activities in Wistar Rats with Cadmium-induced Oxidative Stress

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ABSTRACT

Background: Lycopene is a phytochemical exhibiting a wide range of health benefits and bioactivities. The present study focuses on lycopene's *in vivo* antioxidant properties and evaluates the efficiency of dietary lycopene supplements in alleviating cadmium-induced oxidative stress.

Methods: The experimental rats were divided randomly into four groups (n=20): untreated control, lycopene-treated, cadmium-exposed and cadmium-lycopene groups.

Result: The cadmium-exposed and Lycopene-accessed rats revealed improvements in both haematological and biochemical profiles. It was concluded that the efficient antioxidant properties of lycopene significantly help alleviate the alterations of the cadmium-induced oxidative stress.

Key words: Antioxidant, Biochemical profile, Cadmium toxicity, Lycopene, Oxidative stress.

INTRODUCTION

Lycopene ($C_{40}H_{56}$) is a bioactive phytochemical classified as a non-provitamin A carotenoid (Yin *et al*., 2019). It is produced as an intermediate metabolite during the synthesis of carotenoids in plants (Mozos *et al*., 2018). Lycopene is a lipid-soluble organic pigment found primarily in tomatoes, red and orange-colored vegetables, fruits such as watermelon, pink grapefruit and apricots (Arballo *et al*., 2021). The highest concentrations of lycopene are encountered in tomatoes (Hedyati *et al*., 2019). Around 90% of dietary lycopene being sourced from tomato and tomato-based products (Przybylaska, 2020).

Research has demonstrated that lycopene has various health benefits, serving as a preventative measure against a wide range of diseases (Joshi *et al*., 2020). The clinically beneficial effects of lycopene include anticancer properties, cardioprotection, antiobesity effects, renoprotection, osteoprotective, neuroprotection, antidiabetic effects, treatment for skin diseases, anti-inflammatory properties, hepatoprotection and addressing reproductive disorders (Doyle, 2020).

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them with its antioxidant systems. Excess generation of ROS is a major contributor to oxidative stress and the associated damage (Melendez-Martinez, 2019; Hasan *et al*., 2024).

The endogenous antioxidant system is specifically designed to accurately detect free radicals (an example of type oxidative metabolite), block their reaction sequences and mitigate their potentially damaging effects (Ellis *et al*., 2019; Rebai *et al*., 2023).

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Cadmium (Cd) is a well-known toxic heavy metal and its presence is associated with oxidative damage in tissues, particularly in the liver and kidneys. This metal significantly contributes to the initiation and progression of oxidative stress (Naviglio *et al*., 2019).

There is growing interest in natural antioxidants as dietary supplements (Basheer *et al*., 2023; Hidayatik *et al*., 2024), which can serve as preventive and therapeutic agents for various significant health conditions, including cancer, cardiovascular diseases, neurodegenerative

disorders, arthritis and age-related changes (Joshi *et al*., 2020; Moatasem *et al*., 2023).

This study aims to evaluate the antioxidant properties of lycopene in male Wistar rats subjected to heavy metal toxicity. Specifically, it investigates how lycopene can alleviate the harmful effects of oxidative stress induced by cadmium toxicity.

Materials and Methods

Ethical considerations

Laboratory rats were cared for and utilized according to the guidelines established by the Research Ethics Committee of Imam Mohammad Ibn Saud Islamic University (IMSIU), which comply with both institutional and national regulations (LAB-rats-2023-0223).

Experimental rats

Eighty adult male Wistar rats, aged three months weighing between 130-210 g, were used in this investigation. The rats were obtained from the inbred colonies at the animal house of the College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. The standard laboratory conditions, ambient temperature of 24±1°C, a 12-hour dark-light cycle and relative humidity ranging from 35-70%, were maintained.

Lycopene

Lycopene (Carotene,2,6,10,14,19,23,27,31-Octamethyl-dotriaconta-2,6,8,10,12,14,16,18,20,22,24,26,30-tridecaene) ($C_{40}H_{56}$) ≥98% (HPLC) from tomato (Molecular Weight: 536.87), was purchased from Sigma-Aldrich (Darmstadt, Germany) (CAS Number: 502-65-8). Lycopene was dissolved in chloroform to achieve a final concentration of 5 mg/mL.

Cadmium

Cadmium (Cd) was used in the form of cadmium chloride (CdCl2) of analytical grade (Merck, Darmstadt, Germany) (Product No. 655198). Cadmium was dissolved in purified water to prepare the required aqueous solution.

Experimental design

The experimental work was carried out at Biology Department, College of Science, Imam Mohammad Ibn Saud Islamic University over a period extending from September to December, 2023. The rats were acclimatized for one week and then randomly allotted into four groups; of 20 rats each, designated as Groups 1, 2, 3 and 4. Group 1 served as the untreated control (not exposed to cadmium and did not received lycopene). Group 2 rats were administered daily with lycopene via oral route at a dose rate of 80 mg/kg b.wt. (Baz *et al*., 2022) at a rate of 1 mL/kg b.wt. Rats in Group 3 received $CdCl_2$ as an aqueous solution through oral gavage at a final concentration of 5 mg/kg b.wt. (Adeleke *et al*., 2023)/day at a rate of 1 mL/kg b.wt. The control rats received an equivalent volume of saline. Rats in Group 4 were administered with $CdCl_2$ and lycopene orally at the same aforementioned doses. A 10-hour gap was maintained between the daily administration of $CdCl_2$ and lycopene. The experimental duration was eight weeks. The rats were fed *ad libitum* with pellet feed and water.

Hematological and biochemical assays

The rats were anesthetized with 3% isoflurane at the termination of the experiment and blood samples were collected *via* cardiac puncture from all experimental rats. Various haematological indices were assessed using blood samples collected with an anticoagulant (EDTA). Serum harvested from coagulated blood samples was stored at -20°C until biochemical assays were performed. Rats were then sacrificed after silencing with diazepam and with suitable anesthetic then liver and kidney tissues were removed and homogenized in 150 mM NaCl. The homogenates were centrifuged at 3000 × g at 4°C for 10 minutes and various biochemical parameters were measured using the collected supernatants.

Blood cadmium level

To assess cadmium levels in the blood, 1 mL blood samples were digested using a mixture of $HClO_4$ and HNO_3 and blood cadmium levels were determined using an atomic absorption spectrophotometer (CBC 906 AA).

Statistical analysis

Data in this study are expressed as means±standard deviation (S.D.). To compare means between different groups, one-way ANOVA and SPSS software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The normality and homogeneity of variances were checked and the independence of observations was ensured. The normality of the data was verified using the Shapiro-Wilk test. Results with a *P*-value less than 0.05 ($P<0.05$) were considered statistically significant.

Results and Discussion

Rats that were given lycopene, both alone and in combination with exposure to cadmium, showed normal behavioral activity and food intake when compared to the untreated control rats. In contrast, rats that were exposed to cadmium without lycopene treatment displayed a decrease in activity and food intake starting from third week of the experiment compared to the control rats. No deaths were reported in any of the experimental groups.

The blood cadmium level in control rats was measured at 0.0024±0.0001 ppm, which significantly increased ($P<0.05$) in rats exposed to cadmium (0.573±0.018 ppm). Blood cadmium levels were comparatively lower in rats exposed to cadmium and received lycopene (0.217±0.016 ppm) than in cadmium-exposed rats.

Table (1) shows the estimated hematological parameters in rats that received lycopene, rats exposed to cadmium and rats exposed to cadmium and administered with lycopene compared to the control rats.

Tables (2) (a, b, c) shows the biochemical parameters (serum levels) in rats that received lycopene, rats exposed to cadmium and rats exposed to cadmium and lycopene compared to the control rats.

Table (3) shows the levels of total thiols, glutathione, catalase, glutathione peroxidase, superoxide dismutase, TAC, H_2O_2, MDA in the liver and kidney homogenates of rats that received lycopene, rats exposed to cadmium and rats exposed to cadmium and lycopene compared to the control rats.

The toxic effects of cadmium include the oxidation of cell membrane lipids, which significantly reduces the production of ATP and glutathione in the mitochondria. Additionally, cadmium toxicity impairs the function of antioxidant enzymes, thereby exacerbating existing oxidative stress. Ultimately, cadmium-induced toxicity leads to apoptosis due to the activation of the caspase cascade (Kawata *et al*., 2018).

Indicators of antioxidative status, such as total thiols, glutathione, superoxide dismutase, glutathione peroxidase, catalase and total antioxidant capacity, were remarkably decreased in rats exposed to cadmium. It is postulated that the generated ROS in the course of cadmium toxicity caused oxidation of these endogenous antioxidants and consequently dramatically suppressed their capacity to overcome the resultant oxidative damage.

Table 1: Haematological assay of rats that received lycopene, cadmium and cadmium with lycopene.

Parameter	Untreated control	Lycopene	Cadmium	Cadmium and lycopene
RBCs count (10^6/mm^3)	5.53±0.07	5.61±0.09	4.03*±0.11	5.43**±0.02
Total leucocytic count (10^3/mm$^{3)}$	6.44±0.36	6.48±0.21	5.04*±0.25	6.21**±0.06
Haemoglobin (Hb) concentration (g/dL)	12.61±0.31	12.73±0.26	9.51*±0.34	12.13**±0.31
Packed cell volume (PCV %)	44.26±0.27	45.03±0.27	36.02*±0.53	43.54**±0.81

Table 2a: Levels of total proteins (g/dL), albumin (g/dL), and globulin (g/dL), creatinine (mg/dL), urea (mg/dL), blood urea nitrogen (BUN) (mg/dL) and bilirubin (mg/dL). The estimation of biochemical parameters in rats exposed to cadmium, lycopene and cadmium with lycopene.

Parameter	Untreated control	Lycopene	Cadmium	Cadmium and lycopene
Total proteins	7.51±0.15	7.54±0.21	5.26*±0.16	7.06**±0.13
Albumin	3.30±0.02	3373±0.16	2.32*±0.14	3.03**±0.15
Globulin	3.84±0.08	3.83±0.17	2.33*±0.16	3.54**±0.28
Creatinine	0.53±0.13	0.55±0.13	0.94*±0.07	0.63**±0.27
Urea	40.62±0.41	40.61±0.38	74.19*±0.61	48.15**±0.64
BUN	15.34±1.02	15.85±1.05	29.33*±1.32	17.73±1.46
Bilirubin	6.39±0.41	6.47±0.37	11.54*±0.24	7.16**±0.41

Table 2b: Levels of alanine transferase (ALT) (IU/L), aspartate transferase (AST) (IU/L), and alkaline phosphatase (ALP)(IU/L) in rats exposed to cadmium, lycopene, and cadmium with lycopene.

Parameter	Untreated control	Lycopene	Cadmium	Cadmium and lycopene
ALT	26.64±1.12	26.53±1.08	69.12*±1.13	30.51**±1.07
AST	41.33±1.09	41.39±1.07	139.17*±3.41	53.17**±1.19
ALP	25.17±1.21	25.16±1.03	75.75*±1.38	28.16**±1.59

Table 2c: Levels of antioxidant enzymes in rats exposed to cadmium, lycopene and cadmium with lycopene.

Parameter	Untreated control	Lycopene	Cadmium	Cadmium and lycopene
Total thiols	2.44±0.27	2.37±0.21	0.27*±0.03	2.03**±0.81
Glutathione	40.95±1.13	41.58±1.08	13.93*± 0.63	36.94**±1.29
Catalase	51.87±1.52	52.69±1.49	28.88*±1.05	46.81**±1.21
SOD	6.32±1.71	6.21±1.61	3.44±1.29	5. 71±1.34
GSH-Px	133.01±2.40	128.03±2.11	76.05±1.67	120.07 ±1.64
TAC	35.4±1.02	35.74±1.09	16.76*±1.04	29.68**±1.08
MDA	311.15±3.04	313.61±3.12	445.31*±3.41	332.23**±3.51
H_2O_2	40.73±1.51	40.65±1.43	90.17*±1.14	49.19**±1.03

Table 3: Showing levels of various antioxidant enzymes in the tissue homogenates of rats treated with cadmium, lycopene and cadmium with lycopene.

Parameter	Untreated control		Lycopene		Cadmium		Cadmium and lycopene	
	Liver	Kidney	Liver	Kidney	Liver	Kidney	Liver	Kidney
Total thiols	1.93±0.26	1.05±0.26	1.77 ±0.26	1.09±0.27	0.22*±0.05	0.22*±0.04	1.84**±0.35	1.67**±0.45
Glutathione	16.51±1.13	14.73±1.13	16.55±1.07	14.77±1.03	5.02*±0.61	4.98*±0.69	14.72**±1.39	14.84**±1.44
Catalase	20.21±1.52	19.13 ±1.21	19.85±1.32	18.87±1.11	9.19*±1.03	9.12*±1.07	17.74**±1.11	17.46**± 1.56
SOD	6.23±1.71	6.15±1.74	6.17±1.66	6.19±1.61	3.42±1.56	3.14±1.58	5.26±1.81	5.07±1.64
GSH-Px	132±2.41	127±2.33	131±2.21	114±2.37	81±1.48	76±1.89	116±1.78	113±1.38
MDA	126.18±3.18	122.11±3.75	123.0 ±13.13	122.11±3.15	412.61*±3.39	493.31*±3.64	147.28**±3.11	145.08**±3.61
H_2O_2	14.92±1.49	14.84±1.13	16.49±1.17	14.41±1.09	88.91*±1.17	98.11*±1.62	18.44**±1.01	19.22**±1.08
TAC	15.72±1.12	14.60±1.09	15.18±1.02	14.89±1.03	7.38*±1.09	8.63*±1.08	13.77**±1.09	13.37**±1.01

Values are shown as means±S.D., Number of rats/groups=20.

*Significantly different means from that of untreated control rats (P<0.05).

**Significantly different means from that of cadmium-exposed rats.

Glutathione and catalase are among the endogenous antioxidants that work directly to eradicate free radicals (Liu *et al*., 2018). Oxidation of these antioxidants leads to the accumulation of free radicals and exacerbation of oxidative stress. Catalase decomposes hydrogen peroxide (H_2O_2), which accounts for lipid peroxidation. Inhibited catalase activity allows hydrogen peroxide to induce severe oxidizing effects in rats. H_2O_2 action is the base of the Fenton reaction, which generates the highly oxidizing hydroxyl radical (OH) (Shi *et al*., 2024).

The present significant increase in the levels of malondialdehyde (MDA) in cadmium-intoxicated rats is ascribed to lipid peroxidation of the cell membranes. MDA, being a marker of lipid peroxidation, is one of the consequences of oxidative damage (Wang *et al*., 2018; Shamsi *et al*., 2020).The antioxidant activity of lycopene is related to its scavenging of free radicals as evidenced by its direct action to eliminate H_2O_2, NO and hydroxyl OH radicals and its capability to inhibit lipid peroxidation (Ilhane *et al*., 2022; Juan *et al*., 2021).

Lycopene down-regulates gene expression of iNOS, decreases NO level and increases tissue glutathione (GSH) (Leh and Lee, 2022; Graboswka *et al*., 2019; Kiran *et al*., 2023). In addition, it prevents oxidative stress-induced apoptosis (Francenia *et al*., 2019). Under the circumstances of oxidative stress, Lycopene elevates the total antioxidant status. Lycopene could enhance the activities of all antioxidant enzymes including catalase, superoxide dismutase and glutathione peroxidase and inhibit oxidative enzymes (Bin-Jumah *et al*., 2022; Swiatkiewicz *et al*., 2023). It reduces the level of malondialdehyde (MDA) and reduces the synthesis of ROS in general. Lycopene reduces the mitochondrial and intracellular concentrations of ROS. Through these activities, lycopene could protect proteins, DNA and lipids against oxidative damage.

It was concluded that lycopene as a carotenoid could counteract and prevent the progression of the effects of ROS. Lycopene acts through diverse mechanistic pathway to alleviate ROS-induced oxidative damage (Rejali *et al*., 2022; Abir *et al*., 2023).

The present results are in accordance with those of the relevant published studies (Przyloylska, 2020; Guo *et al*., 2023) as evidenced by the currently recorded improved levels of antioxidant markers (total thiols, glutathione, catalase and TAC in rats exposed to cadmium and had access to Lycopene. These findings may confirm the positive effect of lycopene on the activity of these antioxidant molecules and consequently reinforcing significant effect on endogenous antioxidant capacity.

The significant decrease in cadmium blood levels in presently cadmium-intoxicated rats and administered lycopene may be interpreted by cadmium chelation. Chelation is one of the postulated roles of lycopene to mitigate the damaging effects induced by chemical toxins (Nadeem *et al*., 2019; Hedayati *et al*., 2019). Cadmium is the trigger of oxidative overload and decreasing its level in the blood greatly limiting the initiation of oxidative stress and thus helps recover the endogenous antioxidant system. The currently assayed haematological and biochemical parameters in rats exposed to cadmium and treated with lycopene revealed improvements toward the control levels. These results may reinforce the proposed synergistic antioxidant role of lycopene in alleviating cadmium-induced oxidative stress.

CONCLUSION

The present investigation might represent evidence of the antioxidant efficiency of lycopene in countering the outstanding oxidative stress induced by cadmium toxicity. However, detailed research work is recommended to highlight the molecular mechanisms that could explain clearly the antioxidant properties of lycopene in heavy metal-induced oxidative stress. The current findings provide evidence of the efficient antioxidant activity of lycopene. However, further investigation is recommended to reveal the detailed molecular mechanisms through which lycopene exerts its antioxidant properties.

Authors' contribution

Mohammed Al-Zharani and Hassan Rudayni conducted the laboratory work. MAE supervised the experiments. Nada H. Aljarba, EAA, Saad Alkahtani and Fahd A. Nasr managed the lab work, software and statistical analysis of the data. Mohammed Mubarak designed the study, oversaw the methodology and wrote the manuscript.

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Disclaimers

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Informed consent

All animal procedures for experiments were approved by the Committee of Experimental Animal care and handling techniques were approved by the University of Animal Care Committee.

Conflict of interest

There are no conflicts of interest to disclose.

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