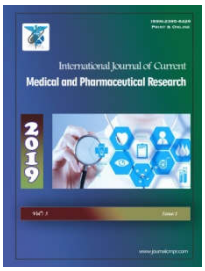
Research Article

INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 5; Issue 01(A); January 2019; Page No. 3977-3982
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr201901603



LYCOPENE ACTIVITY ON CYCLOOXYGENASE AND LIPID PEROXIDATION IN DEXAMETHASONE-INDUCED OXIDATIVE STRESS IN WISTAR RATS

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ARTICLE INFO

Article History:
Received 12th October, 2018
Received in revised form 23rd November, 2018
Accepted 7th December, 2018
Published online 28th January, 2019

Key words:
Dexamethasone, Lycopene, Cyclooxygenase, Lipid peroxidation, Liver enzyme

ABSTRACT

This study was aimed at investigating lycopene activity on cyclooxygenase and lipid peroxidation in dexamethasone treated Wistar rats**.** Twenty (20) male Wistar rats weighing between 150g-250g were randomly selected into four groups containing five rats each. Control rats received standard feed and water. Group two received 3mg/kg body weight of dexamethasone intraperitoneally every two days for 9 days. Group 3 received 3mg/kg body weight of dexamethasone intraperitoneally every two days for 9 days plus daily oral administration of 1mg/kg of lycopene for 28 days. Results showed that there was no significant difference in activity of dexamethasone and lycopene on COX and THX-A_2 in all the groups. Dexamethasone increased AST ALT and ALT level. Treatment with Lycopene significantly ($p<0.01$) decreased AST, ALT and ALP in all the groups. Lactate dehydrogenase activity was significantly ($p<0.01$) decreased in the dexamethasone and further lowered upon treatment with lycopene when compared to the DEX group. Malondealdehyde (MDA) concentration in Dex was increased ($p<0.01$), Catalase activity was reduced while SOD concentration was not altered. Treatment with lycopene Significantly ($p<0.01$) decreased serum MDA and increased catalase concentration. Triglyceride and LDL components of the lipid were elevated in Dex with a decreased HDL but without alteration in total cholesterol level. Lycopene decreased the TC, LDL and TG and significantly ($p<0.01$) increased HDL. It is concluded that dexamethasone suppresses cyclooxygenase expression but potentiates lipid peroxidation and increases liver enzymes. Lycopene inhibits Cox activity, protect against lipid peroxidation and is hypolipidemic and hepatoprotective.

INTRODUCTION

Dexamethasoneis a synthetic glucocorticoid commonly used for inflammatory disorders such as asthma, allergy, infection and alsoautoimmune disease such as rheumatoidarthritis, glomerulonephritis, sclerosis[1]. The anti-inflammatoryproperty of glucocorticoids is based on itsability to suppress the activity of genesthat have a major role in inflammation such as cytokines and nitricoxide synthase [2]. Cytokines particularly, directly stimulates the formation of reactiveoxygenspecies [3,4] that are potentoxidative stress markers. Some researchers however, have opined that one mechanism by which dexamethasone carries out its anti-inflammatory activity is by inhibition of cyclooxygenase (COX) which is assumed to be detrimental to the body because of its involvement in the formation of prostaglandin E_2 and thromboxane but whose inhibition readily provides relieve to pain and symptoms of inflammation [5,6]. Beyond the anti-inflammatory property of dexamethasone, research has also implicated it to wear a detrimental face. For instance, glucocorticoid therapy, depending on the dosage, leads to serious systemic side effects such as, immunosuppression, hypertension, adrenal gland depression and steroid diabetes [7], disrupts lipid metabolism thereby potentiating lipid peroxidation and formation of reactive oxygen species[8].

Lycopene, a natural plant product with high level of antioxidant property has been reported to exhibit free radical and singlet oxygen species scavenging property caused by lipid peroxide[9]. The aim of the present study was to investigate the MDA level, liver enzyme concentration and cyclooxygenase / thromboxane A2 activity in dexamethasone treated rats and the antioxidant status of lycopene supplementation.

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Experimental Design

Fifteen male Wistar rats weighing between 180 and 250 g were obtained from the animal House, Physiology Department, Cross River University of Technology, Calabar, Nigeria and randomly selected into three groups of 5 rats each. The animals were housed in plastic cages and kept in room temperature of 28°C ± 2°C with 12 h light/dark cycle. Group 1 (control) was fed on normal rat feed. Group 2 (Dex) received 3mg/kg body weight of dexamethasone intraperitoneally every two days while group 3 (Dex + Lyco) received 3mg/kg body weight of dexamethasone every 2 days plus daily oral administration of 1mg/kg of lycopene for 28 days. All groups had access to water and standard feed *ad libitum*. Ethical approval for the study was obtained from the Faculty of Basic Medical Science Animal Research Ethical Committee of Cross River University of Technology, Calabar, Calabar, Nigeria (approval number FBMS/CRUTECH/12/015).

Collection of blood samples and biochemical analysis

Animals were anesthesized, blood samples were collected by cardiac puncture into EDTA blood sample bottles for determination of COX, THX-A_2 and liver enzymes and also into plain bottles for lipid profile analysis. Samples were allowed to stand for two hours to clot. The blood was centrifuged at 2000rpm for 10 minutes to obtain serum. The serum was stored at 10°C till further use. The methods described by [10,11] were used to determine total cholesterol (TC) and triglyceride, respectively. lowdensity lipoprotein cholesterol was calculated using the equation of [12]

Determination of superoxide dismutase/catalase activity and lipid peroxidation

Superoxide dismutase activity was determined by the method of [13] catalase was determined using the method of [14] Lipid peroxidation was determined by the method of [15]

Statistical analysis

Data obtained were presented as mean ± standard error of the mean (SEM). Statistical analysis was done using One-way analysis of variance (ANOVA). The GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, CA, USA) was used for the analysis. Bonferroni multiple comparison test was also used for pair-wise comparison, and differences were considered significant at p <0 .01.

RESULTS

Effect of dexamethasone and lycopene on lipid profile

The effect of dex and lycopene on total cholesterol, triglyceride, HDL and LDL is shown in table 1.. Total cholesterol was not affected by dex. Triglyceride and LDL were significantly (p<0.01) elevated while HDL was reduced. Treatment with lycopene significantly (p<0.01) decreased TC, TG and LDL. HDL was significantly (p<0.01) increased.

Table 1 Effect of lycopene administration on lipid profile in dexamethasone treated Wistar rats

Variables	Control	Dm	Dm+lyco
TC	3.617±0.05	3.767±0.12	2.75±0.06[b]
TG	0.7450±0.03	0.828±0.03	0.380±0.05**[,b]
HDL	0.9200±0.01	1.317±0.16	2.267±0.3**[b]
LDL	2.55±0.06	2.917±0.07*[,c]	1.767±0.04

Values are expressed as mean±SEM. n=5; **=p<0.01vs Control; b=p<0.01 vs Dm, c=p<0.01vs dex+lyco

Effect of lycopene on Cyclooxygenase and Thromboxane A2 in dexamethasone-induced oxidative stress

The antioxidant activity of lycopene on cyclooxygenase (COX) and thromboxane A_2 (THX-A_2) is shown in figures 1 and 2. The result showed that there was no significant difference in activity of dexamethasone and lycopene on COX and THX-A_2 in all the groups. This indicates suppression of inflammation.

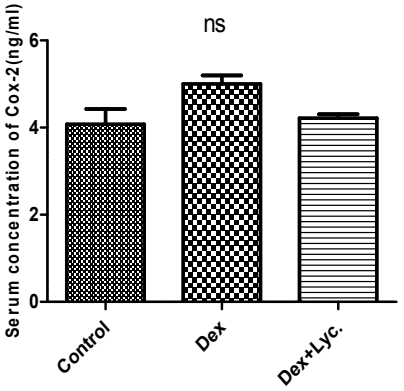


FIGURE 1: Showing effect of lycopene on cycloxygenase in dexamethasone treated rats. Values are expressed in Mean ± SEM n=5,

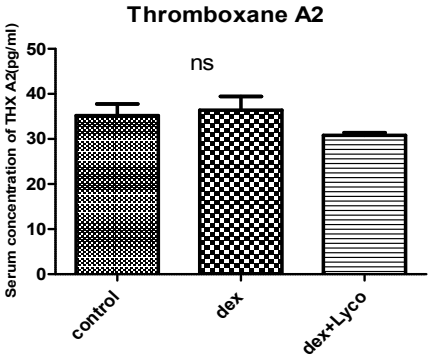


FIGURE : 2 Showing effect of lycopene on thromboxane A2 in dexamethasone treated rats. Values are expressed in Mean ± SEM n=5, ns= not significant

Effect of dexamethasone and lycopene on liver enzymes

The result of dexamethasone treatment and lycopene administration on AST, ALT and ALP is shown in figures 3, 4 and 5. All groups treated with dexamethasone significantly increased serum AST,ALT and ALP when compared with the control. Treatment with Lycopene significantly (p<0.01) decreased AST, ALT and ALP in all the groups.

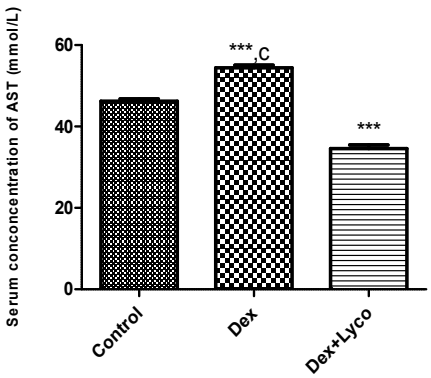


Figure 3: showing effect of daily oral administration of lycopene on aspartate transferase(AST) in Dexamethasone induced-oxidative stress. Values are expressed in Mean ± SEM n=6; ***=p<0.001 vs Control; b=p<0.01 vs Dex; c=p<0.001 vs Dex+Lycopene

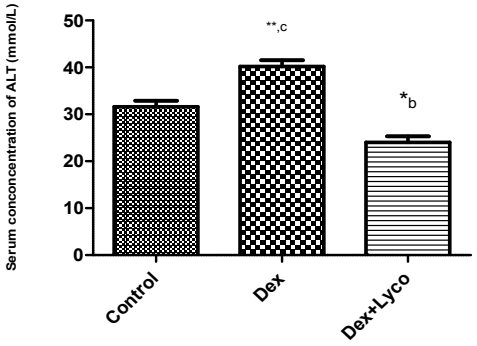


Figure 4: showing effect of daily oral administration of lycopene on alanine aminitransferase in Dexamethasone induced-oxidative stress. Values are expressed in Mean ± SEM n=5; ***=p<0.001 vs Control; c=p<0.001 vs Dex+Lycopene

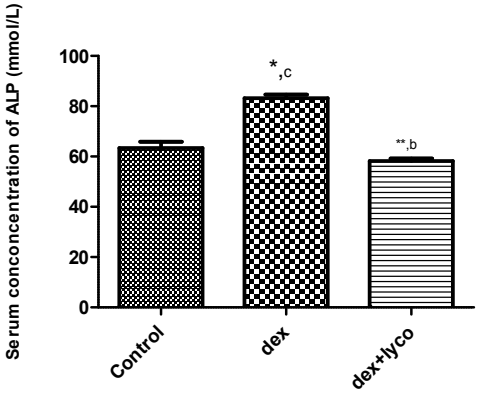


Figure 5: showing effect of daily oral administration of lycopene on ALP in Dexamethasone induced-oxidative stress. Values are expressed in Mean ± SEM n=5; **=p<0.001 vs Control; b=p<0.01 vs Dex; c=p<0.01 vs Dex+Lycopene

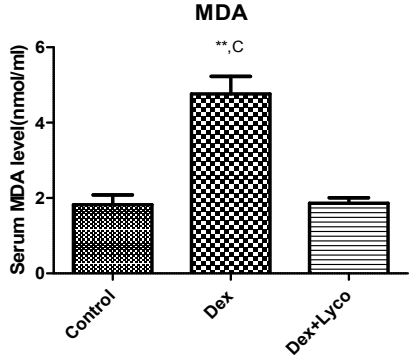


Figure 6: showing effect of daily oral administration of lycopene on Lipid peroxidation in Dexamethasone treated rats stress. Values are expressed in Mean ± SEM n=5; ***=p<0.001 vs Control; c=p<0.001 vs Dex+Lycopene

Effect of dexamethasone and lycopene on lipid peroxidation and lactate dehydrogenase

Lipid peroxidation product, MDA in the dexamethasone group was significantly ($p<0.01$) higher when compared to control and the test group. Treatment with lycopene Significantly ($p<0.01$) decreased serum MDA, (Figure 6). There was no significant difference in superoxide dismutase (SOD) concentration in all the groups (figure 7) while the activity of catalase in DEX was significantly ($p<0.01$) reduced. Treatment with lycopene significantly ($p<0.01$) increased catalase concentration when compared to the dexamethasone group as shown in figure 8. Lactate dehydrogenase activity was significantly($p<0.01$) decreased in the dexamethasone group when compared to control and further lowered upon treatment with lycopene when compared to the DEX group(figure 9).

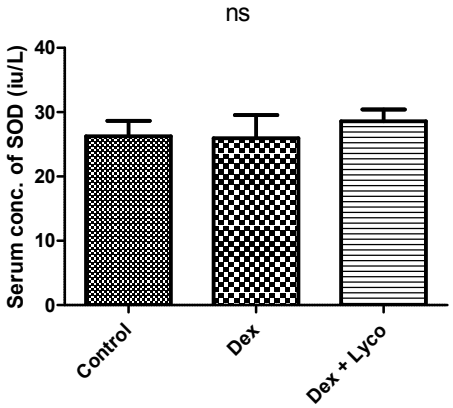


FIGURE. 7: Showing effect of lycopene on Superoxide dismutase enzyme activity in dexamethasone induced oxidative stress in rats. Values are expressed in Mean ± SEM n=5, ns= Not significant

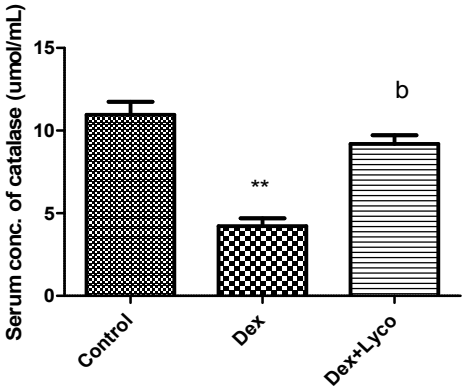


FIGURE. 8: Showing effect of lycopene on Catalase enzyme activity in dexamethasone induced oxidative stress in rats. Values are expressed in Mean ± SEM n=5, **=p<0.01 vs Control; b=p<0.05 vs Dex.

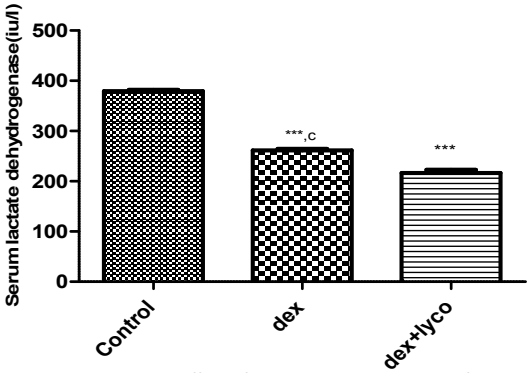
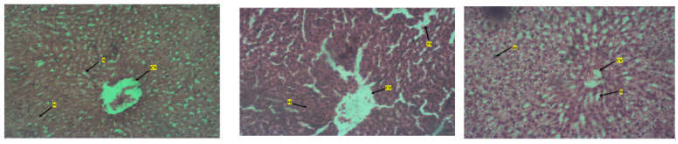


Figure 9: showing effect of daily oral administration of lycopene on lactate dehydrogenase in Dexamethasone induced-oxidative stress. Values are expressed in Mean ± SEM n=5; ***=p<0.001 vs Control; c=p<0.001 vs Dex+Lycopene



A B C

Plate 2: Photomicrograph of liver of (A) control with normal Hepatic sinusioids. (B) Dexamethasone group (DM) showing gross isolation and depletion of hepatocytes, **(C**) Dex. group treated with Lycopene (DEX. + LYCO) showed no legions. H & E. X100

DISCUSSION

The use of Dexamethasone in the treatment of various inflammatory conditions as well as in pain relief cannot be over emphasized. These peculiarity of glucocorticoid is as a result of based on its cell-specificity dependending on the expression of various receptor proteins and protein synthesis[16]. In this study, we examined the activity of dexamethasone and effect of lycopene supplementation on cyclooxygenase/thromboxane A2 levels, serum liver enzyme concentration, and lipid peroxidation in Wistar rats. Our results on the cyclooxygenase and thromboxane activity in both dexamethasone and the lycopene supplemented groups did not show any statistical difference when compared to control. The reported activity of dexamethasone as an anti-inflammatory agent on one hand, and as an oxidative stress inducer on the other hand therefore raises some concern. Some researchers,[17,18],have speculated that dexamethasone induces oxidative stress and overproduction of reactive oxygen species and contributes to the development of cardiovascular problems via upregulation of ACE expression and angiotensin II type -1 and α-1 receptors[19]. Increased production of this free radicals without inhibition by either endogenous or exogenous antioxidants infringes on the balance of the immune system causing a break down in physiological activity and eventually resulting in deleterious assaults on vital organs [20]. The overwhelming increase in lipid peroxidation and their products, triglyceride and LDL and also the reduction in catalase enzyme activity, and HDL in dexamethasone treated animals observed in this study suggests a possible distortion in the detoxification system. Studies have shown that lipid peroxides and their products can cause significant injury to membrane bound enzymes and biomolecules such as mRNA, and DNA [21].

The superoxide dismutase activity in this study was not altered. Naturally, endogenous antioxidants such as superoxide dismutase, catalase and glutathione**,** scavenge and represses the formation of ROS[22].Catalase functions to metabolizes the hydrogen peroxide produced at the course of peroxidation into water and oxygen while SOD scavenges superoxide radicals and promotes speedily its conversion to hydrogen peroxide which is then detoxified by glutathione peroxidase[23,24]. The ability of lycopene to protect against free radical-induced damage and lipid peroxidation process induced by dexamethasone is evidenced by the significant decrease in the levels of peroxidation product, malondialdehyde (MDA) and essentially, favorable modulation of lipid profile observed in this study. The result obtained is in line with an earlier reported work by [25,26,27,28,29.]who demonstrated the antioxidant effect of lycopene on peroxidation of phospholipids, proteins and nucleic acids. The total cholesterol (TC), Triglyceride (TG) and low density lipoprotein (LDL) were lowered while HDL concentration was increased following lycopene supplementation. Flavonoids and saponins in plant products have been implicated in the lowering of lipids. One outstanding mechanism of reduction of the lipids is suggested to be by inhibition of hepatic HMG-CoA reductase[30] and also the reduction of the bad cholesterol (LDL) by increased hepatic detoxification or purification of LDL precussors.[31,32,33].Similarly, our study has shown that dexamethasone treatment and lycopene supplementation did not alter cyclooxygenase and thromboxane activity. This may be interpreted to mean inhibition or a no activity outcome. This is evident by various experimental reports that the anti-inflammatory activity demonstrated by dexamethasone in vivo, is via the suppression of basal constitutive cyclooxygenase synthesis [34,35,36] and COX-mRNA [37]. Cyclooxygenase is the enzyme responsible for the formation of prostanoids (thromboxane and prostaglandins).It catalyzes the conversion of arachidonic acid to form prostaglandin E2 and thromboxane[5] whose biological actions include vasoconstriction and is pathogenic in various disease like hepatic inflammatory process[38]and acute hepatotoxicity[39]

Interestingly, available literature suggest that lycopene because of its phytochemical components such as carotenoids, flavonoids, saponins and tannis[40] and its strong activity in scavenging singlet oxygen species [41]suppresses Cox-2,[42] prostaglandin E_2, ERK 1/2 phosphorylation [43], therefore suggesting an anti-inflammatory activity.

Furthermore, the fact that AST, ALT and ALP were considerably elevated in dexamethasone treatment in this study presumes a possible injury to the liver. This is observed in the liver histology with gross isolation and depletion of hepatocytes.

This may be seen as one side effect of effective use of the synthetic glucocorticoid. Nevertheless, lycopene showed apparently a favourable biological activity by reversing the compromised liver integrity and by lowering the AST, ALT and ALP enzymes. Aspartate amino transaminase (AST) is largely found in the muscles and liver parenchymal cells. When there is an elevated concentration in AST and serum alanine amino transferase (ALT) it invariably suggests possible liver disease or damage. On the other hand, ALP is often used to establish plasma membrane integrity such that any reasonable change in its concentration may suggest damage to the plasma membrane. However, there are also reports on the contrary that Lycopene does not alter AST, ALT and ALP.[44].

CONCLUSION

We conclude that dexamethasone inhibits COX and thromboxane A_2 activity, induces lipid peroxidation and may cause devastating liver damage while lycopene is hepatoprotective, hypolipidemic and inhibits COX-2 and thromboxane A2 activity.

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How to cite this article:

Etah E. Nkanu *et al* (2019) ' Lycopene Activity on Cyclooxygenase and Lipid Peroxidation in Dexamethasone-Induced Oxidative Stress in Wistar Rats', *International Journal of Current Medical And Pharmaceutical Research,* 05(01), pp. 3977-3982.

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