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Research Article

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Investigation of Curcumin Effects on ovaries and the hormones of LH and Progestron in Wistar rats Treated with Cadmium Chloride.

Aida Ashrafzadeh[1], Hossein Kargar Jahromi[2,3*], Shahrzad Kamfiruzi[1], Mohammad Hassan Davami[3]

[1]Student Research Committee, Jahrom University of Medical Sciences, Jahrom, Iran.
[2]Research Center for Noncommunicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran.
[3]Zoonoses Research Center, Jahrom University of Medical Sciences, Jahrom, Iran.
[*]Correspondence to: Hossein Kargar Jahromi, PhD, Research Center for Non- Communicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran, 2nd Zoonoses Research Center, Jahrom University of Medical Sciences, Jahrom, Iran. hossein.kargarjahromy@yahoo.com. Telephone/Fax: +98- 7154340405.

ABSTRACT

The aim of this study was to determine the effects of curcumin on ovarian histopathology of the LH hormone and progesterone. In cell culture, cadmium induces the production of oxygen free radicals damaging DNA, causing mutations and prevents proliferation with it. Curcumin (CMN), the yellow spice derived from the dried rhizome of turmeric, has many medicinal properties including anti-inflammatory and antioxidant effects.

***Procedure**: 72 Wistar mature rats were divided into 9 groups of 8 control, experimental receiving cadmium chloride (CdCl (2) 5mg / kg), CMN (at concentrations of 25, 50, and 100 mg / kg) and CdCl (2) with different concentrations CMN. Cardiac puncture was performed at day 21 and serum hormones LH and progesterone were measured. Ovarian tissue was removed and histological study was performed on it.*

***Findings:** The results of this study showed that CdCl (2) caused a significant increase ($p < 0.05$) in average concentrations of LH and a significant reduction ($p < 0.05$) at concentrations of progesterone, but CMN increased the average level of LH and progesterone compared with the control group, and the increase in the concentration of 100mg / kg of CMN was only significant. CdCl (2) caused a significant decrease and in all concentrations, CMN caused a significant increase in the number of primordial, primary, secondary and graph follicles, and CdCl (2) caused a significant increase in atretic follicles, but CMN had no effect on number of follicles. In the recipient groups, CdCl (2) with CMN, the number of primordial , primary, secondary and graph follicles was increased compared to the group receiving CdCl (2) and the number of atretic follicles was significantly decreased. The number of follicles in a dose of 100 mg / kg of CMN showed the best effect.*

***Conclusion**: According to our results, CMN decreased damaging effects of CdCl (2) on the concentration of these hormones and adjusted serum concentrations of hormones and improvement of ovarian function and oogenesis in mice of CdCl (2). Hence, CMD could be possibly used as a combination of protect against the toxic effects of CdCl (2).*

Keywords: *Curcumin, cadmium chloride, female rats*

INTRODUCTION

Cadmium is one of the most important industrial and environmental contaminants that have diverse effects on the surrounding area. This toxic and heavy metal is easily absorbed by plants, animals and microorganisms, and in higher doses, can cause acute injury in vivo cell and tissue (1). Inhaling of polluted air and cigarette smoke leads to respiratory infection in humans. In total, food and cigarette smoke are known of the biggest sources of human

exposure to cadmium. Intracellular concentrations of cadmium cause lesions in organs such as the liver, kidney, lung, brain, testes, placenta, ovary, etc. (2, 3). Turmeric is an herbaceous plant which its rhizome is widely used for coloring and flavoring to food. Its rhizome extraction is called Curcuminoid and contains Curcumin, Demtoosky curcumin and bis Demtoosky curcumin (4). Among the three Curcuminoids, curcumin in turmeric is most abundant. Curcumin (CMN) has suitable yellow color, which allows using it as a colorant agent in food industry (5). CMN contains a pure, crystalline powder, insoluble in water and is dissolved in solvents such as ether and alcohol, glacial acetic acid, alkalis and certain oils such as olive oil (6, 7) and has significant functions. The various properties of the compound including anti-cancer and anti-tumor activity (5, 8), lowered blood cholesterol and liver (5), inhibition of cardiovascular disease, (8) an increase in immune function (9), preventing biological membranes against oxidative damage (10), anti-inflammatory properties (11) and a decrease in rheumatoid arthritis (12), protection against Alzheimer's disease (13) have been reported. In many studies, CMN antioxidant properties and protection of male reproductive system against environmental pollutants and oxidative stress inducers such as cadmium (14), acrylamide (15), lindane (16) have been reported. However, no study has been reported on the protective effects of the pigment in the physiology of female reproduction. So CMN may be used as a powerful antioxidant in the prevention of major malformations caused by cadmium's oxidative stress and free radicals produced in the ovaries. Therefore, due to the strong antioxidant properties of curcumin, the present study aimed to investigate the protective effects of these antioxidants with cadmium chloride (CDCl (2)) on the LH and progesterone hormones and ovarian tissue in rats.

Procedure

According to articles published in the field, this study is carried out on healthy adult female Wistar rats in the weight range of 180 to 200 grams. Mice are kept in Animal Medical University room in Jahroom for a week to adapt. Bright and dark cycle is included 12 hours of light and 12 hours of darkness at 1 ± 23 and humidity 50 to 55 percent. First of all, smear vaginal of mice are taken and Mice in the estrous cycle are selected and randomly divided into 9 groups of 8 animals and after weighing, will be stored in their own cage (4 mice per cage). Their food is called Pellet. Glass water bottles are provided for them. Cages are cleaned and disinfected 3 times a week. The total number of mice required is 72 rats. According to the former articles, the injected concentration in CMN in doses of 25, 50 and 100 mg per kg body weight was found (17, 18), so the experimental and control groups in this study are the following groups:

Control group: this group (21 days) does not receive any treatment during the experiment (n = 8).

Control group: this group receives 1 ml of olive oil and 2.0 ml of normal saline intraperitoneally as a solvent and body weight during the experimental period of 21 days (n = 8).

Group 1: This group receives 5 mg / kg CdCl (2) dissolved in saline normal intraperitoneally for 28 days and based on body weight (n = 8).

Group 2: This group receives 25 mg / kg CMN dissolved in 1 ml olive oil intraperitoneally for 28 days and based on body weight (n = 8).

Experimental group 3: This Group receives 50 mg / kg CMN dissolved in 1 ml olive oil intraperitoneally for 28 days and based on body weight (n = 8).

Experimental group 4: This Group receives 100 mg / kg CMN dissolved in 1 ml olive oil intraperitoneally for 28 days and based on body weight.

Experimental group 5: This Group receives 25 mg / kg CMN dissolved in 1 ml olive oil + mg / kg 5-cadmium chloride dissolved in saline intraperitoneally for 28 days and based on body weight (n = 8).

Experimental group 6: This Group receives 50 mg / kg CMN dissolved in 1 ml olive oil + mg / kg 5 CdCl (2) dissolved in saline intraperitoneally for 28 days and based on body weight (n = 8).

Experimental group 7: This Group receives 100 mg / kg CMN dissolved in 1 ml olive oil + mg / kg 5 CdCl (2) dissolved in saline intraperitoneally for 28 days and based on body weight.

At the end of the study (day 21), after direct weighing of animals, blood samples were taken from the heart by syringe in 5 cc (anesthetized by ether) and their serum will be collected by centrifugation (3000 rpm for 15 minutes) and kept in the freezer in -20 until testing. For the measurement of LH and progesterone, ELISA kits for rats provided from Dyametra company in Italy will be used. For the histological examination of rats after treatment for 21 days, ovarian tissue was quickly separated from the anesthetized animals using a standard method in 22 days, (left and right) and placed in the container containing formalin 5% after weighing down by a digital scale with precision 0.001. After 48 hours, ovarian tissue was removed from the solution and after the normal process of tissue, paraffin sections will be produced for 5 micron in serial sections. 10 sections were selected from each ovary, and stained with hematoxylin (H & E) and primary, secondary, and Graph follicles will be also studied by light microscope.

Results

The results of this study are presented in Table 1 and Figures 1 to 8. As can be seen in Figure 1, in the group receiving CdCl (2) (Group 3), and control groups (groups 1 and 2), there was no significant difference in levels of the hormone LH.

CdCl (2) decreased significantly ($p < 0.05$) the average concentrations of progesterone and the average number of primordial, primary, secondary follicles, graphs, yellow flesh and also caused a significant increase ($p < 0.05$) compared to the average number of atresia follicles in group 3 with group 1 and 2. The comparison of the results did not show significant differences between experimental and control groups. CMN received in doses of 50, 25 mg / kg (groups 4 and 5) did not cause a significant change in the level of LH and progesterone compared with groups 1 and 2, but at a dose of 100 mg / kg (Group 6), it was significantly increased ($p < 0.05$) (Tabel 1) and in the comparison of curcumin recipient groups, it was found that the concentration of 100 mg / kg showed increased effect in LH and progesterone compared to the other concentrations. All concentrations increased LH concentrations (Table 1). At all concentrations, Curcumin did not significantly increase the number of primordial, primary, secondary follicles and graph and did not influence the proportion of atretic follicles (Tabel 2). As seen in Table 1, in comparison of recipient groups CMN (in 3 doses) with CdCl (2), it was found that the concentration 100 mg / kg had more effect in the modulation of LH than other concentrations and further reduced LH compared to the group receiving CdCl (2). The investigation of mean of progesterone concentration in recipient groups CMN and CdCl (2) (Group 7, 8 and 9) compared to 1 and 2 groups, there showed no significant change in the level $5 \leq 0/P$, but a significant increase ($p < 0.05$) compared to group 3, respectively. The comparison of three groups 7,8 and 9, it was found that all concentrations have moderating effects on progesterone hormones and cause a significant increase of progesterone compared to the group receiving cadmium chloride (Table 1). In addition, the number of primordial, primary, secondary follicles and graph was increased compared to group 3 and the number of atretic follicles was significantly decreased. The number of follicles in a dose of 100 mg / kg curcumin showed the best effect. The results suggest that CML can adjust hormone levels and reduce the damaging effects of CdCl (2) on the ovarian tissue. Average in each row having at least one common letter are not significantly different according to Duncan test.

Tabele 1: Mean comparison of different groups about LH and Progestron hormones

PAREMETERS GROUP	LH (IU/L)	Progestron (PG/L)
Control	9.68± .21 **ab**	122.98± 3.59 **b**
Sham	9.68± .25 **ab**	123.36± 2.15 **b**
Experimental 1	10.04± .17 **ab**	105.52± 2.47**a**
Experimental 2	9.72± .20 **ab**	129.66 ± 2.14 **bc**
Experimental 3	10.5± .24 **bc**	133.2 ± 2.27 **bc**
Experimental 4	10.84± .28 **c**	140.26± 4.76 **c**
Experimental 5	9.84± .25 **ab**	124.34± 3.15 **b**
Experimental 6	9.88± .47 **ab**	125.46± 3.53 **b**
Experimental 7	9.5± .17 **a**	131.4 ± 9.1 **bc**

Based on Duncan's test, means in each column with at least one letter in common are not significantly different at the 5% significance level

- The means are presented in the form of Mean ±SEM

- P< 0.05 is considered statistically significant

Tabele 2: Mean comparison of different groups about kind of Follicles and Corpus Luteum

PAREMETERS GROUP	Primordial	Primary	Secondary	Graaf	Atretic	Corpus Luteum
Control	5.6± .51 **bcd**	5.4± .24 **cd**	4.8± .37 **cd**	4± .32 **cd**	0± .0 **a**	4.8± .37 **cd**
Sham	5.6± .24 bcd	5.4± .25 **cd**	4.9± .2 **cd**	4± .33 **cd**	0± .0 **a**	4.4± .24 **bcd**
Experimental 1	4.2± .37 **a**	3.6± .4**a**	2.6± .24 **a**	1.8± .37 **a**	4± .32 **c**	2± .32 **a**
Experimental 2	6± .32 **cd**	5.6± .51 **cd**	5.2± .37 **d**	4± .32 **cd**	0± .0 **a**	5.2 ± .37 **d**
Experimental 3	5.8± .37 **bcd**	6± .32 **d**	5.4± .24 **d**	4.2± .2 **cd**	0± .0 **a**	5.4± .4 **d**
Experimental 4	6.6± .4 **d**	6± .31 **d**	5.6± .25 **d**	5± .32 **d**	0± .0 **a**	5.4± .24 **d**
Experimental 5	4.6± .6 **ab**	4± .33 **ab**	3.4± .26 **b**	2.4± .4 **ab**	2.4± .24**b**	3.6± .25 **b**
Experimental 6	4.8± .37 **abc**	4.8± .37 **bc**	3.8± .2 **b**	3.2± .38 **bc**	2.4± .25**b**	3.8± .37 **bc**
Experimental 7	5± .32 **abc**	5.4± .25 **cd**	4± .32 **bc**	3.8± .36 **c**	2± .32 **b**	4 ± .32 **bc**

Based on Duncan's test, means in each column with at least one letter in common are not significantly different at the 5% significance level

- The means are presented in the form of Mean ±SEM

- P< 0.05 is considered statistically significant

Discussion

The present results suggest that exposure of rats exposed to CdCl (2) cause toxic effects and changes in the levels of LH and progesterone. CMN with three different doses with CdCl (2) caused a significant increase in progesterone hormone levels compared to the group receiving CdCl (2) and since the progesterone is produced from luteum, the increased production was observed by significant increase in the average number of luteum in the groups and the significant increase has been observed in progesterone in three doses. By creating negative feedback, progesterone and estrogen inhibit the secretion of FSH and LH preventing from the creation of new follicles in the luteal phase. Many studies have been conducted concerning the detrimental effects of CdCl (2) including reducing the level of steroid hormones FSH and LH, ovulation disorders, and ultimately induced infertility in females. Studies by Lienesch et al., (2000), Priya (2004), Zhang et al., (2007) have shown that through the inhibition of binding of the hormone FSH to granulosa cells, cadmium chloride inhibits proper functioning of the cells in the production of steroid estrogen and progesterone hormones in rats (19 -21). The results by Paksy (1989) showed that cadmium chloride injection before ovulation in rats reduces the levels of LH, FSH and ovulation dysfunction in these animals (22). Unlike other studies to reduce the level LH hormone by CdCl (2) referred to in (3), this hormone has not been significantly increased in the recipient CdCl (2). Probably the difference with other studies is due to the time of bloodletting and investigation of level of this hormone as well as changes in the pattern of plasma progesterone level for 24, because blood samples were taken at day 21 in the present study and it is likely that due to a significant decrease in progesterone levels in the groups receiving CdCl (2) compared to the control group, LH secretion will be increased to compensate for this loss. But in other studies, such as Saksena et al., (1983) on different days of the estrous injection cycle CdCl (2) was conducted. Also day later, blood samples were taken to check hormone levels and the result is that if the injection is done on the days closer to the LH wave in proestrus day, it has more effect on infertility and decreased progesterone (23). The result of combination of CMN and CdCl (2) in the number of follicles compared to the group receiving CdCl (2) was increased number of primordial, primary, secondary follicles and significant reduction in the number of follicles. The number of follicles in a dose of 100 mg / kg of curcumin showed the best effect. The result is consistent with other studies by Wan et al., (2010) on the texture and morphology of ovarian follicles in rats. Their results have shown that cadmium chloride reduces mature and natural ovarian follicles, increased number of atrophy follicles and dysfunction in the oocyte maturation (24). In many studies, cadmium-induced oxidative stress as a mechanism for malicious action on different organs of the metal has been raised. Cadmium induces and increases production of reactive oxygen species in cells (25). On the other hand, by reducing intracellular antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) as well as growth-stimulating hormone (GSH) and disrupting balance between antioxidants and oxidizing agents in cell, valuable vital molecules, such as enzymes, proteins and lipid membranes will be damaged. The best way to tackle it is an increase in antioxidants cells and increased cell survival time to cadmium poisoning. It seems that by binding to cadmium in the blood, antioxidants inhibit the substance or reduce its harmful effects by blocking the cadmium activity inside the cell (26, 27).

CMN is a known antioxidant and is one of the most powerful free radical cleansing capable of preventing production of all kinds of oxygen free radicals (Reactive Oxygen Species-ROS) (7, 28, 29), so that studies have shown that antioxidant property of CMN is equal to C and E vitamins (30, 31). What is important is good absorption in the body and its very low toxic effects and its beneficial properties are useful for public health (32). Several studies like Oguzturk, H et al., (2012) and Alghasham, et al., (2013) have checked and confirmed CMN protective effect against CdCl (2) (27, 33). In the groups receiving alone a dose of 100mg / kg, it caused a significant increase in the level of LH and progesterone and generally more effective results have been shown. According to the reports, CMN antioxidant properties have anti-inflammatory and protective potentials (32).This study shows that due to the effects of CMN through its potential properties, this combination can be used to protect against the damaging effects of cadmium on reproductive system.

Conclusion

The results of this study suggest that due to the antioxidant property, CMN modulates and regulates the secretion of hormones LH and progesterone and improves ovarian function and process of oogenesis in mice receiving CdCl (2).

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Conflict of interest

The authors have declared no conflicts of interest.

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