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RESEARCH ARTICLE

IMPACT OF CURCUMIN AND VIRGIN OLIVE OIL AGAINST LEAD ACETATE-INDUCED GENETIC VARIATION IN THE MAJOR HISTOCOMPATIBILITY COMPLEX REGION IN MICE

Mohammad Allam[1*]; Fayza M. Aly[1]; Zeinab A. Mar'ie [1,2]

[1]Zoology Department, Faculty of Science, South Valley University, Qena, Egypt
[2]Science Department, Faculty of Education, South Valley University, Hurghada, Red Sea, Egypt

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***Correspondence:**
Mohammad Allam
Zoology Department
Faculty of Science
South Valley University
Qena, Egypt
E-mail:
Mohammad_allam10@sci.svu.edu.eg

ABSTRACT

Lead acetate – which results in significant damage to the genetic structure of living organisms – is found in many sources that humans use daily. Histocompatibility complex (*MHC*) genes in the vertebrate play a critical role in immune responses, and are highly polymorphic. Virgin olive oil (VOO) and curcumin are natural compounds having several healthy features including antigenotoxic activities. The present study aimed for determining the effects of VOO and curcumin (versus $ZnCl_2$, as an antioxidant agent) on *Mhc* genetic variation of renal tissues of lead acetate-treated mice by using the microsatellite loci. Thirty male albino Swiss mice (*Mus musculus*) were randomly allotted into 5 groups (n = 6): group "1", the control group; groups "2–5" that received orally lead acetate (400 mg/kg body weight, by gavage for 15 consecutive days) + either distilled water (orally), or $ZnCl_2$ (4 mg/kg body weight, intraperitoneally injected), or curcumin (500 mg/kg body weight, orally), or VOO (8 mL/kg body weight, orally) for additional 15 consecutive days, respectively. Comparing to the control group, the 2nd and the 4th groups showed high polymorphism value (17%) and (21%), respectively; while the 3rd and 5th groups showed low polymorphism value (12%) and (15%), respectively, in *Mhc* genes. The obtained data illustrated the usefulness of virgin olive oil, as compared with the curcumin, in limiting *Mhc* genetic variation induced by lead acetate in mice.

INTRODUCTION

Lead acetate is a white crystalline toxic chemical compound with a slightly sweet taste, soluble in water and glycerin, and poorly soluble in alcohol[1]. Humans exposed daily to lead acetate sources, such as car fuel, dyes, preserved food in metal cans, water pipes, and some children toys[2,3]. Depending on the period of exposure, lead may enter the body through the skin, mouth, and nose causing a large toxicity[4,5]. Damage to many organs inside the body, as heart, liver, kidneys, brain, and testes could causes death due to the exposure to large amounts of lead acetate[6-9]. Zinc is famed as an antioxidant agent, where it has the ability to decrease membrane lipid peroxidation, and hence protecting from

organ injury caused by oxidative stress[10,11]. In addition, it decreases Pb intoxication[11-13].

Turmeric (*Curcuma longa*) has a yellow color fraction in its rhizome called curcumin, which has anti-inflammatory, anticarcinogenesis, and antioxidant activities[14,15]. Curcumin reduces the oxidative effect of lead ions by preventing its accumulation in different tissues, resulting in an improvement of serum biochemical parameters, reducing inflammation, protecting the cells from damage, and repairing it[16].

Virgin olive oil is a successful dietary manipulation due to its unique features, by having high content of oleic acid and antioxidant molecules specially phenolic compounds[17]. Salvini *et al*.[18] and Machowetz *et al*.[19] illustrated the protective role of olive oil against DNA damage; in addition, its antioxidant features lowering cancer incidence. The role of olive oil in reducing the toxicity of lead acetate in the experimental animals needs more investigations[20].

Microsatellites are useful for discriminating alleles at single loci in the *Mhc* region of mice[21]. The genotypes at three linked microsatellite loci were identical in a sample of humans sharing the same *MHC* haplotype, so it may be useful for distinguishing distinct *MHC* haplotypes[22]. Dietrich *et al*.[23] reported that the *Mhc* genes affect immunological mechanisms, parasite resistance, and mate choice; this information comes from the recent description of over 7000 microsatellites for *Mus*. The present study aimed to investigate the roles of curcumin and olive oil (*versus* zinc chloride) against the genetic variation-induced by lead acetate in *Mhc* region of mice.

MATERIAL AND METHODS

Chemicals and natural products

Lead acetate 3-hydrate powder [$(CH_3COO)_2Pb$ $3H_2O$, purity: 98%, manufactured by Rankem] and zinc chloride anhydrous ($ZnCl_2$, purity 98%, manufactured by Apollo Scientific) were obtained from Gene Tech, Cairo, Egypt. Pure curcumin powder was obtained from Health and Food Store, Giza, Egypt. Virgin olive oil (VOO, 100% natural, cold pressed, acidity: <0.8%) was obtained from Isis Co, Cairo, Egypt.

Animals

Thirty male albino Swiss mice (*Mus musculus*), about 6-8 weeks old and weighing 23±2 g, were obtained from College of Veterinary, South Valley University, Qena, Egypt. The animals were kept in cages in animal's house for two weeks, for acclimatization to laboratory conditions before the start of the experiments, and were given free access daily to water and rodent food pellets.

Experiment design

Mice were randomly allotted into 5 groups (n = 6): group "1", the control group; groups "2-5" that received lead acetate (400 mg/kg body weight, orally by gavage for 15 consecutive days) + either distilled water (orally), or $ZnCl_2$ (4 mg/kg body weight, as an antioxidant agent, intraperitoneal injection[24]), or curcumin (500 mg/kg body weight, orally[25]), or VOO (8 mL/kg body weight, orally[26]) for additional 15 consecutive days, respectively. The lead acetate dose was determined according to our preliminary experimental. All mice were killed 24 hours after the last dose. The kidneys were rapidly removed and stored in –20°C until used for DNA extraction.

DNA Extraction

DNA was extracted from the preserved renal tissues using the DNA extraction method of QIAamp DNA Mini kit (Qiagen, Hidden, Germany) by following the manufacturer's guidelines.

Microsatellite loci

After the extraction of DNA, a set of seven microsatellite loci closely linked to the *Mhc* genes was used (Table 1). These microsatellites lie between 18.00 and 19.50 centimorgan from the centromere of chromosome 17 and are located within the conventional H-2 region (bounded by the K and L genes), where most of the highly

polymorphic antigen-presenting *Mhc* loci are found[27]. The polymerase chain reaction (PCR) amplification was done using a total volume of 20 µL containing 10 µL of PCR master mix (OnePCR™ ready-to-use, catalogue number: MB203-0100, GeneDireX, Miaoli County, Taiwan), 0.5 µL of each forward and reverse primer (10 pmol/µL), 8 µL of nuclease-free water, and 1 µL genomic DNA as a template. The PCR amplification conditions were: initial denaturation at 95°C for 180s, then 30 cycles each one containing denaturation at 94°C for 60s, annealing for 60s at primer specific temperature (50°C for D17Mit21, 53°C for D17Mit214, 55°C for D17Mit28, D17Mit83, and D17Mit103, 56°C for D17Mit33, and 57°C for D17Nds3), 72°C for 60s for extension, followed by a final extension at 72°C for 7 minutes. After PCR amplification, The PCR products and 100bp DNA Ladder ready-to-use (Catalogue Number: DM001-R500, GeneDireX) were electrophoresed on 1.5% agarose gel stained with ethidium bromide at 80 volts for 2-3 hours. Expected heterozygosity (HE), polymorphic information content (PIC), average heterozygosity (H.av), marker index (MI) were evaluated by online marker efficiency calculator iMEC[28]. The genetic similarity and dendrogram were calculated by palentological statistics (PAST) software version 2.17c[29].

Table 1: Primers, total of alleles (TA), monomorphic alleles (MA), polymorphic allele (PA), %polymorphic (%P), Frequency (F), expected heterozygosity (HE), polymorphic information content (PIC), average heterozygosity (H.av), marker index (MI).

Primer	TA	MA	PA	%P	F	HE	PIC	H.av	MI
D17Mit21	15	4	11	73	0.6	0.45	0.35	0.0080	0.0211
D17Mit28	17	13	4	24	0.9	0.36	0.30	0.0050	0.0153
D17Mit83	9	2	7	78	0.7	0.47	0.36	0.0146	0.0366
D17MitNds3	9	6	3	33	0.9	0.26	0.23	0.0082	0.0278
D17Mit214	9	3	6	67	0.6	0.47	0.36	0.0146	0.0366
D17Mit33	8	5	3	38	0.9	0.34	0.28	0.0120	0.0377
D17Mit103	7	0	7	100	0.8	0.47	0.36	0.0195	0.0488
Mean	10.6	4.7	5.9	59	0.8	0.40	0.32	0.0117	0.0319

RESULTS

The results revealed that the number of alleles ranged from 7 to 17 in all groups (Table 1). From the seven used micro-satellites, D17Mit21 and D17Mit28 showed the highest number of alleles. On the contrary of that, D17Mit103 display a smaller number of alleles. The maximum number of alleles was obtained in D17Mit28 locus, and the minimum number of alleles was found in D17Mit103 locus. The mean of observed number of alleles for all the loci was 10.6. The maximum expected hetero-zygosity (0.47) was obtained in D17Mit83, D17Mit214, and D17Mit103, and the minimum expected heterozygosity was in D17MitNds3 as 0.26 with a mean of 0.40 for all loci. The PIC values ranged from 0.23 in D17MitNds3 to 0.36 in D17Mit83, D17Mit214, and D17Mit103. The mean of PIC value was 0.32. Average heterozygosity was measured maximum in the marker D17Mit103 (0.0195) and minimum in D17Mit28 (0.0050) with a mean of 0.0177. The MI values among the 7 microsatellite loci ranged from 0.0153 (D17Mit28) to 0.0488 (D17Mit103), and the average value of MI was 0.0319 (Table 1). More details about the number of alleles, monomorphic alleles, and polymorphic alleles in the four groups comparing to the control group were given in (Table 2).

Table 2: Number of alleles (NA), monomorphic alleles (MA), and polymorphic allele (PA) in the four tested groups comparing to the control group.

Primer	Control	Lead acetate			Lead acetate + $ZnCl_2$			Lead acetate + Curcumin			Lead acetate + VOO		
	NA	NA	MA	PA	NA	MA	PA	NA	MA	PA	NA	MA	PA
D17Mit21	9	10	14	5	11	18	2	11	14	6	7	10	6
D17Mit28	15	14	28	1	15	30	0	16	28	3	14	26	3
D17Mit83	8	6	12	2	5	10	3	6	10	4	6	10	4
D17MitNds3	9	8	16	1	7	14	2	7	14	2	9	8	0
D17Mit214	6	5	6	5	3	6	3	8	10	4	5	8	3
D17Mit33	8	5	10	3	6	12	2	7	14	1	8	8	0
D17Mit103	5	5	8	2	5	8	2	2	2	5	6	10	1
Sum	60	53	94	19	52	98	14	57	92	25	55	80	17

VOO: virgin olive oil.

The genetic similarity of the five groups was calculated by PAST software. Comparing to the control group, the lead acetate- and the lead acetate+curcumin-treated groups showed highly polymorphism value (17%) and (21%), respectively, while lead acetate+$ZnCl_2$- and lead acetate+VOO-treated groups showed low polymorphism value (12%) and (15%), respectively (Table 3). The dendrogram consisted of two main groups (Figure 1). The first main group encloses one group, the 4th group (lead acetate+ curcumin-treated group). The second main group includes all the remaining groups.

Table 3: The similarity matrix UPGMA Jaccard's coefficient among the five groups. Group "1": the control group, group "2": lead acetate-treated group, group "3" lead acetate+$ZnCl_2$-treated group, group "4": lead acetate+curcumin-treated group, group "5" lead acetate+virgin olive oil-treated group.

	Group 1	Group 2	Group 3	Group 4	Group 5
Group 1	100%				
Group 2	83%	100%			
Group 3	88%	85%	100%		
Group 4	79%	78%	75%	100%	
Group 5	85%	80%	80%	77%	100%

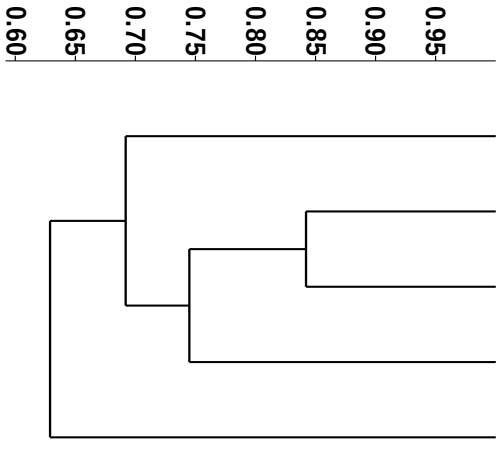

Figure 1. Dendrogram demonstrating the relationship among the five groups based on data recorded from Microsatellite. 1: The control group, 2: lead acetate-treated group, 3: lead acetate+$ZnCl_2$-treated group, 4: lead acetate+curcumin-treated group, 5: lead acetate+virgin olive oil-treated group.

DISCUSSION

It can be said that the *MHC* region has been recognized as the region of the genome with the largest number of human disease associations[30]. The *Mhc* genomic region in the mouse was located on chromosome 17[31]. In the current study, we used seven microsatellites situated between the K and D locus on chromosome 17 because this region contains the highest number of alleles. In *M. domestics* strains, the average number of alleles found between the K and D loci is higher than those loci either near or away from this region[27].

Our finding of microsatellite revealed that lead acetate caused genetic variation in the *Mhc* loci especially D17Mit214 locus, where polymorphism was 45.45%, comparing to the control group. The total number of alleles in both control and lead acetate groups was 113. Out of them 19 were polymorphic alleles (17% polymorphism). This finding agrees with several researches proved the harmful effect of lead on DNA. Snow[32] reported that the genotoxic effects could be the result of many mechanisms, like the inhibition of DNA metabolism, the induction of cellular immunity and oxidative stress, and the formation of DNA and/or protein cross-links. Furthermore, Acharya *et al*.[33] reported that lead ions are believed to reduce the fidelity of DNA synthesis. Some indirect mechanisms by lead also induced reactive oxygen species (ROS) and can inhibit DNA polymerase B, which possibly pointing to the failure of DNA repair mechanisms. Also, Gargioni *et al*.[34] observed damage effect of lead on DNA of mice, that is because of the direct effect of lead on the DNA structure and oxidative mechanisms[35]. Ibrahim[36] indicated the sensitivity of microsatellite sequences located at the fragile sites at D6mit3, D9mit2, and D15Mgh1 loci, as well as the sensitivity of the simple sequence repeats assay for the detection of small variations in DNA sequence in rats, after exposure to four heavy metals including lead acetate.

The total number of alleles in both control and lead acetate+$ZnCl_2$-treated groups was 112. Out of them 14 were polymorphic alleles (13% polymorphism). These results indicated that zinc chloride has a positive effect against lead acetate-induced *Mhc* genetic variation. Grüngreiff[37] also reported that zinc is involved in several important biological processes such as cell division, growth, and differentiation, as well as it protects the DNA strand from damage.

The total number of all alleles in control and lead acetate+curcumin-treated groups was 117. Out of them 25 were polymorphic alleles (21% polymorphism). These results indicate that the curcumin did not improve the genetics effect of lead acetate, but it increased the genetic polymorphism comparing to the control group. Mukhopadhyay *et al*.[38] reported the slight increase in the number of chromosomal aberrations in acutely treated mice by curcumin. Curcumin increased both the number of abnormal metaphase and the frequency of chromosomal aberration at the highest concentration in Chinese hamster ovary cell lines and did not prevent bleomycin-induced chromosomal damage in any phases of the cell cycle[39]. Morimoto *et al*.[40] concluded that curcumin inhibited the hypertrophy-induced acetylation and DNA-binding abilities of a hypertrophy responsive transcription factor "GATA4" in rat cardiomyocyte, indicating that inhibition of histone acetyltransferase p300 (p300 HAT) activity by curcumin may also provide a novel therapeutic strategy for heart failure in humans. Curcumin induces epigenetic changes, and has effects on the regulation of histone deacetylases, histone acetyl transferases, DNA methyl transferase I, and mi RNAs[41].

In the lead acetate+VOO-treated group, olive oil reduced the harmful genetic effect of lead acetate on the *Mhc* genes in mice, where the genetic similarity was 85%, while the polymorphism was 15%, i.e. better than that in the lead acetate+curcumin-treated group. This may be due to that curcumin displays low oral bioavailability because of its poorly absorption by small intestine, coupled to an extensive reductive associated

with metabolism in the liver and an elimination through the gall bladder[42,43]. On the other hand, olive oil contains a high concentration of antioxidant compounds, involving phenolic compounds. The anti-oxidant activities of the phenolic compounds have the ability to protect DNA, proteins, and lipids from damage caused by exposure to ROS[44]. Reducing oxidative stress by olive oil was probably related to the activities of its phenolic compounds (especially oleuropein and hydroxytyrosol) as strong free-radical scavengers and metal chelators. Oleuropein and hydroxytyrosol possess a catechol group, which is essential for their scavenging activity of hydroxyl radicals and superoxide anions[45]. In this sense, virgin olive oil may thus be important component of effective dietary manipula-tions aimed to partially modify the structure, and the features, of biological membranes in the daily conflict against free radicals and oxidative stress-induced damage[17]. Fabiani *et al*.[46], showed a potent DNA damage preventive activity of olive oil phenols, providing new evidence to support a possible role of these compounds in the prevention of cancer.

In conclusion, using the microsatellite loci linked to *Mhc* genes in the determina-tion of the genetic variation in *Mhc* region in mice, which caused by lead acetate, is useful. The data of the present study illustrated the beneficial effects of VOO, in contrast to curcumin, against lead acetate-induced *Mhc* genetic variation in mice. The current study may encourage the using of VOO as food-adjunct to inhibit the harmful genetic effects of lead.

COMPLIANCE WITH ETHICAL STANDARDS

All experimentation and care of the animals used in this study were in compliance with the Faculty of Science, South Valley University's policy on animal use and ethics. All mandatory laboratory health and safety measures have been adhered while performing the experimental work of this study.

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CONFLICT OF INTEREST

The authors have no potential financial conflict of interest.

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تأثير الكركمين وزيت الزيتون البكر علي التباين الجيني المُستحث بخلات الرصاص في منطقة معقد التوافق النسيجي الرئيسي في الفئران

محمد علام[1]، فايزة محمد علي[1]، زينب عبد الخالق مرعي[1،2]

[1]قسم علم الحيوان، كلية العلوم، جامعة جنوب الوادي، قنا، جمهورية مصر العربية
[2]قسم العلوم، كلية التربية، جامعة جنوب الوادي، الغردقة، البحر الأحمر، جمهورية مصر العربية

يوجد خلات الرصاص – الذي ينتج عنه ضرر كبير للبنية الجينية للكائنات الحية – في العديد من المصادر التي يستخدمها البشر يوميًا. تلعب جينات معقد التوافق النسيجي الرئيسي (*MHC*) في الفقاريات دورًا هامًا في الاستجابات المناعية، وهي متعددة الأشكال بشكل كبير. زيت الزيتون البكر والكركمين من المركبات الطبيعية التي لها العديد من الميزات الصحية بما في ذلك الأنشطة المضادة للسموم الجينية. هدفت الدراسة الحالية إلى تحديد تأثيرات زيت الزيتون البكر والكركمين (مقارنة بكلوريد الزنك كعامل مضاد للأكسدة) على التباين الجيني في منطقة "*Mhc*" في الأنسجة الكُلوية للفئران المعاملة بخلات الرصاص باستخدام التكرارات المترادفة القصيرة. وقد تم توزيع عشوائي لثلاثين فأر ذكر سويسري أمهق (*Mus musculus*) إلى 5 مجموعات (ن = 6). المجموعة "1": المجموعة الضابطة؛ المجموعات "2–5": عوملت بخلات الرصاص (400 مجم/كجم من وزن الجسم، عن طريق الحقن بالأنابيب لمدة 15 يومًا متتاليًا) + إما الماء المقطر (عن طريق الفم)، أو بكلوريد الزنك (4 مجم/كجم من وزن الجسم، الحقن داخل التجويف البريتوني)، أو بالكركمين (500 مجم/كجم من وزن الجسم، عن طريق الفم)، أو بزيت الزيتون الخام (8 ملي/كجم من وزن الجسم، عن طريق الفم) لمدة 15 يومًا إضافية متتالية، على التوالي. وبالمقارنة بالمجموعة الضابطة، أظهرت المجموعتان الثانية والرابعة قيمة تعدد أشكال عالية (17%) و (21%) على التوالي، بينما أظهرت المجموعتان الثالثة والخامسة قيمة تعدد أشكال منخفضة (12%) و (15%) على التوالي، في جينات "*Mhc*". وأوضحت النتائج التي تم الحصول فائدة زيت الزيتون البكر، مقارنة بالكركمين، في الحد من التباين الجيني الناجم عن المعاملة بخلات الرصاص في الفئران.