Possible antioxidant and anticancer effects of plant extracts from *Anastatica hierochuntica, Lepidium sativum and Carcia papaya* against Ehrlich ascites carcinoma cells

Rasha Aly Ahmed El Sayed[1], Zeinab Eid Madboly Hanafy[1], Hend Fouad Abd El Fattah[2] and Asmaa Kutb Mohamed Amer[1]

[1]Zoology and Entomology Department, Faculty of Science, Al-Azhar University (Girl's), Cairo, Egypt
[2]Pathology department, National Cancer Institut, Cairo University, Cairo, Egypt.
Asmaakutb86@gmail.com

Abstract: This study is undertaken to investigatethe antioxidant and antimutagenic effects of three natural extracts of *Anastatica hierochuntica* (AH), *Lepidium sativum*(LS)and *Carcia papaya*(CP) against *in vivo* Ehrlich ascites carcinoma (EAC) in Swiss albino mice. EAC was induced by intraperitoneal injection of EAC-cells in the female mice. EAC-bearing mice were orally treated with 500 mg/kg bodyweight of AH, LS and CP extracts for 7 days after EAC intraperitoneal transplantation. Ninety female mice were divided into nine groups (10 mice/group), control group, oil, AH, LS and CP groups, EAC group (mice were inoculated with 2.5×10^6 intraperitoneally (i.p), EAC+AH, EAC+LS and EAC+CP. The antitumor activity of AH and LS was pronounced in the results of this study as indicated by the increase of EAC tumor-bearing mice lifespan. Liver enzymes were greatly improved by treatment with AH and LS. However, the increase in glutathione peroxidase (GPx) activity that was accompanied by the marked decrease of MDA indicate the antioxidant activity of these plants. Furthermore, the reduction in MPO level in serum of EAC bearing mice revealed an obvious anti-inflammatory activity of these plants specially CP. Also, the three plants decreased chromosomal aberration and DNA fragmentation induced by EAC in mice.
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1. Introduction

Recently, the use of synthetic or natural agents (alone or in combination) to treat the development of cancer is a promising sterategy. Various class of anticancer drugs or chemotherapeutic agents are available widely which either undergoes alkylation of DNA or microtubules arrest or altering the cells at various mitotic phases (**Estrela *et al.*, 1992 and Samanta, *et al.*, 2016**). With regard to the bad effect of chemotherapeutic drugs, major attention has been drawn recently to natural products with antioxidant and anti-inflammatory potential that may be treat various kinds of diseases (**Huang *et al.*, 2013**).

Brassicacaeae family triggera great attention as the phytochemicals present in the Brassica vegetables showed potential in chronic disease, oxidative stress, the risk of cancer, carcinogenic mutations and proliferation of cancer cells prevention(**Chauhan *et al.*, 2016** and **Šamec *et al.*, 2018**). In addition, vegetables in the Brassicaceae family contains vitamins, catalase, superoxide dismutase and peroxidase so these vegetables are a prominent source for antioxidants activity (**Ching *et al.*, 2007**). With regard to the above mention, three plant of this family, *Anastatica hierochuntica*, *Lepidium sativum* and *Carica papaya* were chosen in this study.AH is a desert plant. It is a species of Anastatica genus that commonly called as Kaff Maryam (Mary's hand), Rose of Jericho and Genggam Fatimah (**Friedman and Stein, 1980**). This herb has been well regarded for its aid in the management of various ailments (**AlGamdi *et al.*, 2011**) as well as important properties like antimelanogenesis (**Nakashima *et al.*, 2010**), nitric oxide inhibitor (**Yoshikawa *et al.*, 2003a**), hepatoprotective (**Yoshikawa *et al.*, 2003b** and **Sobhy *et al.*,2011**), gastro protective (**Shah *et al.*, 2014**), anti-inflammatory (**Rizk *et al.*, 1985 and Abou-Elella *et al.*, 2016**)and immunostimulatory action (**Abdulfattah, 2013**).However, LS (garden cress)that is commonly known as ''Hab el Rashaad" or ''Thufa", (**Gilani *et al.*, 2013**) showed a great antioxidant (**Zia-Ul-Haq *et al.*, 2010** and **Agarwal and Verma, 2011**) and anti-inflammatory (**Raval *et al.*, 2013**) propertiesas a result for the presence of many components such as tannins, benzyl isothiocyanate and flavonoids(**Adamu and Boonkaewwan, 2014; Bahrami *et al.*, 2016 and Raish *et al.*, 2016**).CP is a plant called as pawpaw and has been cultivated in most of the tropical countries (**Roshan *et al.*, 2014**).Many researchers studied the anticancer effect

of Papaya leaves (**Bergonio and Perez, 2016&Kavimandan and Saraf, 2016**).Papaya leaves have shown the presence of anti-cancer, hepatoprotection, anti-inflammatory and antioxidant properties *in-vitro* and *in-vivo* studies (**Nugroho *et al.*, 2017**).

2. Materials and methods

Plants Extracts

The dried aerial part sof AH, seeds of LSand CP leaves were purchased from Egyptian local marketand grounded to fine powders. Each powder was soaked in dichloromethane for 24 hours to remove the chlorophyll, resinous and waxy materials, and then extracted with ethyl acetate several times. The extracts were filtered and evaporated under reduced pressure until the complete removal of ethyl acetateand kept in a sealed vessel for further investigation (**Liu *et al.*, 1989).**

Animals

Female Swiss albino mice were used in the study aged 8-10 weeks' old with weight of 20-25 g were obtained from the animal house of National Cancer Institute, El-Giza, Egypt. Mice were kept for accommodation one week before onset of the experiment. Animals provided with standard feed pellets and water *ad libitum* under 12h of light/dark cycle.Animal use followed guidelines stated by Institutional Animal Care and Use Committee (IACUC) guidebook 8th edition **(2011)** found at NIH website http://www.grants.nih.gov/grants/olaw/Guide-for-the-Care-and-use-of-laboratory-animals.

Experimental design

Ninety mice were divided into 9 groups (10/group),Group I (control); Group II: (oil); Group III (AH); Group IV (LS); Group V (CP); Group VI (EAC); Group VII (EAC+AH); Group VIII (EAC+LS) and Group IV (EAC+CP). The three plant extracts were applied orally by gastric intubation at dose of 500 mg/kg body weight /day. Five animals of each group were anesthetized with diethyl ether and sacrificed after seven days of tumor transplantation, whole blood was withdrawn and left to coagulate at 37˚C for 15 min. Serum was then separated and stored at -20˚C until further analysis (**Medhat *et al.*, 2017)**days,bone marrow was flushed from for mice femur for chromosome preparation and 5 mice/group were left for calculation of life span.

The animals were weighed at the beginning and the end of the treatment. The animal organs; liver, spleen, and kidneys were excised, washed with normal saline then weighed. Also, the organ-to-body weight ratios were evaluated according to formula adopted (**Ashafa *et al.*, 2012**).

Life span:

The effect of each extract on the percentage increase in life span was calculated on the basis of mortality of the experimental mice (**Radha, *et al.*, 2011**) was evaluated. ILS (%) = [(Mean survival time of treated group/Mean survival time of control group) -1] ×100. Mean survival time (days) = (first death + last death)/2 **(Samanta *et al.*, 2016).**

Biochemical Parameters

Aspartate transaminase (AST) and alanine transaminase (ALT) were determined in the serum of different groups by the method of **Reitman and Frankel (1957)**,glutathione peroxidase (GPx) activity (**Paglia and Valentine, 1967**),MDA content (**Uchiyama and Mihara, 1978**)and Myeloperoxidase (MPO) activity (**Manktelow and Meyer, 1986)**were also analyzed.

Chromosome aberration (CA)assay

The CA assay was carried out as described by **Evans (1987).**Animals were injected with 2mg/kg b.w. of colchicine 1.5 h prior to sacrifice. Bone marrow cells were collected by flushing with phosphate buffer from femur bone, treated with 0.56% KCl (pre-warmed at 37˚C) and incubated for 20 min at37◦C, centrifuged,fixed in freshly prepared aceto-methanol (1:3, v/v), refrigeration for 30 min.,spread on slides and staining was done in 5% buffered Giemsa stain (pH 7.0).Metaphase plates were studied per animal (5 animals/group).

DNA fragmentation

Animal tissues were used to determine the quantitative profile of the DNA fragmentation (**Gibb *et al.*, 1997**) and DNA fragmentation was qualitatively analyzed according to **Lu *et al.* (2002).**

3. Results:

Effect of plants on body and organ weight:

LS and CP increased animal body weight, although organs weight did not show any significant changes compared to the control group. In EAC infected female mice, EAC increased the body and liver weight significantly comparing to control group, AH and CP did not affect significantly on body weight comparing to the EAC group, but in EAC+LS mice, body weight was significantly reduced as compared to EAC only mice group. Spleen weight was decreased for AH treated mice, while in LS and CP groups it did not show significant change as represented in table (1)

Table (1) shows the mean body and organs weights for mice treated with the three plants extracts with and without EAC:

Groups	Body weight	Liver weight	Liver ratio	Spleen weight	Spleen ratio	Kidney weight	Kidney ratio
control	21.66 ± 1.18	1.17 ± 0.07	0.054	0.2 ± 0.02	0.009	0.13 ±0.01	0.006
EAC	34.5 ± 2.5[a]	1.54 ± 0.23[a]	0.044	0.16 ±0.02	0.004	0.13 ±0.01	0.003
oil	27.25 ± 0.85[b]	1.38 ± 0.07	0.05	0.2 ±0.03	0.007	0.13 ±0.006	0.004
AH	23 ± 0.4[b]	1.15 ± 0.03[b]	0.05	0.11 ±0.01[a]	0.004	0.12 ±0.009	0.005
LS	37 ± 2.3[a]	1.42 ± 0.07	0.038	0.17 ±0.01	0.004	0.13 ±0.006	0.003
CP	33.75 ± 4.5[a]	1.46 ± 0.09	0.043	0.18 ±0.02	0.005	0.14 ±0.002	0.004
EAC+AH	35 ± 1.22[a]	1.42 ± 0.15	0.04	0.23 ±0.04	0.006	0.13 ±0.01	0.003
EAC+LS	27.75 ± 2.17[b]	1.31 ± 0.15	0.047	0.15 ±0.04	0.005	0.12 ±0.005	0.004
EAC+CP	31.75 ± 1.93[a]	1.39 ± 0.07	0.044	0.14 ±0.01	0.004	0.105 ±0.006[ab]	0.003

AH: Anastatica hierochuntica; LS: Lepidium sativum; CP: Carica papaya; EAC: Ehrlich ascites carcinoma.

Determination of life span:

The effect of AH, LS and CP extracts on life span of EAC-bearing mice were investigated (table 2). The administration of LS was found to increase the percentage of life span by 37.14% followed by AH that increased life span of EAC-bearing mice by 28.7%.However, the administration of CP did not show an increase in life span as compared to the EAC group.

Table (2): Mean survival time and percentage of increased life span for mice treated with the three plants extracts with and without EAC:

Groups	Mean survival time (days)	%ILS
EAC	17.5 ± 0.23	0
EAC+AH	22.5 ± 0.11[b]	28.57142857
EAC+LS	24 ± 0.11[b]	37.14285714
EAC+CP	17.5 ± 0.23	0

Biochemical parameters:

An elevation of liver damaging marker enzymes (ALT and AST) were reported by injection of EAC cells in mice when compared to the normal group as represented in table (3). The treatment with *Anastatica hierochuntica* significantly increased AST and ALT activity, however, in AH+EAC group, the enzyme level of both AST and ALT enzymes significantly decreased comparing to the EAC group. By comparing, the serum levels of ALT and AST in EAC-bearing mice with the EAC+LS, a significant reduction in the ALT and AST enzyme levels were recorded. No significant change in the AST level were reported at the LS group as compared to the control group. CP leaf extract significantly increased the serum activity of AST and reduced ALT compared to control group and restored the AST and the ALT level in EAC mice, recording the best effect of all.

With regard to the glutathione peroxidase (Gpx), a significant reduction in the serum level of GPxin the mice of EAC group was recorded. Moreover, the extract caused a significant elevation to Gpx activity in EAC-bearing mice as compared to the EAC group. Meanwhile, the serum MDA level of the EAC mice showed marked increase compared with mice in the control group. The results indicated that mice treated with AH+EAC, LS+EAC and CP+EAC showed a significant reduction in the mean values of serum MDA level compared to the EAC group.

Anti-inflammatory activity of the three plant extracts was investigated by MPO activity. CP+EAC achieved the highest degree of reduction in MPO level even than that of control mice, followed by LS then AH which recorded a significant reduction compared to EAC group.

Chromosome aberration:

Low percentages of structural chromosomal aberration were scored (0.67±0.33) in control group, while the oil group recorded (0.83±0.31) (Table 4).On the other hand, after 7 days of EAC inoculation, major chromosomal aberrations in bone marrow were recorded as represented in table (4). This aberration includes: cells with more than one aberration, structural (chromatid gaps, chromatid breaks, deletions, fragments and centromeric attenuation). Meanwhile, EAC inoculation showed a significant numerical aberration (polyploidy and aneuploidy) that reached 8.17±1.58 as compared to control.

No significant changes were recorded in groups treated with AH, LS and CP compared to the control as represented in table (4), while the three extracts revealed a significant decrease in aberration level in AH+EAC, LS+EAC and CP+EAC mice compared to the EAC group. CP extract effect was the best of all in

chromosomal aberration reduction.

Table 3: Effect of *Anastatica hierochuntica L.* (AH), *Lepidium sativum* (LS) and *Carica papaya* (CP)in biochemical parameters in experimental mice with Ehrlich ascites carcinoma (EAC) at seven days treatment:

Group	AST	ALT	GPx	MDA	MPO
C	193.3± 3.3	42.3± 0.88	15.4± 0.31	2.71± 0.19	7.54 ± 0.12
EAC	339.6± 0.33 [a]	74.6± 0.33[a]	2.78 ± 0.3 [a]	12.2 ± 0.12 [a]	11.1 ± 0.1 [a]
Oil	189.6 ± 5.7 [b]	34.3± 0.88 [b]	12.57 ± 0.34 [a]	7.59± 0.25 [a]	8.83 ± 0.22 [a]
AH	234.3± 2.3 [ab]	67 ±3[a]	12.22 ± 0.21 [ab]	6.75 ± 0.17 [ab]	8.07 ± 0.37 [b]
LS	203.3± 3.3 [b]	52.3± 3.7[ab]	13.66 ± 0.2 [ab]	7.49 ± 0.23 [a]	7.46 ± 0.08
CP	229.6± 2.9 [ab]	27 ± 0.57[ab]	12.87 ± 0.05 [ab]	8.5 ± 0.04 [a]	8.76 ± 0.36 [a]
EAC+AH	160± 5.7 [ab]	40.3± 4.9 [b]	8.55 ± 0.39 [ab]	9.47 ± 0.2 [ab]	10.11 ± 0.16 [ab]
EAC+LS	195± 5 [ab]	25.6± 1.2[ab]	11.5 ± 1.18 [ab]	8.03 ± 2.63 [ab]	8.13 ± 0.9 [b]
EAC+CP	176.6± 6.6 [b]	30 ± 5[ab]	13.26 ± 0.03 [ab]	3.36 ± 0.2 [b]	5.53 ± 0.1 [ab]

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No significant changes were recorded in groups treated with AH, LS and CP compared to the control as represented in table (4), while the three extracts revealed a significant decrease in aberration level in AH+EAC, LS+EAC and CP+EAC mice compared to the EAC group. CP extract effect was the best of all in chromosomal aberration reduction.

Table (4): Mean ±SE. of Chromosomal aberration frequency of in bone marrow cells of mice treated with the three plant extracts (*Anastatica hierochuntica: AH,lepidium sativum:LS andCarica papaya: CP*) for seven days with/without Ehrlich ascites carcinoma (EAC)

Groups	Abnor-mal cells	Cells with more than one aberra-tion	Chromatid type aberrations		Chromosome type aberrations			Total structural aberrations	Numerical aberrations		Total num. aberr.	Total aberrationExcluding g.
			Chd.g.	Chd.br	D	F	CA		Poly-ploidy	Aneu-ploidy		
Control	.67 ±.33	0.0 ± 0.00	0.00 ± 0.00	.33 ±.21	0.00 ± 0.00	.17 ±.17	.17 ±.17	.67 ±.33	0.00 ±.00	0.00± 0.00	0.00 ± 0.00	.67 ±.33
EAC	14.33a ±.92	1.5 a ± 0.43	0.50 a ± 0.22	.50 ±.22	0.67 a ± 0.21	.67 a ±.21	1.33 ±.67	4.67 a ± 1.17	1.00 a ± 0.00	7.17a ± 1.58	8.17 a± 1.58	13.83 a ±.75
Oil	1.00b±.45	0.2 b ± 0.17	0.17 b ± 0.17	.00 ±.00	0.17 ± 0.17	.33 ±.21	.17 ±.17	.83 b ±.31	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	.83 b ±.31
AH	.67b±.33	0.0 ± 0.00	0.00 ± 0.00	.00 ±.00	0.33 ±0.21	.17 b ±.17	.17 ±.17	.67 b ±.33	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	.67 b ±.33
LS	1.00b±.52	0.0 ± 0.00	0.00 ± 0.00	.00 ±.00	0.33 ± 0.21	.17 b ±.17	.50 ±.34	1.00 b ±.52	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	1.00 b ±.52
CP	.33b ±.21	0.0 ± 0.00	0.00 ± 0.00	.00 ±.00	0.00 ± 0.00	.17 b ±.17	.17 ±.17	.33 b ±.21	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	.33 b ±.21
AH + EAC	5.33ab± 2.43	0.8 a ± 0.48	0.00 ± 0.00	.00 ±.00	0.50 ± 0.34	.17 b ±.17	1.50 a ± 1.02	2.50 ± 1.63	0.00 ± 0.00	2.00 ab ± 0.68	2.00 ab ± 0.68	5.17 ab ± 2.27
LS + EAC	6.33ab ±1.69	0.2 b ± 0.17	0.33 ± 0.21	.33 ±.21	0.00 ± 0.00	.33 ±.21	.67 ±.33	2.17 b ±.79	0.17 ab ± 0.17	3.83 ab ± 0.95	4.00 ab ± 0.93	6.00 ab ± 1.51
CP + EAC	2.33b±.76	0.2 b ± 0.17	0.17 ± 0.17	.00 ±.00	0.00 ± 0.00	.00 ±.00	0.5 ± 0.22	1.17 b ±.60	0.00 ± 0.00	1.00 ± 0.52	1.00 b ± 0.52	2.17 b ±.70

The number of scored cells is 250/group

G: group, Chd. g.: chromatid gap, Chd. br: chromatid break, D.: deletion F.: fragment, C. A.: centromeric attenuation.

DNA fragmentation

The results revealed that the control group observed very low DNA fragmented bands (Figure 4). The rate of DNA fragmentation in control group and oil group was significantly lower than EAC (Figure 3). Moreover, DNA fragmentation in the group treated with CP was relatively similar to that in control and oil treated groups.

The treatment of mice with EAC induced highest rate of DNA fragmentation with high significant differences than control and all other treated groups as well as it showed high increase in the fragmented DNA bands (Figure 4).On the other hand, treatment of EAC-exposed animals with the three plant extracts AH, LS and CP decreased significantly the rate of DNA fragmentation as well as decreased the damage in the DNA bands induced by EAC cells.

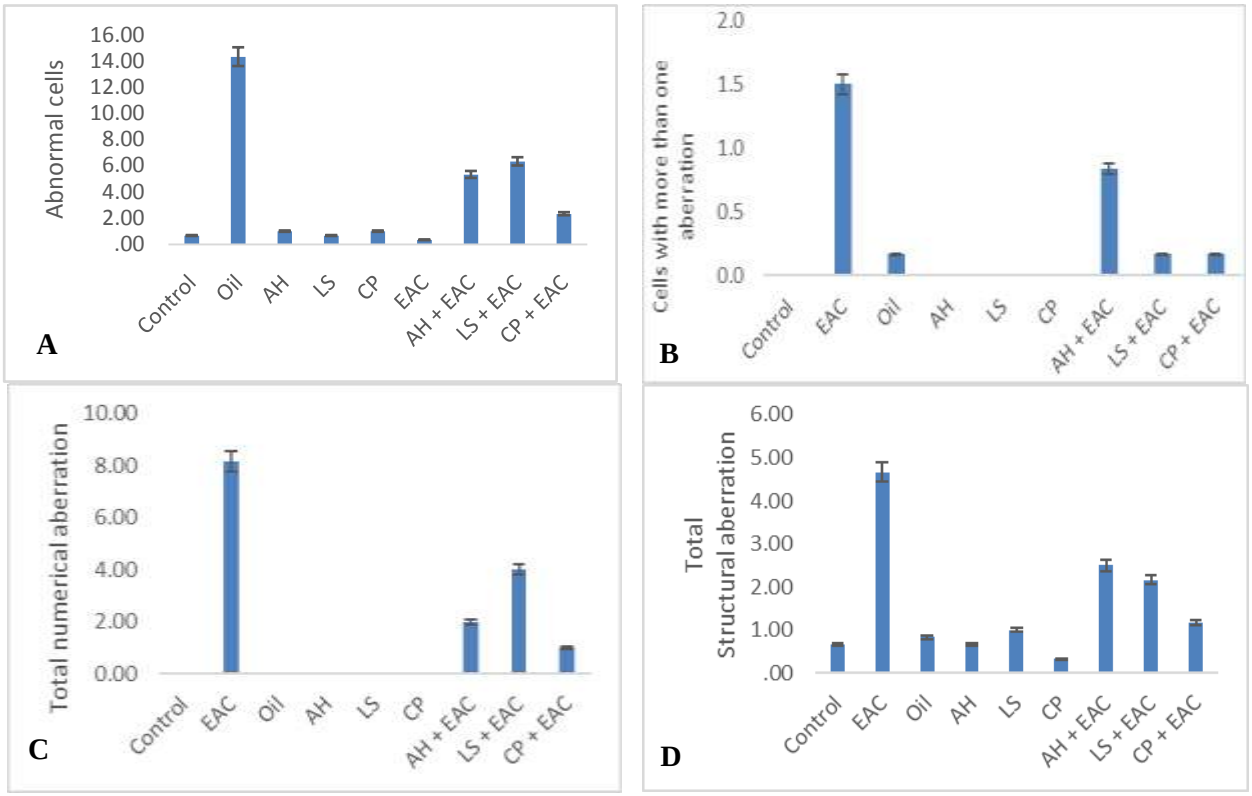

Fig. (1): Effect of *Anastatica hierochuntica L.* (AH), *Lepidium sativum* (LS) and *Carica papaya* (CP), extracts (7 days treatment) on bone marrow chromosomes of mice with/without Ehrlich ascites carcinoma (EAC) where A: abnormal cells; B: cell with more than one aberration, C: total numerical aberration and D: total structural aberration.

Furthermore, treatment of EAC-bearing mice with CP exhibited highest protection, where it decreased significantly the rate of DNA fragmentation as well as decreased the damage in the DNA bands induced by EAC more than the other two extracts AH and LS as shown in table (5).

Table 5: DNA fragmentation detected in liver tissues of mice with/without EAC treated/untreated with *Anastatica hierochuntica L.* (AH), *Lepidium sativum* (LS) and *Carica papaya* (CP) extracts for seven days:

Treatment	DNA Fragmentation %(M± SEM)	Change	Inhibition %
Control	5.7±0.29^{c}	0.0	0.0
Oil	6.3±0.30^{c}	0.6	0.0
EAC	21.4±0.32^{a}	15.6	173.68
AH	9.3±0.31^{c}	3.6	0.0
LS	10.7±0.28^{bc}	5.0	0.0
CP	6.4±0.67^{c}	0.6	0.0
EAC+ AH	14.0±0.58^{b}	8.3	45.61
EAC+ LS	16.7±0.33^{b}	11.0	92.98
EAC +CP	11.6±0.65^{bc}	6.0	5.26

Means with different superscripts (a, b, and c) between groups in the same column are significantly different at P<0.05.

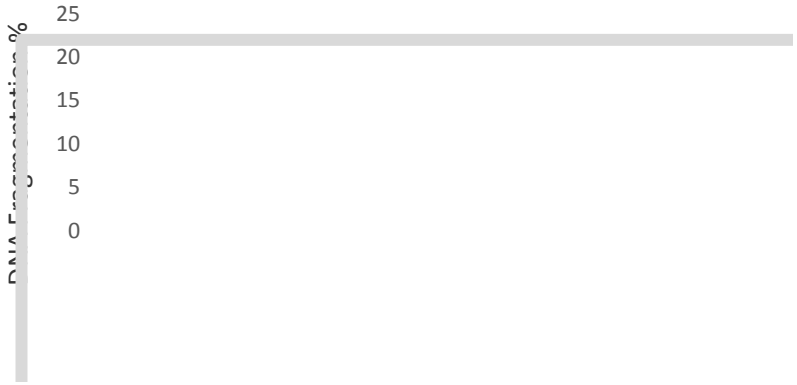

Figure3: DNA fragmentation in liver tissues exposed to EAC and treatments with different plants extracts (AH, LS and CP). Results are expressed as mean±SEM of data from analyzed samples. [a,b,c] Mean values within tissue with unlike superscript letters were significantly different (P< 0.05).

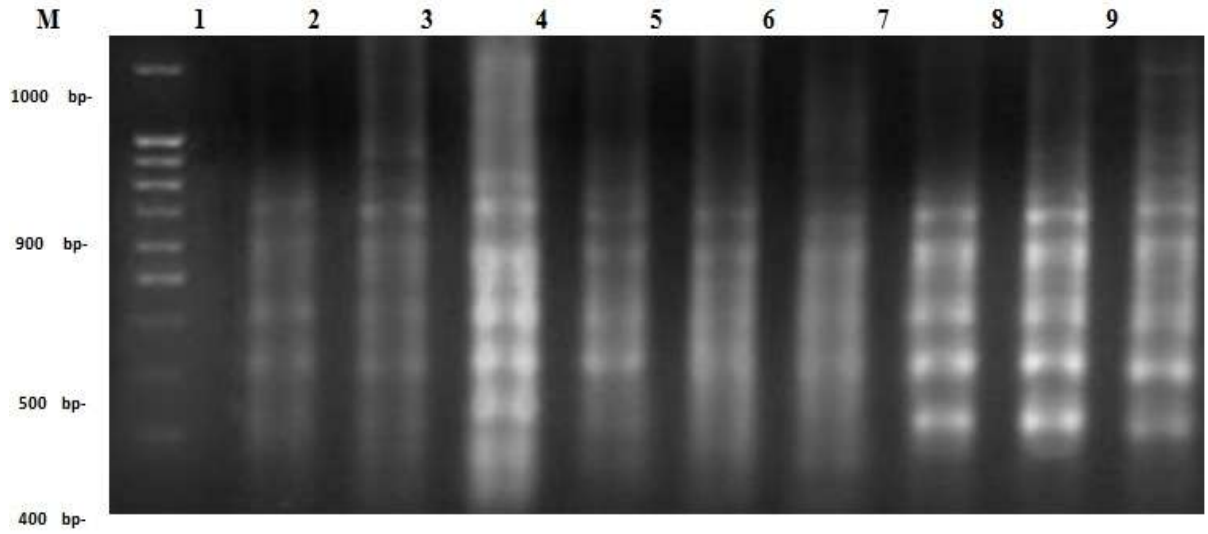

Figure 4: DNA fragmentation detected with agarose gel of DNA extracted from liver tissues by DNA gel electrophoresis laddering assay. Lane 1 represents control group. Lane 2 represents oil treatment. Lane 3 represents group treated with EAC. Lanes 4-6 represent groups treated with AH, LS and CP extracts, respectively. Lanes 7-9 represent groups treated with AH+EAC, LS+EAC and CP+EAC respectively.

4. Discussion

Ehrlich ascites carcinoma (EAC) is one of the commonly used experimental breast tumor that derived from spontaneous mouse adenocarcinoma that characterized by accumulation of ascitic fluid in the peritoneal cavity (**Ulakoglu and Altun, 2004**).The *in vivo* antitumor and antiproliferative activity was evaluated against EAC using mean survival time (MST) and increased life span percentages (%ILS) as reported by **AbuOsman *et al.* (2011).**Treatment of EAC-bearing mice with AH and LS extracts separately by oral gastric tube at 500 mg/kg. body weight in EAC-infected mice, revealed an increase in the mean survival time (MST) and life span (%ILS) with a reduction in body weight that may be attributed to up-regulation of humoral factors and diminished rate of cell division by the effect of the extracts (**Bhattacharya and Halder,2012).**It is suggested that the extract might be absorbed by the tumor cells which involved in lysis of these cells by cytotoxic mechanisms **(Samanta *et al.*, 2016).** Meanwhile, this effect may be attributed to the induction of apoptosis

or the inhibition of neovascularization and tumor progression or an indirect local effect, which may involve macrophage activation and vascular permeability inhibition as reported by many studies (**Dolai *et al.*, 2012** and **Samanta *et al.*, 2016).**This effect probably caused by the quercetin content in these plantsthat was reported to induced cytotoxicity in tumor cells without significantly affecting the normal cells**(Elsisy *et al.*, 2017)**.

The serum level of liver enzymes (ALT and AST) that are considered as reliable indices of hepatotoxicity (**Singh *et al.*, 2011**and **Dolai *et al.*, 2012),** showed a significant increase in EAC – bearing mice as compared with that of the normal mice that mayindicates the loss of functional integrity of the liver as reported by **Halaby*et al.* (2015).**However, **Salem *et al.*, (2011)** and **Dolai *et al.* (2012)** attributed this raised activities of liver enzymes to the hepatocellular damages. Meanwhile, **Abu-Sinna *et al.* (2003**) have suggested that the consumption of free amino acids in building the proteins of rapidly dividing tumor cells might result in the disturbances of the enzyme activity in the liver. Treatment of EAC-infected with AH,LS and CP extracts separately for seven days in the present study resulted in reduction in AST and ALT activities. Reduced level of these hepatic enzymes in serum is one of the indications of the antitumour potential **(Sundaram *et al.*, 2012).** The hepatoprotective effect of AH may be revealed to its content of Anastatins A and B that effect on d-galactosamine induced cytotoxicity in hepatocytes as reported by **Yoshikawa *et al.*(2003b**) or via antioxidant property of its polyphenolic compounds (**Shah *et al.*, 2014**).LS extract significantly reduced the mean values of serum AST and ALT in EAC-bearing mice revealing hepatoprotection, chemopreventive and chemotherapeutic activity as confirmed by **Behrouzian *et al.* (2014)**, **Halaby *et al.* (2015)**and **Abd El-Kaream (2019).**This effect may be due to the presence of phenolic compound in the extract **(Al-Asmaria *et al.*, 2015)** or prevention the oxidative stress related liver damage **(Lee *et al.*, 2013).** In agreement with these results, **Sakran *et al.* (2014)** and **Raish *et al.* (2016)** proved that LS seed extract (LS) has the ability to reduce hepatotoxicity by limiting damage to the liver cells, with a significant improvement and normalizing of the liver enzyme levels that effect may attributed to the presence of isoflavonoids and glycosilated phenols (**Aranda *et al.*, 2007; Sakran *et al.*, 2014**)such phenols was found to markedly restoring these enzymes to their normal levels **(Al-Otaibi *et al.*, 2019).**

EAC-bearing mice in the present study recorded a significant decreased level of glutathione peroxidase. This result agrees with that of **Das *et al.* (2014**) who stated that, the cellular proliferation of tumors is involved in the decrease of GPx activity. Meanwhile, **Samudrala *et al.* (2015)** found that EAC-mice had a decrease in the activity of SOD, CAT and GSH, that may be due to elevated MDA level that is claimed to be an inhibitor to protective enzymes, hence, it could have both mutagenic and carcinogenic effects (**Ziech *et al.*, 2010**).

AH, LS and CP extracts increased the level of Gpx in EAC mice with the effect increasing respectively. AH effect may be due to its content of flavonoids, chlorogenic acids, and phenolic compounds with antioxidant (**Jaiswal *et al.*, 2011**) and free radical scavenging potential (**Nakashima *et al.*, 2010** and **Jaiswal *et al.*, 2011**). Luteolin was found to increase the levels of SOD, CAT, GPx as mentioned by **Sharma *et al.* (2007**).

On the other hand, there is a significant increase in the antioxidant enzymes in the EAC-mice administered LS compared with EAC-mice only. This increase is due to the ability of LS extract to enhance the endogenous antioxidant activity owing to the presence of alkaloids, amino acids, flavonoids, glycosides, phytosterols, saponins and tannins **(Thoppil and Bishayee, 2011** and **Abd El-Kaream, 2019)** beyond its free radical scavenging property and the reduction of lipoperoxide formation (**Lee *et al.* 2013** and **Ebtesam *et al.*, 2016**).

Also, these results were in agreement with **Ojo *et al.* (2017)** who found that administration of C. *papaya* extract considerably increased antioxidant enzymes, signifying the capability of *C. papaya* leaf extract to reduce oxidative stress in Ehrlich-exposed animals by its content of antioxidant compounds that impact on the expression associated with oxidative (**Manu and Kuttan, 2008**and **Shan *et al.*, 2009).**

MDA is a main product of lipid peroxidation that has the potential not only to evaluate the extent of oxidative injury, but also to predict the potential efficiency of therapeutic strategies aimed at restricting the oxidative stress (**Yazdanparast *et al.*, 2007** and **Halaby, *et al.*, 2013).** The present study recorded a significant increase in the amount of MDA in the EAC-bearing mice. This come in line with **Mansour and Anis (2010)** and **Aldubayan *et al.* (2019**) who demonstrated a rise in MDA level associated with impaired hepatic function, indicating general toxicity in EAC mice. Meanwhile, **Al-Rasheed *et al.* (2018**) attributed this elevation to the peroxidation of cell membranes and plasma lipoproteins that released into the blood stream or defect in the antioxidant system as stated by **Kumaraguruparan *et al.*, (2002**).However, treatment with AH, LS and CP extracts, significantly reduced MDA levels in EAC mice. The significant reduction of MDA level by AH extra that may be attributed to their content of flavonoids: Anastatin A and anastatin B, glucosinolates and their derived

isothiocyanate that were confirmed to possess antioxidant (free radical scavenging) properties (**Adewusi and Afolayan, 2010** and **Mota *et al*., 2011)** they act by inhibition of lipoxygenase and cyclooxygenase pathways, and they are useful to explicate fatty acid peroxidation process (**Szabo, 1989** and **Mohammed *et al*., 2010)**. LS extract results was in line with **Halaby*et al*., (2015)** that recorded a significant reduction in the serum MDA level**.** It may be suggested that the activities of the LS plant are due to its free radical scavenging activities and the rich content in antioxidants as vitamin C, E and carotenoids, also phytochemical constituents such as (polyphenols and flavonoids) that have been reported to protect the body system against reactive oxygen species, as mentioned by **Donno *et al*., (2013).**Administration of *C. papaya* extract reduced MDA levels, signifying the capability of C. papaya leaf extract to reduce oxidative stress in EAC-mice as confirmed by **Elsisy *et al*.(2017**). This effect may be due to its content of quercetin that reported to attenuate the oxidative stress and it caused a significant decrease of MDA (**Abd-Elbaset *et al*. 2015).**

EAC was found to increase the amount on MPO in mice serum. This may be due to the fact that several human tumors present high levels of ROS (**Reuter *et al.* 2010**). In this context, the immune system is activated through the inoculation of mice with Ehrlich tumor (**Schneider and Oliveira 2004**).Previous studies that have shown that most of the plant extracts reduce EAC induced myelotoxicity due to their immune boosting, antioxidant and free radical scavenging activity. (**Dolai *et al*., 2012**).In the present study, AH, LS and CP recorded a significant reduction in the amount of MPO.LS may act through suppression of the neutrophil infiltration and inflammatory cytokine release to the injured myocardium (**Mohamed and Safwat, 2016**) **or by** increasing the weight of the spleen (**Mahassni and Khudauardi, 2017)** which may result from the increased production and storage of immune system cells increase in the mean WBC count and attenuates the myeloperoxidase (MPO) level (**Raish *et al*., 2016**). LS extract effect may be due to the presence of lipid compounds including alpha linoleic acid which has anti-inflammatory activity **(Ferrucci *et al*., 2006**and **Zhao *et al*., 2007).** The role of alpha linoleic acid is to down regulate the expression of inflammatory cytokines such as IL-6, IL-1β and TNF-α (**Zhao *et al*., 2007**).CP exhibited a significant inhibition in MPO value in EAC-bearing mice.A study on the *C. papaya* leaves extract showed that it increased the levels of white blood cells, thrombocytes, lymphocytes and neutrophils of rats. (**Nwiloh *et al*., 2009**). *Papaya* is known for its antimicrobial, anti-inflammatory, immunomodulatory (**Otsuki *et al*., 2010**), and antioxidant properties (**Owoyele *et al*., 2008** and **Oboh *et al*., 2013**). Anti-inflammatory and antioxidant properties of papaya are attributed to primary and secondary bioactive components such as papain, chymopapain, papaya lipase, and carotenoids (**Nafiu and Rahman, 2015**).

The flavonols and flavonoids have stimulant effect on blood cell production. **(Sundarmurthy *et al*., 2017).**Researchers have found that *C. papaya* leaf extract can mediate Th1-type shift in human immune system, which could potentially help regulate the immune system, treat or prevent cancer, and also serve as an immune adjuvant for vaccine therapy (**Otsukia *et al*., 2010**). Furthermore, it is shown to influence platelet production and aggregation by activating arachidonate 12-lipoxygenase (ALOX 12) and platelet-activating factor receptor (PTAFR) genes **(Sundarmurthy *et al*., 2017**). However**,** saponins (present in AH and CP) demonstrated to have immunomodulatory potential via cytokine interplay (**Sun *et al*., 2009**), cytostatic and cytotoxic effects on malignant tumor cells (**Bachran *et al*., 2008**). Quercetin(present in AH, LS and CP) inhibits pro inflammatory cytokine gene expression through the modulation of NF-kβ system (**Nair *et al*., 2006**).

In the present study, the EAC inoculated intraperitoneal in female mice caused high incidence of chromosomal aberration in mice bone marrow cells. These findingsimply that Ehrlich's solid tumor (EST) caused loss in chromatin as results of a damage to either chromosome structure (fragmentation) or dysfunction of the spindle apparatus or centromere kinetochore complexes (**Fenech, 2000**). Many studies suggested that EAC induced oxidative stress in mice **(Gupta *et al*., 2004 a, b)** thatcan cause hypoxia, reoxygenation and damage to cellular macromolecules and lead to increased genetic instability (**Vafa *et al*., 2002**; **Moeller *et al*., 2004** and **Corn and El-Deiry, 2007**).

Kondoh *et al.* (2013) reported that hypoxia induced chromosomal abnormalities (aneuploidy) in endothelial cells through the induction of reactive oxygen species and excess signaling of vascular endothelial growth factor in the tumor microenvironment. This concept was in agreement with **Salah *et al.* (2011**) who found that, oxidative stress produced great chromosomal aberrations, this damage DNA and block the action of RNA polymerase and so prevent replication process. Also, **Pang, 1995** stated that,cells exposed to reactive oxygen species will incur a range of genetic aberrations, which may either be structural (e.g. deletion. DNA strand breaks) or numerical (e.g. chromosomal loss/ gain).

Oral administration of LS, AH and CP extracts at 500 mg/kg b.wt. was found to reduce chromosome aberration induced in mice bone marrow cells after EAC intraperitoneal inoculation with their effect increasing respectively indicating that the best effect was for CP extract.

In agreement with **Salah *et al.* (2011),** AH extract and revealed an inhibition in the frequency of chromosomal aberrations significantly in both somatic and germ cells of diabetic rats.The therapeutic effect of AH may have attributed to its content of polyphenols including flavonoids which have known protective activity (**Zayachkivska *et al.*, 2005**). The positive effect of LS on mice bone marrow chromosomes may be due to its antitumor activities.LS extract activity was studied by **Ait-Yahia *et al.* (2015)** who showed its antitumor activities towards Hep2.

The present results on chromosomes was in agreement with the study of **Ojo*et al.*, (2017)** who found that the treatment with *C. papaya* extract significantly decreased chromosomal aberrations and, micro nuclei induction in arsenic induced genotoxicity in Wistar rats.

The leaves of *Carica papaya* L. contain the alkaloid carpaine (**Ramasawamy and Sirsi, 1960**), that has been found to possess antitumor activity *in-vitro* against mouse lymphoid leukemia L1210, lymphocytic leukemia P388 and Ehrlich ascites tumor cells. The leaves of papaya also have been shown to contain many active components that can increase the total antioxidant power in blood and reduce lipid peroxidation level, such as papain, chymopapain, cystatin, α-tocopherol, ascorbic acid, flavonoids, cyanogenic glucosides and glucosinolates which elucidate its highest effect on chromosome improvement (**Seigler *et al.*, 2002** and **Sundarmurthy *et al.*, 2017**).

The three plant extracts were reported to contain quercetin and luteolin that were known with their chemo preventive activity against chromosomal alterations. Luteolin suppressed genetic damage in the micronucleus assay and chromosome aberrations induced by fish extract. Mutton extract-induced micronuclei and chromosome aberrations were reduced by luteolin and quercetin (**Taj *et al.*, 1996)**. Anotherstudies have shown that quercetin administration to mice led to a decrease in the amount of chromosomal aberrations induced by methotrexate in bone marrow cells and diminished the number of cells with methotrexate-induced aberrations (**Sekeroğlu & Sekeroğlu, 2012**).

In this study, we observed high level of DNA fragmentation induced in mice liver after 7 days of EAC intraperitoneal injection. These results come in a close resemblance to the study done by **Hanafy (2009)** who found an increase in DNA fragmentation in mice liver of EAC-mice and the finding optained by **Khalil *et al.*, (2014)** who found high degree of DNA damage in bone marrow cells of Ehrlich's solid tumor (EST). Free radicals may lead to a decline in the level of glutathione and increased oxidative damage to normal proliferating cells and may lead to oxidative damage to macromolecules, including DNA damage, which in turn contributes to the formation of DNA strand breaks, (**Sallmyr *et al.*, 2008** and **Papież, 2014**).

More evidence suggests that the potentially cancer-inducing oxidative damage might be prevented or limited by antioxidant. Antioxidant may mediate their effect by direct reaction with ROS, quenching them or chelating the catalytic metal ions **(Sun *et al.*, 2002).** It has been shown that antioxidant rich diets can reduce oxidative damage to DNA, thus preventing a critical step in the onset of carcinogenesis **(Meyskens *et al.*, 2005).** Many cancer chemopreventive agents possess antioxidant potential due to their bioactive phytochemicals that may play a vital role in protecting the cell from oxidative stress (**Ozben, 2007**).

The present study found a positive effect of the three extracts on DNA fragmentation, they significantly reduced the incidence of DNA fragmentation. Previous studies have suggested that the DNA damage was decreased by antioxidant supplementation (**Bingöl *et al.*, 2014; Abraham *et al.*, 2016** and **Koyuncu, 2018**).AH and CP recorded better effect than LS effect, which may be due to their content of Saponins that interfere with the replication of cellular DNA and they prevent the proliferation of cancer cells. (**Yıldırım and Kutlu, 2015**). The higher preotective effect against DNA damage was exeted by CP leaf extract that may be owing to its content of tannins which have the properties of the binding metallic ions and also the display of anti-oxidant activities (**Yıldırım and Kutlu, 2015**). *Carica papaya* L or papaya is one of the plants that are known for anticancer therapy by increasing the apoptosis and inhibiting the proliferation (**Puspitasari and Peristiowati, 2016**).

Quercetin that present in the three plant extracts AH, LS and CP. **Srivastava *et al.* (2016)** reported a change in DNA bands in quercetin antitumor efficacy in animal models and cancer cell lines. **Lin *et al.* (2002)** reported the role of quercetin in protection against cooking oil fumes-induced DNA damage in human lung adenocarcinoma. Quercetin also significantly reduced the oxidative DNA damage caused by etoposide both *in vitro* and *in vivo* (**Papież, 2014**). **Sashi *et al.* (2016)** studied the potential roles of dietary agents (including Quercetin) exerting antioxidant properties that may impede cancer progression, and reported an anti-oxidative effect

against oxidative stress status in cancer. The efficacy of Quercetin as antitumor agent where it caused an elevation in Quinone Reductase 1 (QR1). QR is an important phase II cytoprotective enzyme that converts quinones to hydroquinones, reducing oxidative cycling It exhibits cancer protective activity mainly by inhibiting the formation of intracellular semiquinones radicals, and by generating α-tocopherol hydroquinone, which acts as a free radical scavenger. Induction of QR1 often coincides with induction of other phase II enzymes, and is therefore useful in the study of chemopreventive agents (**Cuendet *et al.*, 2006**).

Conclusion

The natural extracts of *Anastatica hierochuntica* (AH), *Lepidium sativum* (LS)and *Carcia papaya* (CP) revealed great antioxidant, anti-inflammatory, antimutagenic and antitumor effectsagainst *in vivo* Ehrlich ascites carcinoma (EAC) in Swiss albino mice. These effects were indicated byan increase of EAC tumor-bearing mice lifespan, increase in glutathione peroxidase (GPx) and marked reduction of MDA and MPO levels in the sera of EAC bearing mice. Also, the three plants specially *Carica papaya* decreased both of chromosomal aberration and DNA fragmentation in EAC tumor-bearing mice.

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