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Effects of Consuming Camel and Goat Milk on the Risks of Cancer Treatment by Cisplatin in Affected Female Mice

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ABSTRACT

Cancer is the second major reason of death worldwide. Chemotherapy treatment causes various adverse effects. Co-administration of immuno-modulatory agents with chemotherapy may result in better responses with fewer side effects. This work evaluated camel and goat milk (CM and GM) consuming pre and/ or post (neo-adjuvant and /or adjuvant) on the risks of cisplatin treatment in cancerous mice. Camel and goat milk nutritional and active composition were estimated. 20 mice kept healthy, 20 mice injected with cisplatin only and Ehrlich ascites carcinoma injection used to induce Ehrlich solid carcinoma in 120 mice. Cisplatin was injected once (3.5mg/kg mouse intra-peritoneal). CM or GM was orally (0.4ml /20g mouse) co-treated with cisplatin as neo-adjuvant and /or adjuvant. After 39 days mice were sacrificed, blood, tummor and bone marrow were separated to perform biochemical, genetic, tummor immunohistochemical, and histo-pathological studies. CM and GM were full of nutritional and immuno-modulatory components. Pre and/ or post CM or GM co-administration caused a significant ($p \leq 0.05$) improvement in hematological profile, antioxidant status, reversed the cisplatin-induced inflammation and elevated liver enzyme activities. CM or GM co-treatment with cisplatin resulted in a significant decreases ($p \leq 0.05$) in bone marrow tissues apoptosis, DNA damage and tumor cell proliferation. Also both milk enhanced the anti-tumor effects of cisplatin by a reduction of tumor size and weight. Microscopic examination of bone marrow tissues and tumor masses confirmed these results. Both milk modulated the risks of cisplatin treatment in cancerous mice without compromising its antitumor efficacy. Pre and post camel milk co-administration recorded the most significant improvements.

1. Introduction

Cancer is the malignant tumor, acts as group of diseases in which genetically destroyed cells propagate autonomously. Cancer can result from environmental, genetic and life style agents. Cancer cells keep to proliferate, robbing nearby ordinary cells of nutrients, and finally conflicting with normal body tasks [1],

[2].

In spite of progression of various treatment approaches, chemotherapy stays the major regimen for different forms of malignancies. However, classical chemotherapy has many severe side effects [3].

Cisplatin, cis di-ammine di-chlorido platinum (CDDP), is an extensively utilized chemotherapeutic medication with wide spectrum activity. Despite its strong antitumor potency, it has organs serious cytotoxic impact due to DNA damage, raised propagation of endogenous reactive oxygen species (ROS) in mitochondria, loss of antioxidants and high danger for the development of secondary malignancies in healthy and cancerous tissues [4].

Immuno-modulatory agents can improve the anti-tumor ability of cisplatin with retarding its possible adverse effects. Milk is recognized as complementary and alternative medicine factor due to its composition. Composition of milk differs widely with species, breed, season and nutrition case [5].

Camel (*Camelus dromedaries*) milk (CM) has unparalleled benefits for human validity. Proteins (whey proteins and casein), vitamins (A,E B2, B6 and C), minerals (iron, manganese, zinc, and others); as well as small sized immuno-globulins (IgG, IgA and IgM) that are easily absorbed from the gut and strengthen the immune system are the major components which gives special characteristics to CM and effectively impacts its nutritional value [6].

Camel milk have also protective enzymes as lactoferrin, lacto-peroxidase and lysozyme. Lactoferrin (major iron adhering protein) has antioxidant, antibacterial, antiviral and anti-inflammatory characteristics. Peptidoglycan in CM has the capacity to prevent cancer metastasis. CM is beneficial in the treatment of food allergy, geno-toxicity, HIV, diabetes mellitus, autism, tuberculosis, viral hepatitis, cardiovascular diseases, stomach and intestine disorders [7].

Goat (*Capra hircus*) milk (GM) is one of the major milk heads for human use. It varies from camel, human and cow milk in composition and nutritional properties. Goat milk and derived products contain various nutritional and active components as vitamins, carotenoids, fats, flavonoids, polyphenols, minerals (higher levels of Ca, K and P), oligosaccharides, casein peptides and whey proteins such as lysozyme, lactoferrin, immuno-globulins and β-lactoglobulin that could be helpful competing against different chronic diseases. It has been proved to have strong immuno-modulatory, antioxidant, antiviral, antibacterial and antifungal activities [8], [9]

The target of the existing work was to assess the ameliorative effects of consuming camel or goat milk on the risks of cancer treatment by cisplatin in cancerous mice.

2. Materials and Methods

2.1 Camel and goat milk (CM and GM)

Fresh whole camel and goat milk were purchased from local market Cairo, Egypt.

2.2 Ehrlich Ascites Carcinoma (EAC) cell line

The Ehrlich Ascites Carcinoma (EAC) cells were provided by the Oncology Unit, National Cancer Institute (NCI), Cairo University, Egypt. A single dose of 2.5×10^6 viable EAC cells present in 0.2 ml of diluted ascitic fluid (1:10) with saline was shot intramuscularly (IM) in the left thigh of 120 mice to prompt solid

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tumors [10].

2.3 Chemical

Cisplatin (CDDP) (Mylan, Saint-Priest, France) was purchased from El Ezaby pharmacy, Heliopolis, Cairo, Egypt in the form of ampoules; each contained 50 mg of CDDP in 50 ml sterile saline solution.

2.4 Animals

160 Healthy adult female albino mice (BALB/c strain), (22 ± 3) g, aged five weeks were obtained from Medical Ain Shams Research Institute (MASRI), Egypt.

2.5 Diet

Standard commercial pellet diet was bought from National Research Council (NRC), Dokki, Giza, Egypt.

2.6 Determination of major constituents in the whole tested milk samples

Major milk constituents; protein, fat, lactose, total solid nonfat, and ash percent were automatically determined using milk analyzer according to [11].

2.7 Determination of total immuno-globulins content, lacto-peroxidase enzyme activity and total antioxidant capacity in the tested milk samples

Milk whey protein was separated using [12] method. Total immuno-globulins content, lacto-peroxidase enzyme activity and total anti-oxidant capacity (TAC) in the tested milk whey proteins were determined following to [13- 15] respectively.

2.8 Experimental mice groups design

160 mice were housed individually at random in stainless steel coops with barred environmental conditions. Mice were given the standard commercial pellet diet with drinking water *ad libitum*. Mice were adapted to laboratory situations for 7days before beginning the experiment. Mice were sectioned into eight groups; 20 mice each as following:

Group *I*: [Healthy control group]: Act as negative control; healthy mice were shot with physiological saline intra-peritoneally (I.P.) at a single dose and given distilled water orally.
Group *II*: [Cisplatin group]: Healthy mice were intra-peritoneally (IP) shot with CDDP at a single dose of 3.5 mg/ kg body weight (B. Wt) [16] and given distilled water orally.
Group *III*: [Cancer group]: Healthy mice were inoculated with EAC cells intramuscularly (IM) in the left thigh of each mouse to prompt solid tumor and given distilled water orally.
Group *IV*: [Cancer + Cisplatin group]: Cancerous mice were shot IP with a single tested dose of CDDP and given distilled water orally.
Group *V*: [CM Neo-adjuvaant-adjuvant group]: Healthy mice were administered daily fresh whole CM orally at dose of (0.4ml /20g mouse) [17] for two weeks, then inoculated with EAC cells IM in the left thigh. After 10 days of inoculating the EAC, mice were IP shot with a single tested dose of CDDP and given daily tested dose of fresh whole CM orally for two weeks.
Group *VI*: [GM Neo-adjuvant-adjuvant group]: Healthy mice were administered daily fresh whole GM orally at dose of (0.4ml /20g mouse) [18] for two weeks, then inoculated with EAC cells IM in the left thigh. After 10 days of inoculating the EAC, mice were IP shot with a single tested dose of CDDP and given daily tested dose of fresh whole GM orally for two weeks.
Group *VII*: [CM Adjuvant group]: Cancerous mice were shot IP with a single tested dose of CDDP, then were given daily tested dose of fresh whole CM orally for two weeks.

Group *VIII*: [GM Adjuvant group]: Cancerous mice were shot IP with a single tested dose of CDDP, then were given daily tested dose of fresh whole GM orally for two weeks.

On the 39th day of the experiment; mice were fasted for 12hr, weighed and sacrificed under anesthesia. Blood samples were gathered and serum was separated to determine hematological and biochemical parameters. Femur bone (for bone marrow analysis) and tumor tissues were disconnected, washed by saline solution and dried by blotting on filter paper. Tumor was weighed, part of the bone marrow and tumor tissues were picked and fixed in 10%formalin for microscopic and immuno-histological check, while the remaining stocked frozen at -80 °C until utilized for genetic tests. Muscle tissue of non-tumor bearing groups was dissected as opposed for tumor in tumor bearing groups.

2.9 Biochemical evaluations

2.9.1 Hematological measurements

Complete blood count (CBC) were determined according to [19] using Beckman Coulter MAXM automated hematology analyzer.

2.9.2 Oxidative stress biomarkers

Serum nitric oxide (NO) and malondialdehyde (MDA) levels were estimated according to [20], [21] using (*Biodiagnostic, Egypt*) *kit, CAT No (NO 25 33)* and *(MD 25 29)* respectively.

2.9.3 Enzymatic and non-enzymatic antioxidant biomarkers

RBC's superoxide dismutase (SOD), serum catalase (CAT) enzyme activities and blood reduced glutathione (GSH) level were assessed according to [22- 24] using *(Biodiagnostic, Egypt) kits, CAT.NO (SD 25 21), CAT.NO (CA 25 17) and CAT.NO (GR 25 11)* respectively.

2.9.4 Inflammatory and anti-inflammatory biomarkers

Serum tumor necrosis factor alpha (TNF- α), interleukin - 6 (IL-6) and interleukin -10 (IL-10) concentrations were estimated according to [25- 27] using *(CUSABIO, USA) kit [CAT. NO. CSB-E04741m (1)], (Quantikine®, USA) ELISA kit, CAT.NO (M6000B) and (MyBioSource, USA) ELISA kit, (CAT. NO. MBS8800145)* respectively.

2.9.5 Liver function tests

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) enzyme activities were measured according to [28], [29] using *(NS Biotec, Egypt), kit CAT.NO (GOT-MC-02100), (BioMed Diagnostics, Egypt), kit CAT.NO (GPT113100)* and *kit CAT.NO (GGT12460)* respectively.

2.10 Genetic study

2.10.1 Relative gene expression of p53, Bax, Bcl-2, and caspase-3 in bone marrow tissue using real time quantitative polymerase chain reaction (RTq PCR) method

p53, Bax, Bcl-2, and caspase-3 genes were analyzed in bone marrow tissue by real time quantitative polymerase chain reaction (RT-qPCR) method, according to [30] using SV total RNA isolation system *(CAT. NO. #Z3500, Promega, USA)* tissue extraction kit, high capacity cDNA reverse transcription kit *(CAT. NO. #K4374966, Thermo Fisher Scientific, USA)* and Maxima SYBR Green qPCR Master Mix (2X) kit with ROX solution *(CAT. NO. #K0252, Thermo Fisher Scientific, USA)* following table (1) primers.

Table (1): Primers sequence of studied genes

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Gene	Primer sequence	Gene bank accession no.	Size
P 53	**Forward:** 5'- GTATTTCACCCTCAAGATCC -3' **Reverse:** 5'- TGGGCATCCTTTAACTCTA -3'	**M13874.1**	**1322 bp**
Bax	**Forward:** 5'- CTACAGGGTTTCATCCAG -3' **Reverse:** 5'- CCAGTTCATCTCCAATTCG -3'	**L22472.1**	**579 bp**
Bcl-2	**Forward:** 5'- GTGGATGACTGAGTACCT -3' **Reverse:** 5'- CCAGGAGAAATCAAACAGAG -3'	**XM_017025917.2**	**596 bp**
Caspase-3	**Forward:** 5'- TGCGTGTGGAGTATTTGGATG -3' **Reverse:** 5'-TGGTACAGTCAGAGCCAACCTC-3'	**NM_012922.2**	**2484 bp**
GAPDH	**Forward:** 5'- GAGAAACCTGCCAAGTATG -3' **Reverse:** 5'- GGAGTTGCTGTTGAAGTC -3'	**XM_039111296.1**	**466**

2.10.2 DNA-fragmentation and damage using comet assay in bone marrow tissue

DNA-fragmentation was determined in bone marrow tissue using single cell gel electrophoresis (SCGE) [alkaline comet assay] according to [31]. The lengths of the comets' tail from the center of the nucleus until the end of the tail were determined using Ethidium Bromide –stain for visualizing DNA damage utilizing a 40x objective on a fluorescent microscope.

2.11 Determination of tumor cell proliferation using immunohistochemical expression of proliferating cell nuclear antigen (PCNA) in tumor tissues

Immunohistochemical examination of PCNA was done on tumor paraffin sections and skeletal muscles stained using avidin-biotin- peroxidase complex (ABC) method using rabbit anti PCNA antibody, polyclonal antibody *(Elabscience Cat# E-AB-64562, Dil.:1:50)* according to [32]. Slides were then examined and photographed by a light microscope (Olympus BX 41, Japan) to evaluate PCNA immunostaining.

2.11.1 Quantitative scoring of immunohistochemical results "Area Percentage"

Area % was determined for PCNA-stained sections (x 400) via Leica QWin 500 image analyzer computer system (England).

2.12 Physical biochemical tumor study

Tumor growth was examined by studying the following parameters:

2.12.1 Determination of solid tumor weight

Tumor weight (g) was recorded immediately using sensitive digital scale. It was calculated during the experiment to have mean tumor weight without killing or dissecting the mice till the end of experiment according to [33] using the following equation:

Tumor weight (mg) = Length (mm) × {width (mm)}^{2} /2

2.12.2 Determination of solid tumor volume (size)

Mice tumor bearing thigh was shaved, the tumor longest and shortest diameters were measured by a Vernier

caliper. Tumor volume was measured during the experiment and after dissection according to [34] using the following formula:

Tumor Volume (mm3) = (length × width^2) × 0.52.

2.13 Tissue histo-pathological study

Bone marrow and tumor tissues were set in 10% neutral formalin solution for 24 hours according to [35], dehydrated, cleaned, and then embedded in paraffin wax. Serial sections were cut into 4 microns in thickness and were stained with Haematoxylin and Eosin (H&E). The slides were examined under a light microscope and photographs were taken at (40X) magnifications [36].

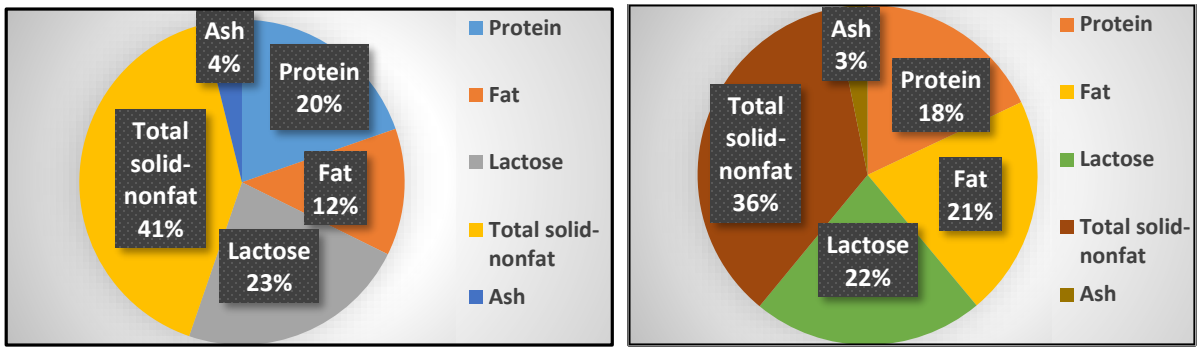
2.14 Statistical analysis

Data were statistically analyzed by Statistical Package for Social Sience "SPSS" version 20.0 Micosoft Windows, SPSS Inc. Values were represented as mean ± standard deviation (S.D). Statistical difference between groups were made using one-way analysis of variance ANOVA, the mean difference was examined using the least significant difference (LSD) at ($P \leq 0.05$) level according to [37].

3. Results

3.1 Determination of major constituents in the whole tested milk samples

Results of major constituents in milk samples analysis fig 1(a and b) showed that both milk are full of nutrients and are with high nutritional value. Camel milk sample contained more total solid nonfat, lactose, protein, and ash contents in comparison with goat milk sample that contained more fat content.



[a] [b]

Fig (1): major constituents in (a) camel milk sample and (b) goat milk sample.

3.2 Determination of total immuno-globulins content, lacto-peroxidase enzyme activity and total antioxidant capacity in the tested milk samples

Results tabulated in table (2) showed that both tested milk samples contain a considerable value of immuno-globulins, lacto-peroxidase enzyme activity and total antioxidant capacity making them precious immuno-modulatory agents. Camel milk sample has a higher content of active constituents in comparison with goat milk sample.

Table (2): Active bio-components in the tested complete mature camel and goat milk

Active Bio-components	Camel milk	Goat milk
Total immuno-globulins (mg/dl)	**7810.1±4.32296**	**3172.8 ± 4.48642**
Lacto-peroxidase enzyme activity (U/min/ml)	**0.447±0.04227**	**0.346±0.01430**

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Total antioxidant capacity mmol/l	**5.76 ± 0.17309**	**3.62 ± 0.11983**

-Values are mean of six replicates, values are mean ± SD.

3.3 Effect of consuming tested camel and goat milk on hematological measurements in experimental mice groups

From table (3) it was observed that a statistically significant (P≤0.05) drop in RBC's, HB, WBC's, and PLT's counts in cisplatin group, while cancer caused significant decrement (P≤0.05) of RBC's and HB contents with increment in WBC's, and PLT's counts. The highest drop was found in cancer + cisplatin group compared to healthy control group. Oral consumption of both milk improved hematological parameters. Camel milk consumption before and after EAC and cisplatin induction caused the greatest significant improvement (P≤0.05) in hematological parameters compared to cancerous mice treated with cisplatin group.

Table (3): Effect of consuming tested camel and goat milk on hematological measurements in experimental mice groups

Parameters / Groups	RBC's count (n x 10^6/µl)	HB (g/dl)	WBC's count (n x 10^3/ µl)	PLT's count (n x 10^3/ µl)
GI: Healthy control group	**9.805 ± 0.501^{a}**	**14.79± 0.142^{a}**	**13.003 ± 1.383^{b}**	**188.521 ± 0.937^{b}**
GII: Cisplatin group	**7.201 ± 0.136^{d}**	**9.119± 0.564^{d}**	**5.501± 0.611^{g}**	**137. 334 ± 2.9007^{h}**
GIII: Cancer group	**7.334 ± 0.156^{d}**	**9.4 ± 0.222^{d}**	**35.105 ± 2.464^{a}**	**207.876 ± 3.205^{a}**
GIV: Cancer + Cisplatin group	**6.66 ± 0.217^{e}**	**7.89± 0.661^{e}**	**8.744± 0.234^{f}**	**153.677 ± 1.695^{g}**
GV: CM Neo adjuvant – Adjuvant group	**9.404± 0.349^{b}**	**13.225 ± 0.51^{b}**	**12.2 ± 0.461^{bc}**	**177.062 ± 1.998^{c}**
GVI: GM Neo adjuvant - Adjuvant group	**9.304± 0.512^{b}**	**12.95 ± 0.49^{b}**	**12.001± 0.431^{cd}**	**174.248 ± 1.9601^{d}**
GVII: CM Adjuvant group	**8.904 ± 0.266^{c}**	**12.01 ± 0.634^{c}**	**11.2 ± 0.303^{de}**	**168.323 ± 2.061^{e}**
GVIII: GM Adjuvant group	**8.702± 0.316^{c}**	**11.605± 0.748^{c}**	**11 ± 0.328^{e}**	**164.079 ± 2.108^{f}**
LSD (P ≤ 0.05)	**0.298**	**0.476**	**0.946**	**1. 391**

-Values are represented as mean ±SD, (n=10). There wasn't significance variation between means have the same letter within the same column (P ≤ 0.05).

3.4 Effect of consuming tested camel and goat milk on oxidative stress and antioxidants biomarkers in experimental mice groups

Based on the tabulated results table (4) of oxidative stress and antioxidants biomarkers, there was a significant upsurge in serum NO and MDA concentrations associated with considerable fall in the enzyme activities of serum CAT , RBC's SOD as well as blood GSH content in cisplatin group, followed by cancer group and the greatest oxidative markers elevation and antioxidants reduction recorded in cancer+ cisplatin group as compared to healthy control group (P≤0.05).However, mice received CM pre and post cancer and cisplatin induction demonstrated the greatest significant (P≤0.05) improvement in oxidative status. Meanwhile mice administrated GM post injecting cancerous mice with cisplatin exhibited the least significant (P≤0.05) improvements in oxidative status compared to cancer + cisplatin group.

Table (4): Effect of consuming tested camel and goat milk on serum oxidative stress and antioxidants biomarkers in experimental mice groups

Parameters / Groups	Serum NO (µmol/L)	Serum MDA (nmol/ml)	Serum CAT (U/L)	RBC's SOD (U/ml)	Blood GSH (mmol/L)
GI: Healthy control group	9.615 ± 1.584^{g}	28.167 ± 2.19575^{g}	115.296± 2.282^{a}	412.27± 2.521^{a}	9.343 ± 0.471^{a}
GII: Cisplatin group	50.085 ± 3.451^{c}	112.00 ± 1.457^{c}	64.666 ± 3.455^{f}	168.61± 3.387^{f}	4.02 ± 0.338^{e}
GIII: Cancer group	56.199 ± 2.857^{b}	118.143 ± 2.947^{b}	62.00 ± 3.422^{g}	161.802± 1.934^{g}	3.54 ± 0.506^{e}
GIV: Cancer+ Cisplatin group	76.382 ± 2.941^{a}	162.73 ± 1.716^{a}	53.046 ± 1.749^{h}	117.43 ± 1.502^{h}	2.574 ± 0.506^{f}
GV: CM Neo adjuvant – Adjuvant group	25.00 ± 3.131^{f}	38.067 ± 3.084^{f}	108.00 ± 2.542^{b}	385.26± 3.027^{b}	8.214 ± 0.875^{b}
GVI: GM Neo adjuvant - Adjuvant group	28.00 ± 2.830^{e}	39.058 ± 2.732^{f}	104.00 ± 1.617^{c}	377.28± 2.564^{c}	8.032 ± 0.389^{b}
GVII: CM Adjuvant group	32.00 ± 2.665^{d}	50.088 ± 3.557^{e}	100.00 ± 2.469^{d}	363.86 ± 0.889^{d}	7.52 ± 0.314^{c}
GVIII: GM Adjuvant group	34.00 ± 2.819^{d}	53.326 ± 1.854^{d}	95.00 ± 2.526^{e}	357.13 ± 3.235^{e}	7.02 ± 0.771^{d}
LSD (P ≤ 0.05)	2.523	2.264	2.304	2.246	0.493

-Values are represented as mean ±SD, (n=10). There wasn't significance variation between means have the same letter within the same column (P ≤ 0.05).

3.5 Effect of consuming tested camel and goat milk on serum inflammatory and anti-inflammatory biomarkers in experimental mice groups

Concerning, the serum inflammatory (TNF-α and IL-6) and anti-inflammatory (IL-10) biomarkers fig (2), there was a significant increase in serum TNF-α and IL-6 associated with a significant decrease in serum level of IL-10 in cisplatin group, followed by cancer group and the highest elevation in inflammatory biomarkers levels accompanied with the greatest decrement in anti-inflammatory biomarker level were found in cancer + cisplatin group compared to healthy control group at (P≤0.05). Intra-gastric consumption of CM as neo adjuvant - adjuvant group led to the most significant reduction with the best improvement in serum levels of TNF-α and IL-6 with the most significant elevation in serum IL-10 level at (P≤0.05).

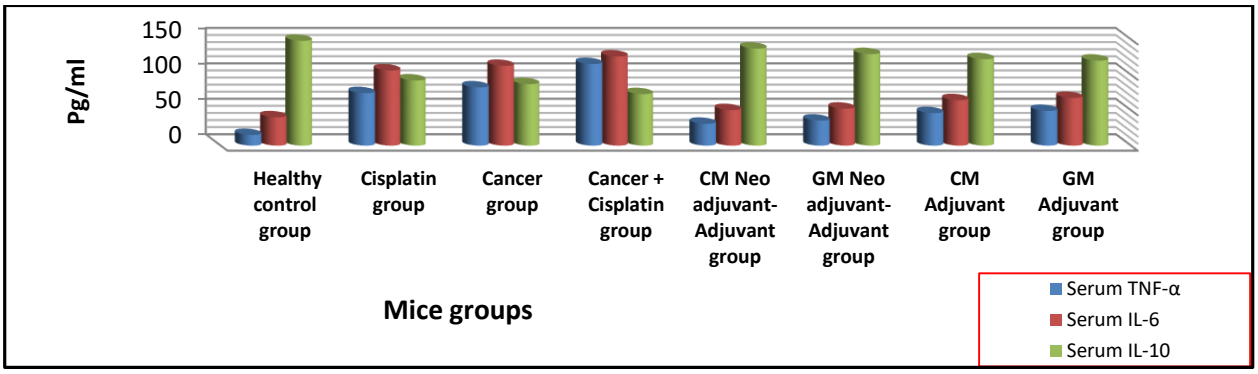

Fig (2): Effect of consuming tested camel and goat milk on serum tumor necrosis factor-α (TNF- α), interleukin-6 (IL-6) and interleukin-10 (IL-10) contents in experimental mice groups.

3.6 Effect of consuming tested camel and goat milk on serum liver enzyme activities in experimental mice groups.

Ehrlich solid carcinoma or cisplatin injection caused hepatic injury and damage fig(3), resulted in serum AST, ALT, and GGT significant enzyme activities elevation indicated in cisplatin group, cancer group and the maximum elevation was found in cancer + cisplatin group correspondingly compared to healthy control group at (P≤0.05). In contrast, oral consumption of both tested milk improved liver functioning enzymes.

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CM neo adjuvant - adjuvant group revealed the most effective treatment while cancerous mice consumed GM orally after their treatment with cisplatin showed the least significant improvement in serum liver enzyme activities compared to cancer + cisplatin group at (P≤0.05).

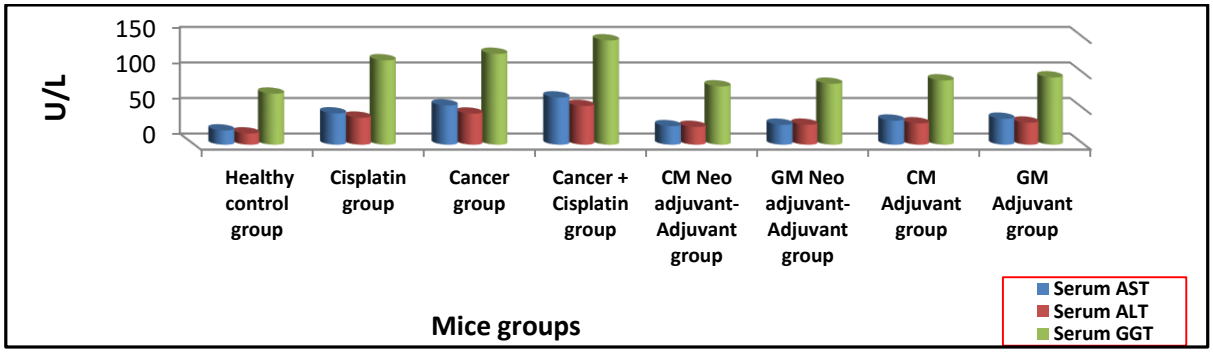


Fig (3): Effect of consuming camel and goat milk on serum liver enzyme activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) in experimental mice groups.

3.7 Effect of consuming tested camel and goat milk on bone marrow apoptotic and anti-apoptotic protein biomarkers in experimental mice groups

The statistical analysis exhibits a highly significant (P ≤ 0.05) up-regulation in the gene expression of apoptotic protein biomarkers P53, Bax, Casp-3, and Bax/Bcl-2 ratio with significant reduction of anti-apoptotic protein; Bcl-2 gene expression in BM tissue of cisplatin group, cancer group, while the highest expression of apoptotic and lowest anti-apoptotic protein biomarkers gene expression were observed in cancerous mice treated with cisplatin as compared to healthy control group table(5). Contrary the intra-gastric consumption of CM and GM improved gene expression of apoptotic and anti-apoptotic protein biomarkers in experimental mice groups.CM neo- adjuvant- adjuvant group caused the highest significant (P ≤ 0.05) improvement followed by GM neo- adjuvant- adjuvant group followed by CM adjuvant group and then GM adjuvant group compared to cancer + cisplatin group.

3.8 Effect of consuming tested camel and goat milk on bone marrow DNA-fragmentation and damage in experimental mice groups

Results in table(6) and fig(4) presented that there was a great significant (P ≤ 0.05) increment in DNA damage of BM cells as manifested by highly extended DNA tail moment, DNA tail length and DNA percent in tail of cisplatin injected group, cancerous group and cancerous mice treated with cisplatin group when compared with healthy control group. On the other hand, DNA damage of BM cells was significantly (P≤0.05) reduced in milk administered groups with the best improvements recorded in cancerous mice consumed CM before and after cisplatin treatment compared to cancerous mice treated with cisplatin.

Table (5): Effect of consuming tested camel and goat milk on bone marrow apoptotic and anti-apoptotic protein biomarkers in experimental mice groups

Parameters / Groups	P53	Bax	Bcl-2	Caspase-3	Bax/Bcl-2 ratio
GI: Healthy control group	1.06 ±0.013^{f}	1.022±0.0112^{g}	1.037±0.0101^{a}	1.009±0.0057^{f}	0.985±0.019^{f}
GII: Cisplatin group	5.548±0.295^{b}	6.03 ± 0.662^{b}	0.2742±0.0312^{g}	6.143 ±1.255^{b}	21.9 ±2.941^{b}
GIII: Cancer group	4.022±0.185^{c}	4.855±0.863^{c}	0.39± 0.0532^{f}	5.033± 0.842^{c}	12.44±2.147^{c}
GIV: Cancer+ Cisplatin	7.346±0.907^{a}	7.5002±0.811^{a}	0.1503 ±0.017^{h}	8.101 ±0.282^{a}	49.9± 3.657^{a}

group					
GV: CM Neo adjuvant - Adjuvant group	**1.846±0.172^{e}**	**2.439±0.205^{f}**	**0.919± 0.026^{b}**	**2.761 ±0.202^{e}**	**2.65± 0.239^{e}**
GVI: GM Neo adjuvant - Adjuvant group	**2.066±0.298^{e}**	**2.887± 0.144^{e}**	**0.887± 0.026^{c}**	**3.116 ±0.158^{e}**	**3.25±0.173^{de}**
GVII: CM Adjuvant group	**2.751 ± 0.27^{d}**	**3.182±0.151^{de}**	**0.822 ±0.0178^{d}**	**3.925±0.40654^{d}**	**3.87±0.149^{de}**
GVIII: GM Adjuvant group	**3.103±0.122^{d}**	**3.559±0 .216^{d}**	**0 .783± 0.028^{e}**	**4.25 ± 0.331^{d}**	**4.54± 0.196^{d}**
LSD (P ≤ 0.05)	**0.338**	**0.442**	**0.028**	**0.518**	**1.6308**

- Values are represented as mean ±SD, (n=10). There wasn't significance variation between means have the same letter within the same column (P ≤ 0.05).

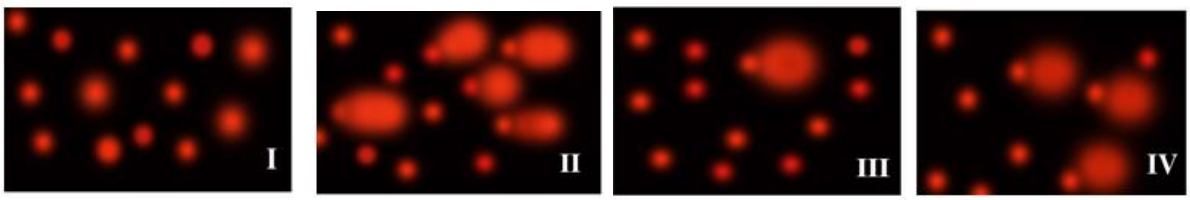
Table (6): Effect of consuming tested camel and goat milk on bone marrow DNA-fragmentation and damage in experimental mice groups

Parameters / Groups	DNA Tail Moment	DNA Tail Length (µm)	DNA Percent in Tail (%)
GI: Healthy control group	**1.046 ± 0.113^{h}**	**1.0 ± 0.037^{f}**	**1.046 ± 0.082^{g}**
GII: Cisplatin group	**15.407 ± 0.695^{a}**	**4.089 ± 0.0776^{a}**	**3.768 ± 0.115^{a}**
GIII: Cancer group	**4.742 ± 0.261^{g}**	**2.1104 ± 0.046^{e}**	**2.247± 0.112^{f}**
GIV: Cancer + Cisplatin group	**13.133 ± 1.108^{b}**	**3.612 ± 0.137^{b}**	**3.636 ± 0.218^{ab}**
GV: CM Neo adjuvant – Adjuvant group	**9.496 ± 0.399^{f}**	**3.1646 ± 0.069^{d}**	**3.001± 0.064^{e}**
GVI: GM Neo adjuvant - Adjuvant group	**10.299 ± 0.429^{e}**	**3.1958 ± 0.093^{d}**	**3.2229 ± 0.061^{d}**
GVII: CM Adjuvant group	**11.033 ± 0.602^{d}**	**3.246± 0.119^{d}**	**3.399±0.239^{c}**
GVIII: GM Adjuvant group	**12.0 ± 0.672^{c}**	**3.3798 ± 0.203^{c}**	**3.5513± 0.228^{b}**
LSD (P ≤ 0.05)	**0.541**	**0.097**	**0.1409**

Values are represented as mean ±SD, (n=10). There wasn't significance variation between means have the same letter within the same column (P ≤ 0.05).

3.9 Effect of consuming tested camel and goat milk on tumor tissues immunohistochemical expression of proliferating cell nuclear antigen (PCNA) in experimental mice groups

The expression of PCNA using immunohistochemical staining table(7) and fig(5)was significantly (P ≤ 0.05) declined in skeletal muscle of cisplatin group while its expression was greatly increased in tumor tissues of cancer and cancer + cisplatin groups as compared to healthy control group. On the other hand, tumor tissues of cancerous mice treated with cisplatin, showed a significant reduced expression of PCNA while the greater reduced expression was found in mice received CM pre and post cancer and cisplatin, then, mice received GM pre and post cancer and cisplatin, after that, mice received CM post cancer and cisplatin and finally mice received GM post cancer and cisplatin respectively at (P≤ 0.05) in comparison with cancer group.



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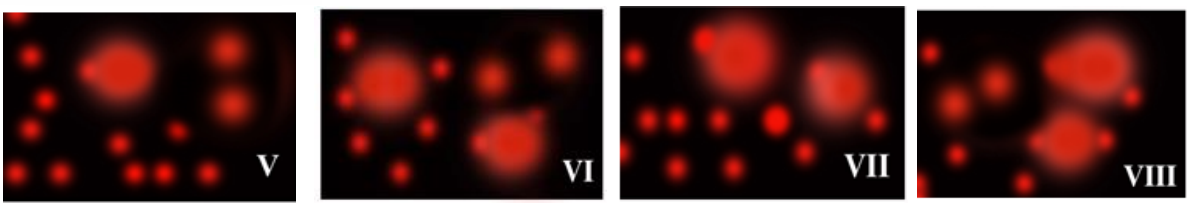

Figure (4): Photomicrographs of DNA damage (comet assay) in different experimental groups (×40). (I) Intact DNA with no tail in Group I, (II) extremely high DNA damage with scattered tail migration observed in Group II, (III) little damaged DNA in Group III, (IV) intensive DNA damage with high comet tail in Group IV, (V) minimal migration and damage of DNA with small tail in Group V, (VI) moderate DNA damage in group VI, (VII) slightly high DNA damage in group VII, (VIII) high DNA damage in group VIII.

Table (7): Effect of consuming tested camel and goat milk on tumor tissues immunohistochemical expression of proliferating cell nuclear antigen (PCNA) in experimental mice groups

Parameters / Groups	PCNA Area %
GI: Healthy control group	**2.984 ± 0.329^{f}**
GII: Cisplatin group	**1.07 ± 0.135^{g}**
GIII: Cancer group	**65.179 ± 2.693^{a}**
GIV: Cancer+ Cisplatin group	**51.394 ± 1.456^{b}**
GV: CM Neo adjuvant – Adjuvant group	**22.293 ± 1.819^{e}**
GVI: GM Neo adjuvant - Adjuvant group	**30.384 ± 2.672^{d}**
GVII: CM Adjuvant group	**31.029 ± 3.684^{d}**
GVIII: GM Adjuvant group	**38.809 ± 1.814^{c}**
LSD (P ≤ 0.05)	**1.912**

-Values are represented as mean ±SD, (n=10). There wasn't significance variation between means have the same letter within the same column (P ≤ 0.05).

3.10 Effect of consuming tested camel and goat milk on solid tumor weight and volume in cancerous mice groups

The incidence of solid tumor was 100% in cancer group and other treated groups table (8). The tumors were very prominent and fast growing in cancer group, while the affected treated groups showed a markedly smaller and slower tumor growth compared to cancer group. With respect to tumor volume, there was significant (P≤0.05) and progressive tumor suppression with reduction in tumor volume of cancerous mice treated with cisplatin compared to cancer group. The most significant reductions were found in CM neo adjuvant- adjuvant group compared to cancer group.

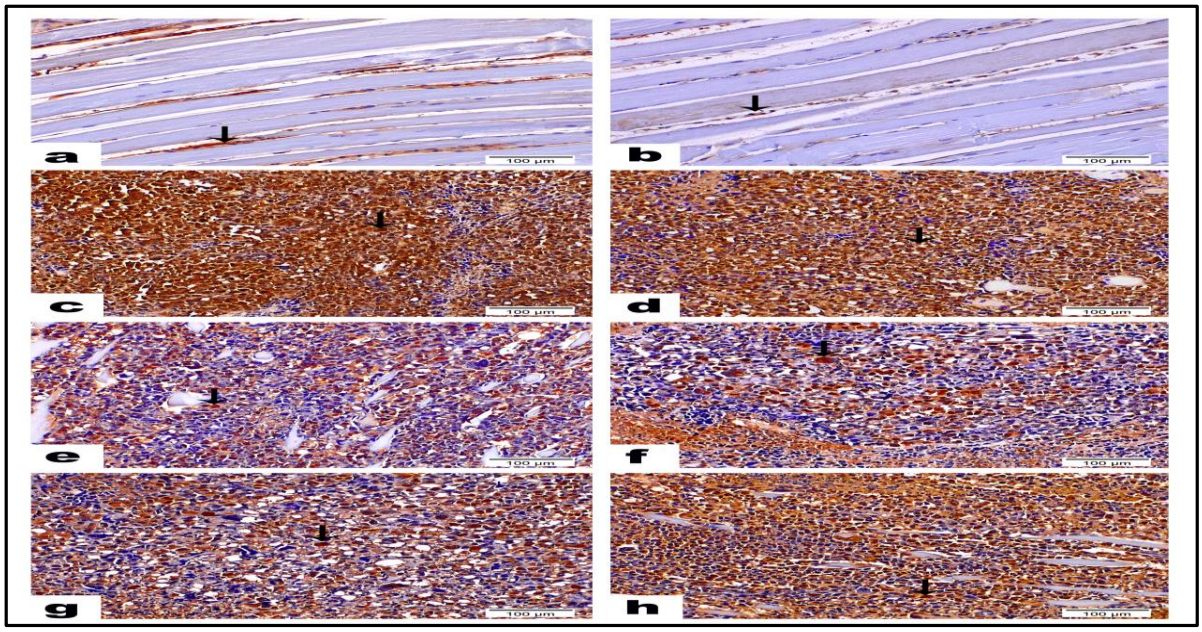

Fig (5): Immunohistochemical staining for PCNA expression (brown color) in skeletal muscle and tumor masses in all experimental mice groups (a-h) respectively.

Table (8): Effect of consuming tested camel and goat milk on tumor weight and volume in cancerous mice groups

Parameters / Groups	Tumor weight (g)	Tumor volume (mm^3)
GIII: Cancer group	**3.611 ± 0.435^{a}**	**3755.473 ±146.231^{a}**
GIV: Cancer + Cisplatin group	**2.689 ± 0.678^{b}**	**1775.291 ± 97.832^{b}**
GV: CM Neo adjuvant – Adjuvant	**0.891 ± 0.115^{d}**	**587.733 ± 9.523^{f}**
GVI: GM Neo adjuvant - Adjuvant group	**0.97 ± 0.162^{d}**	**659.907 ± 10.409 ^{e}**
GVII: CM Adjuvant group	**1.72 ± 0.373 ^{c}**	**772.126 ± 10.772^{d}**
GVIII: GM Adjuvant group	**1.95 ± 0.152^{c}**	**883.756 ± 8.665^{c}**
LSD (P ≤ 0.05)	**0.338**	**64.803**

Values are represented as mean ±SD, (n=10). There wasn't significance variation between means have the same letter within the same column (P ≤ 0.05).

3.11 Effect of consuming tested camel and goat milk on solid tumor and bone marrow tissues histo-pathological examination in experimental mice groups

Histo-pathological examination results confirmed biochemical and genetic determinations. There was no histo-pathological alteration and normal histology of skeletal muscle bundles with nuclei situated in the side of the myofiber, in thigh muscle of healthy control group Fig. (6A), while cisplatin group thigh muscle showed moderate muscle loss and atrophy also losing muscle striation with inflammatory cell infiltration Fig. (6B). Solid tumor tissues examined in cancer group showed that the tumor cells with hyper-chromatic nuclei occupied the most of skeletal muscle bundles as intact anaplastic area with very few areas of necrosis Fig. (6C).

While, cisplatin injection to cancerous mice in cancer + cisplatin group caused the lowest significant necrosis in solid tumor tissues with atrophied fragmented skeletal muscle with pale staining degenerated

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myocytes, nuclear clumps, and fatty vacuoles Fig. (6D).

Meanwhile the highest necrosis in solid tumor tissues with regenerated myofibers and reappearance of normal muscle structure was found in CM neo adjuvant – adjuvant group as illustrated in Fig. (6E), followed by a high necrosis in solid tumor tissues with improvement in muscle structure in GM neo adjuvant – adjuvant group Fig. (6F).

After that, a moderate necrosis in solid tumor tissues with moderate improved skeletal muscle structure of mice from CM adjuvant group Fig. (6G), and then a mild necrosis in solid tumor tissues with mild rejuvenated myofibers were observed in GM adjuvant group Fig. (6H).

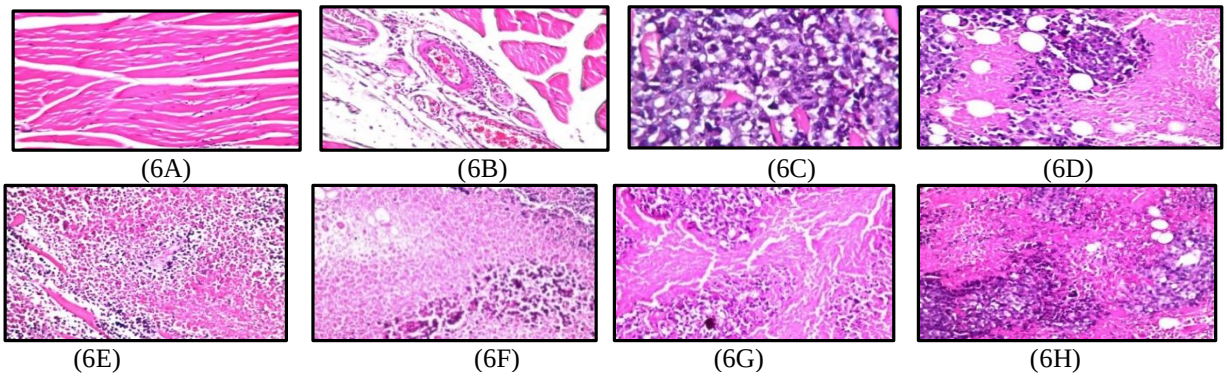
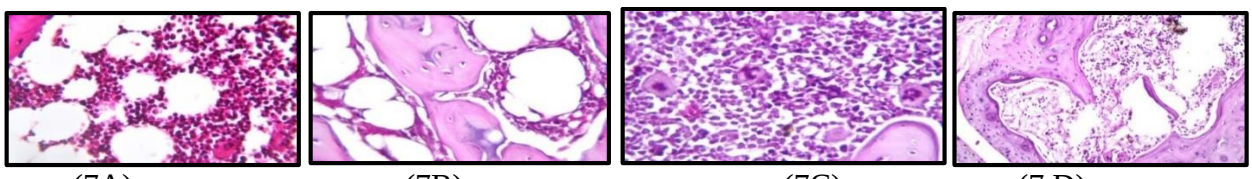


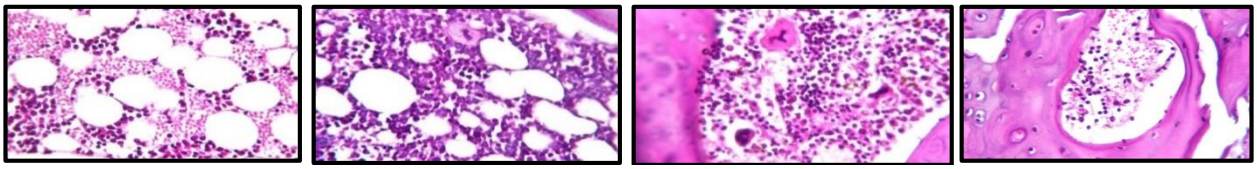
Fig (6): Microscopic examination of tumor tissues using (H&E x40)

Microscopically, BM of healthy control group revealed a normal histological structure with normal formation of RBC's, WBC's, PLT's and adipocytes Fig. (7A), while IP injection of cisplatin in cisplatin group resulted in a severe abnormal hematopoiesis; by sever fall in RBC's, WBC's, and PLT's with increased adipocytes formation Fig. (7B).

On the other hand, BM of cancer group revealed histo-pathological alterations described as great increase in myeloid cells formation and enormous number of mega-karyoblasts with decreased RBC's formation Fig. (7C). The treatment of cancerous mice with cisplatin in cancer + cisplatin group caused noticeable side effects on BM by declined RBC's, WBC's with absence of fat cells Fig. (7D).

The consumption of CM in CM neo adjuvant- adjuvant and CM adjuvant groups alleviated the side effects of cisplatin treatment in cancer group with better regeneration and restoration of BM formation as indicated in Fig. (7E and 7F) as well as consuming GM in GM neo adjuvant- adjuvant and GM adjuvant groups relieved less concomitant effects of cancer treatment with cisplatin and noticeable hematopoiesis Fig. (7G and7 H).





(7E) (7F) (7G) (7H)

Fig (7): Microscopic examination of bone marrow tissues using (H&E x40) in different experimental groups

4. Discussion

Cancerous patients usually suffer from pain and harm due to chemotherapeutic treatment. Co-administration of immuno-modulatory agents may improve chemotherapeutic treatment effect and reduce possible side effects. Camel and goat milk are considered as safe nutritious immuno-modulatory neutral factors.

Milk composition differs widely between different species. Results illustrated that both camel and goat milk are full of nutritional composition as well as biological components as immuno-globulins, lacto-peroxidase enzyme activity and total antioxidant capacity. Camel milk contained more nutritional and active components than goat milk. CM has more free radical scavenging action of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical than whole GM. Camel's immune system is stronger compared with humans. CM immuno-globulins, because of their small size, cross into the milk and are turned into the human blood. Camel milk defenses of the immune system with immuno-modulating and anti-inflammatory activities [38- 40].

Hematopoiesis process affected badly in cancer as a result of bone marrow DNA damage that can lead to mutations and genetic rearrangements which may progress to leukemia [41]. Also, mal-absorption disorders associated with many types of cancer leading to deficiency of macro and micronutrients causing anemia [42].

Cisplatin associated free radicals generation induce DNA damage in erythrocytes promoting their death [43]. Protection of the hematopoietic system against cisplatin is the key strategy for the development of chemo-protective agents.

[44] observed that CM consumption in young children improved HB content and anemic status than cow milk this due to CM higher iron and vitamin C concentrations associated with better iron bioavailability.

Goat milk improved mineral uptake larger than cow milk in affected intestinal absorption mouse model. Bone health and iron absorption were significantly enhanced by goat milk in iron-deficient rats [45], [46].

The clear impact of the CM and GM in reducing total leukocytes, asserted the anti-inflammatory effect of tested milk samples. [47] proved that milk fat conjugated linoleic acid (CLA) which acts as a potent anti-carcinogen modulated the hematological alterations in cancerous mice reflecting the anti-inflammatory and anti-carcinogenic characteristics of CM and GM in improving CBC picture.

Cancer cells increased glycolysis, causing oxidative stress by reactive oxygen species (ROS) formation that accumulate because of an imbalance between their production and removal. Differences in various signaling pathways that affect cellular metabolism lead to elevated ROS levels and decreased antioxidants in cancerous cells [48]. ROS and their byproduct of lipid peroxidation directly interacts with DNA producing oxidative DNA adducts [49].

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The oxidative stress markers; MDA and NO were elevated in sera of all groups associated with depletion of antioxidant enzymes as CAT and SOD as well as non-enzymatic antioxidant GSH level. The rise in MDA levels in the ESC-bearing mice or the treated one with cisplatin might be due to the emission of lipid peroxidation by product during the oxidative breakdown of cancerous tissues. Also NO controls the level of cancer progression and it was also elevated in the sera of mice [50], [51]. On the other hand diminished antioxidants levels is due to the over-use of antioxidants to overcome the increment in lipid peroxidation products as a result of tumor or cisplatin treatment [52].

Cisplatin caused more aggravation in oxidative stress status by the increment in NO and MDA production due to association between ROS, macrophages and leukocyte. Those cells emit inflammatory cytokines leading to overexpression of inducible nitric acid oxidase (iNOS), NO overproduction and causing nitrosative stress [53]. Also, cisplatin is detoxified through binding with GSH. Persistent exposure to large cisplatin doses exhausts GSH stores, reduce CAT enzyme activity, increase ROS production and lipid peroxidation, link to nuclear and mitochondrial DNA and result in cell death [53], [54].

CM α-lactalbumin, β-caseins and vitamin C antioxidant effects work by decreasing or inhibiting the ROS, hydroxyl radicals, nitric oxide (NO), superoxide anions and peroxyl radicals production, likely alleviating oxidative stress [55]. Camel milk consumption caused a significant upsurge in enzymatic and non-enzymatic antioxidants (SOD, CAT and GSH) along with decrement in NO and MDA levels [55], [56]. So, camel milk have protected animal body tissues against cytotoxic effects and oxidative stress induced by cisplatin treatment in cancerous mice.

Goat milk lowers thiobarbituric acid reactive substances (TBARS) levels [57]. Also goat milk yoghurt was found to decrease oxidative stress by reducing inducible nitric oxide synthase (iNOS) expression, serum NO and MDA levels in experimental rats [58].

[59] found that ESC mice had an increased level of serum inflammatory markers; IL-6 and TNF-α with reduction in IL-10 content which is consistent with the results of the present study. In addition, the severity of cisplatin toxicity, it is linked with elevated concentration of TNF-α and IL-6. TNF-α is the most important cytokine induced during cisplatin toxicity, and manifested that inhibition of TNF-α conserves against the deleterious action of cisplatin [54].

Lactoferrin, a major anti-inflammatory CM constituent, curb the production of pro-inflammatory cytokines as TNF-α, IL-1 and IL-6 while increasing anti-inflammatory cytokine; IL-10 which demonstrated that CM displayed marked anti-inflammatory and immuno-modulatory actions [60].

Goats' milk significantly prevented the expression of TNF-α, by reducing inflammatory cascade. Lactoferrin, CLA and chemical composition of GM aids preventing inflammation and infection with providing nutrients, easing digestion, promoting healthy organ development, and protecting against food poisoning [61], [62]. This protective mechanism may also be due to the free radicals scavenging effect, lipid peroxidation inhibition, and antioxidant activity enhancement [18]. Subjects who drank GM also had higher levels of the anti-inflammatory cytokine IL-10 which decreases the formation of pro-inflammatory cytokines as TNF-α [63].

Liver is regarded as the first organ affected by fast-growing EAC cells causing significant elevation in AST, ALT, and ALP enzyme activities due to liver cells damage and their leakage in blood circulation [64]. But CM conjugated linoleic acid (CLA) treatment improved such disturbances reflecting the hepato-protective

effect of CM [47].

[65] found that CM ingestion in the treatment rat groups significantly decreased AST, ALT, and ALP enzyme activities with improved histo-pathological examination of liver tissues.

[66] found that GM had hepato-protective abilities by decreasing the activities of ALT and AST enzymes in cancerous mice sera confirmed by liver tissues histo-pathological examination due to its antioxidants, lactoferrin, immuno-globulins and other protective biomolecules.

Results proved that inoculation of EAC or cisplatin therapy induced BM apoptosis via over expression of P53, and Bax (pro- apoptotic protein) which induce the mitochondrial mediated apoptosis by altering its permeability and emitting of some apoptotic proteins as cytochrome C. This increases the caspase cascade, especially casp-3 (death protein) which down regulate Bcl-2 (anti-apoptotic protein) [67], [68]. The treatment of cancer group (ESC) with cisplatin aggravated apoptosis due to up regulating the mRNA expression of the pro-apoptotic proteins; Bax and casp-3 and down regulating the mRNA expression of the anti-apoptotic protein; Bcl-2 [69].

On the other hand CM and GM adjuvant therapies were shown to decrease the BM apoptosis and suppression as result of cisplatin treatment. This may be due to both milk possesses unique antioxidant and anti-inflammatory features due to their high level of vitamins C,E,A, immuno-globulins, lactoperoxidase and lactoferrin [60], [70].

Chemotherapy induces geno-toxicity or DNA damage. Anticancer drugs are toxic to healthy as well as cancer cells. One of the most affected healthy cells are bone marrow and cells with rapid growth rate. Cisplatin interact with DNA generating superoxide anion and hydroxyl radical that damage the bases and sugars of DNA and induces strand breakage [53].

[71] confirmed that cisplatin treated cancerous mice had a geno-toxic effect on BM cells by increased BM DNA damage and chromosomal aberrations.

The intake of food with chemo-preventive components is an efficient strategy for protection against geno-toxins and carcinogens deleterious effects. The anti-cytotoxic and anti-genotoxic impacts of the CM due to its constituents as casein, zinc, vitamin C, lactoferrin, and selenium have been previously investigated [56].

Goat milk's better bioavailability of zinc and magnesium and its ameliorated fat quality may illustrate why it possess a good effect on genomic integrity [46]. Magnesium is an essential cofactor for all nucleotide excision repair stages [63].

PCNA is a marker of cell proliferation, initiating the cell cycle onset, increasing the G1-S phases, coordinating the DNA replication machinery, and cell survival and maintenance as cell growth and death [59]. In the present study cisplatin decreased PCNA expression in either skeletal muscle of cisplatin group or in tumor tissues in different cancerous groups.

Current research results are in accordance with [72] who stated that immuno-histochemical staining of PCNA in untreated ESC tissues was highly expressed as indicated by extensive brown spots with strong and diffuse nuclear immuno-reactivity meanwhile cisplatin suppressed the proliferation of the neoplastic cells by decreasing the PCNA expression in tumor tissue. Contrary CM or GM bioactive peptides of casein and

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whey fractions as well as lactoferrin prevent the growth of cancer cells inhibiting cancer cell proliferation due to their anti-inflammatory as well as antioxidant abilities [13], [73].

Parallel to the results of a previous finding Ehrlich solid tumor volume at 21th day of inoculation was decreased significantly after cisplatin treatment [72].

Cisplatin as chemotherapeutic agent has grave side effects; so it is necessary to find adjuvant safe functional foods.CM and GM contain active bio-components with significant antioxidant properties. Goat's milk contains different fats as CLA which acts as a potent anti-carcinogen caused significant decrement in tumor weight, viable Ehrlich cells, ascetic volume, and inhibiting tumor growth rate [47].

[54] reported that the histo-pathological investigation of tumor sections in tumor group using H&E stains; illustrated highly vascular bed and massive proliferating neoplastic cells infiltrating the muscle. Whereas cisplatin tretment; revealed marked decrement of tumor vascularity and neoplastic cells density with wide regions of tumor necrosis.

[74] indicated that cisplatin-caused muscle atrophy and loss with necrosis in tumor cells as well due to cisplatin increases the inflammatory cytokines and ROS. In addition, cisplatin not only altered the protein degradation/synthesis progress but also changed the autophagy regulation.

Interestingly, the whey protein had been suggested to attenuate the loss of lean muscle mass [75], so the whey proteins of CM and GM help in reappearance of normal muscle structure with increased necrosis to the remaining tumor cells. CM lactoferrin, exosomes, peptides and kappa casein while GM oligosaccharides and CLA decrease pro-inflammatory cytokines, oxidative stress, apoptosis and arrest cell cycle at the G0/G1 and S phases [76] indicating their role in ameliorating cisplatin side effects while treating cancer.

[77] histo-pathological BM H&E staining showed that cisplatin injured BM tissue, evidenced by loss of bone marrow cells and thinning of trabecular bone, compared with the normal group.BM injury confirms the results of CBC.

CM and GM might be suitable adjunct with cisplatin to improve the accompanying BM myelo-suppression and increased oxidative stress in long term cancer chemotherapy treatment. This protective effect might be due to antioxidant plus the anti-inflammatory potentials of CM and GM, confirmed by improved hematopoiesis [78], [79].

5. Conclusion

Camel and goat milk are neutral, cheap and safe nutritional and immuno-modulatory agents. Their consumption could be an adjuvant remedy to cisplatin in cancer medication by attenuation and prevention of cisplatin-induced risks. Antioxidant and the anti-inflammatory potentials of camel and goat milk due to their nutritional and active content are the major mechanisms. Camel milk pre and post co-administration with cisplatin recorded the most significant improvements.

Conflict of interest No competing interests.

Ethical approval Animal experiments were done according to animal laboratory regulations care documented by Faculty of Women for Arts, Science and Education research ethics committee (#ASU/W/Sci-6P/23-2-39).

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