Study Of The Potential Effect Of Bovine Colostrum On Some Physiological Parameters In Male Rats Receiving Etoposide Therapy

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Abstract: Both radiation and chemotherapy are vital treatments for cancer patients, but they have some disadvantages, for example, a greater chance of adverse effects, limited accessibility, and the non-selective character of chemotherapy drugs. The current study's objective was to look at the function of different concentrations of bovine colostrum in enhancing and activating the immune system, reducing immune suppression, and mitigating the effects of the chemotherapy Etoposide on some physiological and immune parameters in male albino rats. Eight groups, consisting of the control group (C) and several treatment groups (T1-T7), were created from forty adult male rats. After a 4-week experimental period, the animals were anesthetized, and blood was directly drawn from the heart for necessary tests. The tests included blood tests (Red blood cell count, Hemoglobin concentration, packed cell volume **PCV**), immune parameters (C-reactive protein, Interleukin 12, platelet count), and tests for some liver and kidney parameters (Urea, Creatinine, **ALT, AST, ALP**). Additionally, antioxidant and oxidant tests (**MDA, SOD, CAT, GLU**) were conducted. According to the findings, the normal values of the parameters that were tested significantly changed when etoposide was used in group **T1**. However, the use of colostrum at different concentrations with Etoposide for groups **T2, T3, and T4** resulted in improvement in the values of the measured parameters, approaching the control group in some cases, especially in group **T4** exposed to a dose of colostrum and Etoposide of **1500 IU/kg**. On the other hand, groups treated with colostrum alone (**T5, T6, T7**) indicated results similar to the group under control, and no unfavourable side effects were noticed.

In conclusion, the use of chemotherapy Etoposide has negative effects on some physiological and hematological parameters and affects the vital functions of treated rats. Conversely, the study demonstrates the positive role of using colostrum at various concentrations in enhancing immunity and preventing or reducing oxidative stress and inflammation resulting from Etoposide on the vital functions of male albino rats.

Keywords: bovine colostrum, Etoposide, male rats

1. Introduction

Dietary supplements are substances added to the diet to increase the quantity of any nutritional component, aiming to reach its natural threshold. Their primary goal is to provide essential nutrients such as vitamins, minerals, amino acids, and others. These supplements are marketed in the form of tablets or gelatin capsules (Tayyem, 2018). Recently, the use of colostrum as a nutritional supplement has increased because it contains high concentrations of biologically active components and growth factors and works to improve the immune system, regenerate tissues, and treat conditions such as anemia and bleeding resulting from some medications (Kabala-Dzik *et al.*, 2017).

Colostrum is the term for the initial secretion made by the mammary gland in mammals, and its composition is different from that of mature milk. It is more concentrated and denser, transparent or yellow, and has higher levels of proteins, lipids, minerals, vitamins, and immunoglobulins (McGrath *et al.*, 2016). Bovine colostrum has been utilized for human consumption in foods and medical treatments, with studies indicating improvement in various respiratory, digestive, and bone growth disorders, as well as inflammatory conditions; this provides colostrum a new nutritional and functional alternative for customers (Silva *et al.*, 2019).

The non-selective cancer treatment chemotherapy, which damages both diseased and healthy tissues, might have unintended side effects that can be avoided or lessened by taking therapeutic supplements (Alam *et al.*, 2021). Anti-

cancer drugs are used in chemotherapy to kill cancer cells that divide quickly. Etoposide is a medication used in chemotherapy, despite its beneficial effects in treating malignant tumors; it causes many side effects, such as anemia, susceptibility to infection, and infertility (Poorvu *et al.*, 2019).

The study's goal was to investigate how colostrum may enhance and activate immunity, reducing immune suppression, and alleviating the physiological side effects caused by Etoposide treatment.

2.Materials and Methods

Experiment Animals

This experiment was carried out at the animal house, University of Al-Qadisiyah, College of Science. On 20 October 2022, and lasted for 4 weeks. Forty (40) adult male rats, aged between **10-12 weeks**, with weights ranging from **180-200 grams**, were utilized. Rats were placed in cages with a temperature ranging from **22 to 25** °C and a lighting system of **12 hours of light - 12 hours of darkness**.

Dosage Preparation:

1. **Etoposide Dose:** Prepared with a 20 mg/kg weight concentration.
2. **Bovine colostrum Dose:** was purchased ready-made from medical supplies at concentrations of **500, 1000, and 1500 international units/kg**.

Experimental Design:

Forty male rats total were used in the experiment, and eight groups, each consisting of five individuals were created:

1. **Control Group (C):** was given water and standard feed.
2. **(T1):** Administered Etoposide (**20 mg/kg)**.
3. **(T2):** Administered Etoposide **(20 mg/kg)** then colostrum (**500 international units/kg)**.
4. **(T3):** Administered Etoposide **(20 mg/kg)** then colostrum **(1000 international units/kg)**.
5. **(T4):** Administered Etoposide **(20 mg/kg)** then colostrum **(1500 international units/kg)**.
6. **(T5):** Administered colostrum **(500 international units/kg)**.
7. **(T6):** Administered colostrum (**1000 international units/kg)**.
8. **(T7):** Administered colostrum **(1500 international units/kg)**.

Blood tests

After completing the experiment, blood samples (5 ml) were drawn directly from the heart of each group, and (2 ml) were put in EDTA-filled tubes to study hematological parameters. The remaining part of The blood was added to EDTA-free plastic tubes to obtain serum for studying biochemical parameters.

Statistical Analysis

One-way analysis of variance (ANOVA) was used for statistical analysis at a significance level of (0.05), and comparisons were performed using the least significant difference (LSD).

3. Results

Hematological Parameters

Comparing the first group (T1) immunosuppressed with Etoposide and the second group (T2) treated with both Etoposide and colostrum at a concentration of 500 IU/kg, the results in Table (1) indicated a significant decrease ($P<0.05$) in hemoglobin, red blood cell count, and volume of packed cells.
In contrast, groups (T3, T4) handled with the drug and colostrum demonstrated a noticeable improvement in hematological parameters. This improvement can be attributed to the effectiveness of using colostrum at doses of

1000 and 1500 international units/kg in mitigating the negative effects of Etoposide, as for groups (T5, T6, T7) treated with colostrum alone, no significant differences were seen compared to the control group, indicating no impact on the studied hematological parameters.

Table (1) illustrates colostrum concentrations and their effects on some hematological parameters in immunosuppressed rats treated with Etoposide.

Standards / Groups	Hemoglobin	Number Of Red Blood Cells	Volume Of Packed Red Blood Cells(%)
C	14.20±0.45 a	7.46±0.01 a	42.30±1.11 a
T1	7.13±0.02 c	4.65±0.12 c	23.36±1.22 c
T2	8.02±0.05 cb	4.80±1.1 c	30.11±0.71 c
T3	10.33±0.16 b	5.77±0.21 b	36.28±0.53 b
T4	12.05±0.22 a	7.00±0.03 a	39.12±0.61 b
T5	13.56±0.11 a	7.05±0.14 a	39.25±0.15 ba
T6	13.20±0.33 a	7.26±0.06 a	41.15±0.41 a
T7	14.96±0.36 a	7.40±0.01 a	43.09±1.21 a
LSD	2.18	0.478	3.09

Immunological Criteria

The findings in Table (2) presented a significant increase ($P<0.05$) in (C-RP) in (T1) in contrast to the control and other treatments. Meanwhile, treatments (T2, T3) exhibited a significant decrease compared to (T1) and a significant increase compared to the control group. No significant difference was seen between these two groups. However, group (T4) indicated a significant decrease compared to groups (T1, T2, T3) and a significant increase in contrast to the control group and groups (T5, T7), while no significant difference was seen with group (T6). As for groups (T5, T6, T7), their results were close to the control group, and no significant differences were seen with it. The results also demonstrated a significant increase in IL-12 in (T1) in contrast to the control and other groups, except (T2, T3) indicated a significant decrease compared to (T1), and there was no significant difference seen between (T2) and (T3). Statistical analysis indicated a significant decrease in treatments (T4, T5, T6, T7) compared to (T1), with no significant differences seen between them and the control group.

Furthermore, findings demonstrated a significant decrease in platelet count in group (T1) in contrast to control and other treatments. Treatments (T2, T3) indicated a significant increase in platelet count compared to (T1) and a significant decrease compared to the control. Statistical analysis also indicated a significant increase in groups (T4, T5, T6) compared to (T1), which suppressed immunity, while these groups indicated no significant differences compared to the control group. Conversely, group (T7), which was administered colostrum at a concentration of 1500 mg/kg, indicated a significant decrease compared to the control group and other groups.

Table (2) illustrates colostrum concentrations and their effects on some immunological criteria in immunosuppressed rats with Etoposide.

Standards / Groups	(C-RP)	Interleukin12	Platelet count
C	7.09±0.02d	6.37±0.60c	345.88±1.11a
T1	8.50±0.06a	11.51±0.38a	223.36±1.22d
T2	8.01±0.01b	10.19±0.71ab	230.11±0.71c
T3	7.91±0.04b	8.21±0.09bc	235.28±0.53c
T4	7.40±0.02c	7.73±0.05c	340.25±0.61a
T5	7.16±0.01d	7.20±0.71c	340.12±0.15a
T6	7.20±0.30cd	6.99±1.03c	341.15±0.41a
T7	7.10±0.11d	6.53±0.77c	330.09±1.21b
LSD	0.172	2.69	6.09

Tests for some liver and kidney parameters

The results in Table (3) indicated that the levels of creatinine and urea had significantly increased in (T1, and T2) comparable to the other groups and the control group. As for the group treated with the drug and colostrum at a concentration of 1000 international units/kg (T3), it indicated a significant increase comparable to the control group and groups (T4, T5, T6, T7) and a significant decrease compared to the groups (T1, T2). While, groups (T4, T5, T6, and T7) indicated clear improvement in Urea and Creatinine levels and showed any significant difference compared to the control group; they were similar to it, this finding also demonstrated a significant increase in the level of liver enzyme alanine transaminase (ALT) in groups (T1, T2). Group (T3) indicated a significant increase compared to the control group and a significant decrease compared to groups (T1, and T2). However, groups (T4, T5, T6) didn't show any significant difference comparable to the control group, and there were no significant differences between groups (T4, T7). Regarding the liver enzyme aspartate transaminase (AST), groups (T1, T2, and T3) demonstrated a significant increase rise in comparison to the control and other groups. However, groups (T4, T5, T6, T7) indicated improvement in AST levels and didn't show any significant differences with the control group. Furthermore, the results indicated a significant increase in the level of alkaline phosphatase (ALP) enzyme in the group (T1) treated with the drug compared to the control group and other groups. Groups (T2, and T3) indicated a significant decrease compared to group (T1) and a significant increase compared to the control group and other groups. Meanwhile, groups (T4, T5, T6, T7) were similar to the control group and demonstrated a clear improvement in the level of liver enzyme.

Table (3) illustrates the impact of different concentrations of colostrum on urea, creatinine, and some liver enzymes in immunosuppressed rats treated with Etoposide.

Standards / Groups	Urea	Creatinine	ALT	AST	ALP
C	30.66±0.03c	1.17±0.02c	50.08±0.16d	31.09±2.11d	124.11±2.91c
T1	93.25±4.51a	1.98±0.01a	95.20±0.81a	79.58±1.09a	213.60±431a
T2	89.11±3.24a	1.91±0.02a	90.36±1.62a	71.35±0.05b	195.71±2.62b
T3	61.09±2.50b	1.75±0.03b	78.04±1.26b	65.44±0.73c	185.01±3.44b
T4	40.23±1.99c	1.21±0.10c	54.26±1.48cd	35.18±1.13d	133.13±2.71c
T5	32.21±3.25c	1.20±0.04c	51.18±2.23d	34.04±0.88d	130.22±1.32c
T6	34.13±4.34c	1.17±0.01c	52.33±1.11d	32.68±1.35d	129.05±1.15c
T7	32.09±2.96c	1.16±0.02c	56.70±1.60c	32.03±0.73d	127.14±1.62c
LSD	12.11	0.074	4.83	4.19	10.73

Oxidative stress and Oxidants

Table (4) shows that the following groups (T1, T2, T3) indicated a significant increase in MDA level compared to (C) and other groups. While the group (T4) treated with the drug and colostrum at a concentration of (1500 IU/kg) indicated a noticeable improvement in the MDA level and was close to the (C) group. Also, the groups treated with colostrum only were close to the control group and indicated an improvement in the MDA level. This indicates that Colostrum does not have any side effects. As for antioxidants, which include (SOD, CAT, and GLU), the groups (T1, T2, and T3) indicated a significant decrease in the level of antioxidants comparable with the control and other groups, while the group indicated (T4) Treatment with the drug and colostrum at a concentration of (1500 international units/kg) resulted in a clear improvement in the level of antioxidants and was comparable to the control group and the other groups treated with colostrum alone at different concentrations. This indicates that the use of colostrum has improved the level of antioxidants and reduced the side effects of the drug Etoposide.

Table (4) illustrates the impact of different concentrations of colostrum on some indicators of oxidative stress and antioxidants in rats immunosuppressed with Etoposide.

Standards / Groups	SOD	CAT	Glutathione	MDA
C	8.45±0.01a	1.04±0.02a	2.49±0.05a	1.18±0.01e
T1	6.50±0.04d	0.27±0.06d	1.36±0.02d	3.33±0.03a

T2	7.63±0.11c	0.51±0.01c	1.67±0.01c	3.21±0.01a
T3	8.01±0.09b	0.77±0.10b	2.08±0.12b	2.55±0.03b
T4	8.39±0.10a	0.98±0.04a	2.40±0.04a	2.00±0.02c
T5	8.42±0.02a	0.99±0.05a	2.50±0.06a	1.37±0.05d
T6	8.41±0.03a	1.02±0.03a	2.45±0.03a	1.30±0.11de
T7	8.50±0.01a	1.04±0.07a	2.53±0.01a	1.26±0.20e
LSD	0.243	0.127	0.139	0.138

4.Discussion

Hematological Parameters

The results indicated a significant decrease in the concentration of blood hemoglobin, red blood cell count, and volume of packed cells in the immunosuppressed group of rats treated with Etoposide.

This may be related to the chemotherapeutic effect on the bone marrow since stem cells can proliferate and are subject to the cellular toxicity of medications. This could lead to a loss of stem cells in the bone marrow and a possible decrease in hematological criteria. (May *et al.*, 2018). Chemotherapy can affect the liver and red bone marrow, which are places where blood is made. This could lead to a decrease in hemoglobin in the blood; on the other hand, malnutrition could result in a loss of blood protein (Madeddu *et al.*, 2021). Additionally, chemotherapy may change the way that glycoproteins are made and the shape of blood cell membranes, which might lead to cell expansion and phagocytosis. (Wiciński *et al.*, 2020). The decrease in the number of blood cells may be due to a reduction in bone marrow activity brought on by chemotherapy (Eldesouky *et al.*, 2019). Conversely, the study showed that the use of nutritional supplements dramatically raised the hematological criteria in the groups, in contrast to the drug-treated group (T2, T3, T4), and this is explained by the fact that colostrum can reduce the negative effects of chemotherapy since milk includes strong antioxidants, vitamins E and C, and other nutrients that improve blood quality, shield body tissues, and regulate cell growth (Aldulaimi *et al.,* 2020). The colostrum's lactoferrin content, a protein that binds iron that improves intestinal absorption and prevents the development of dangerous bacteria in the body (since iron serves as a food source for these bacteria), may be responsible for the improvement in hematological criteria. This will also likely reduce the growth of cancerous tumors (Artym *et al.*, 2021). Groups (T5, T6, T7) displayed normal rates comparable to the control group, proving that colostrum is risk-free and has no negative impacts on hematological parameters.

Immunological standards

Compared to the control group and other treatments, the present findings indicated a significant increase in the concentration of interleukin-12, C-reactive protein, and a decrease in the number of platelets in (T1). These results agreed with the finding of Noviyani *et al.*, (2019) and with Zhang *et al.*, (2021).

Free radicals also cause an imbalance in antioxidants and cells become vulnerable to oxidative stress, thereby increasing both inflammation and interleukins (Asmat *et al.*, 2016). Increased IL-12 levels Signs of tumor growth, inflammatory responses, and tissue damage are observed in animals receiving anti-cancer medicine that inhibits their immune systems (Uzrail *et al.*, 2019). The high concentration of TNF-ɑ and IL-1 in Kupffer cells is the cause of the elevated IL-12, as this pathway influences the NF-kB pathway, which encodes the production of IL-12 and then activates several pathways involved in tumor growth (Quan *et al.*, 2015). On the other hand, the increase in the concentration of C-reactive protein is due to the high toxicity of the drug, as it causes the demolition of tissues, as RP-C is a potent biomarker for inflammation and an inflammatory indicator (Ahmad *et al.*, 2019).

While the study indicated a significant decrease in platelets in the group treated with the drug, this is consistent with (Zhou *et al* 2023), who stated that chemotherapy leads to a deficiency in platelets. This might be a result of chemotherapy's direct binding to bone marrow cells' DNA, which damages it during replication. The results indicated significant differences in animals that were immunosuppressed with Etoposide and then dosed with colostrum for four weeks in a row because colostrum contains effective components that contribute to preserving cells and scavenging free radicals, as it contains vitamin C which is considered an antioxidant and works to eliminate free radicals and an essential assistant for many enzymatic reactions and maintains cell stability, which causes a

decrease in IL-12 as a result of decreased inflammation (Playford & Weiser, 2021). Vitamin C affects the regulation of the concentration of IL-12 by regulating the immune system because it affects interleukin-producing cells, which include Macrophages, T-cells, and B-cells (Jafari *et al.*, 2019). Vitamin C combats free radicals (ROS) that increase oxidative stress in cells and tissues, as it provides unstable molecules with electrons and turns them into stable ones (Gęgotek & Skrzydlewska, 2023). As for the role of colostrum, it seems clear in reducing the concentration of C-reactive protein because it contains many effective components for example, vitamin E, an antioxidant that protects the liver and kidney, reduces inflammation by reducing the cytokines that cause inflammation (Asbaghi *et al.*, 2020). Conversely, however, the use of colostrum reduced the effects caused by the drug on platelets. It improved the rate of platelets. The reason for the increased platelet formation may be attributed to the ability of colostrum to stimulate bone marrow progenitor cells. Colostrum also contains growth factors that stimulate bone marrow and contains proteins that stimulate stem cells (Singh & Kushwaha, 2021).

Tests for some liver and kidney parameters

Urea and Creatinine concentration

The reason for a significant increase in the levels of Urea and Creatinine in the group of rats immunosuppressed with the drug Etoposide may be due to the accumulation of the drug in the cell membranes, the occurrence of DNA damage, the occurrence of cellular toxicity, a defect in mitochondrial functions, and the occurrence of programmed death (Peres & Cunha, 2016; Fox *et al.*, 2018). Or due to oxidative stress and increased generation of free radicals that cause peroxidation of lipids in cellular membranes in the kidneys (Tejchman *et al.*, 2021). When dosing animals with colostrum, it was noted that it is crucial in reducing the concentration of urea and creatinine. The reason for this may be due to colostrum containing lactoferrin, which plays a part in reducing the toxic effects of chemotherapy, eliminating oxidative stress, increasing autoimmunity, and preventing kidney fibrosis (Hsu *et al.*, 2020; Mohammed *et al.*, 2021). Another unsaturated material called lactoferrin can attach to cells, eliminate free iron radicals that oxidize lipids, and stifle free radicals that lead to urea and creatinine shortage (Superti, 2020).

Concentration of liver enzymes

The mice immunosuppressed with the medication Etoposide (T1) had a significantly higher concentration of liver enzymes (ALT, AST, and ALP) than the control group or other treatments; this might be because of the adverse effects of the chemotherapy, as well as an increase in hydrogen peroxide and free radicals. Free radicals damage DNA and alter the structure of the nucleus, which can lead to the onset of programmed cell death (Taghizadeh *et al.*, 2020).

The groups who received colostrum dosage following the medication, particularly group (T4), showed a noticeable improvement in the concentration of liver enzymes because colostrum includes a significant amount of essential elements that function as antioxidants, including vitamins, minerals, carotenoids, and other substances (Hamed *et al.*, 2018). Colostrum contains sulfur, which improves the activity of liver enzymes, thus eliminating toxins from the body and performing vital functions (Abdelmeguid *et al.*, 2021). The study indicated that using colostrum in different concentrations does not cause any side effects, so it is considered one of the appropriate supplements for treating the liver and increasing its enzymes (Karabacak *et al.*, 2018).

Oxidative stress and Oxidants

Table (4) indicated a significant decrease in the level of antioxidants accompanied by a significant increase in the level of MDA in (T1) compared to the control group and other treatments. The reason for this may be due to fact that fat peroxidation leads to the inhibition of the body's defense mechanisms and prevents them from scavenging free radicals, as well as changing the membrane's composition and purpose and distorting components cell (Turkmen *et al.*, 2022) Some studies have indicated that chemotherapy leads to the depletion of antioxidants and the occurrence of oxidative stress (Darwish *et al.*, 2017; Abdel-Daim *et al.*, 2019). By taking nutritional supplements, including colostrum, which contains antioxidants, it is possible to eliminate free radicals and inhibit oxidative stress (Ponnampalam *et al.*, 2022), as colostrum contains proteins, minerals, vitamins, zinc, and magnesium that stimulate the body's antioxidant enzymes and cause the reduction of free radicals (Bouhaddaoui *et al.*, 2019).

5. Conclusions

The current study concluded that the chemotherapy drug Etoposide has induced oxidative stress and affected various physiological functions in the body. Additionally, a positive role of colostrum is observed in improving physiological, immune, and circulatory parameters, as well as reducing the negative effects of Etoposide. No side effects were observed with the three doses of colostrum used in the experiment on the measured parameters.

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