2024, Scienceline Publication
World's Veterinary Journal
World Vet J, 14(1): 145-150,
ISSN 2322-4568

DOI: https://dx.doi.org/10.54203/scil.2024.wvj18
PII: S232245682400018-14

The Effects of Different Concentrations of Vitamin D3 on Immunological Parameters of Immunosuppressed Rats Induced

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ORIGINAL ARTICLE
Received: January 20, 2024
Revised: March 07, 2024
Accepted: March 10, 2024
Published: March 30, 2024

ABSTRACT

Vitamin D3 receptor is expressed in several types of immune cells suggesting that Vitamin D3 could have immune regulatory roles. The current study was conducted to investigate the role of Vitamin D3 in reducing the toxicity of the cisplatin on some Immunological parameters in the rat model. The current experiment was conducted on 80 adult white male rats within the age range of 9-12 weeks. The animals were divided into eight groups (10 animals in each group). The control group was dosed with the physiological solution until the end of experiment (C). Rats in the second treatment were injected with cisplatin (2 mg/kg, T1). Rats in the third (T2), fourth (T3), and fifth (T4) groups were injected with cisplatin at a concentration (2 mg/kg) and received Vitamin D3 at levels of 5000 IU, 10,000 IU, and 15,000 IU, respectively. The rats in the sixth (T5), seventh (T6), and eighth (T7) groups were subjected to Vitamin D3 at concentrations of 5000 IU,10,000 IU, and 15,000 IU, respectively. At the end of the experiment, which lasted 21 days, the animals were anesthetized, their weights were recorded, and blood samples were collected. The findings revealed a significant elevation in the levels of interleukin-12, tumor necrosis factor-alpha, C-reactive protein, lymphocyte percentage, monocyte percentage, and eosinophil percentage within group T1 compared to the control and other treatment groups that received Vitamin D3. The average percentage of white blood cells and neutrophils in group T1 was significantly lesser than other groups. It can be concluded that supplementation of different Vitamin D3 levels (5000-10,000 IU) have positive influences on the immunological parameters of immunosuppressed rats.

Keywords: Cisplatin, Immunosuppressant, Interleukin, Vitamin D3

INTRODUCTION

Vitamin D is an essential fat-soluble vitamin with multiple functions. Vitamin D receptor is expressed in several types of immune cells suggesting its immune regulatory roles. Vitamin D insufficiency has been suggested to increase the risk of autoimmune diseases (Ao et al., 2021). However, little is known regarding its immunomodulatory effects in the condition of immune suppression. The demand for nutritional supplements has been increasing dramatically worldwide, encompassing a wide range of products including vitamins, protein supplements, herbal supplements, mineral supplements, and essential fatty acids (Abdul Aziz et al., 2020).

Vitamin D is stored in the body tissue as a steroid hormone 25-hydroxycholecalciferol, called calciferol. Vitamin D is the only vitamin that the human body can make. Vitamin D can be produced in the skin when exposed to sunlight. Other sources of vitamin D include supplements and food (Ao et al., 2021). Vitamin D may also act as an antioxidant, anti-inflammatory, immunoprotect, immune regulator, cellular oncogenic signaling, and apoptosis regulator, as well as cell-cycle and angiogenesis controllers (Balasa et al., 2014). A study indicated that the immune response of patients with type 2 diabetes and spinal tuberculosis who receive long-term drug therapy can be improved by supplementation with 1,25(OH)2D3 (Abdul Aziz et al., 2020).

Cisplatin (Cl2H6N2Pt) is a powerful chemotherapy medication comprising platinum, widely utilized to address various cancer types affecting different tissues (Nasiri et al., 2020). This drug necessitates specific precautionary measures due to its serious side effects when used in hospitals. Despite its adverse effects, it remains the primary treatment for many cancer types. Cisplatin toxicity arises from cross-linking within and between nuclear strands, leading to various effects, including nephrotoxicity, hepatotoxicity, cardiotoxicity, thrombocytopenia, anemia, and dysfunction in the peripheral nervous system (Nasiri et al., 2020). Although the mechanism of cisplatin toxicity is well understood, there is still a lack of effective treatments and preventive measures to mitigate these changes.

Hence, there is a pressing need to develop a substance that can enhance the safe usage of cisplatin (Sun et al., 2019). Recent studies have explored the use of potent natural plant-based antioxidants and nutritional supplements

To cite this paper: Kmosh SM, and Al-Naely AJ. (2024). The Effects of Different Concentrations of Vitamin D3 on Immunological Parameters of Immunosuppressed Rats Induced. *World Vet. J.,* 14 (1): 145-150. DOI: https://dx.doi.org/10.54203/scil.2024.wvj18

contain Vitamin D, to prevent or reduce oxidative stress and inflammation caused by cisplatin. These approaches have shown promising effects on the pathophysiological status (Abdel-Daim et al., 2019).

This study aimed to investigate the role of Vitamin D3 in reducing the toxicity of the chemical drug (cisplatin) on some immunological parameters in rat model.

MATERIALS AND METHODS

Ethical approval

All research methods and practices and the use of experimental animals have been approved by the Animal Care and Use Committee (ACUC), Faculty of Veterinary Medicine, College of Education, University of Al-Qadisiyah, Iraq.

Experimental animals

The study was conducted in the animal laboratory of the College of Education / University of Al-Qadisiyah, under standard conditions of temperature (22-28°C), ventilation, and lighting duration (14 hours of light and 10 hours of darkness). The animals were given free feeding (metabolizable energy of 1850 kcal/kg, and crude protein 14 %) and water for the duration of the experiment. All the mice were weighed and sacrificed by cervical dislocation and blood samples (2 ml) were collected immediately at the end of the study (8 weeks of age; Florea and Büsselberg, 2011).

Experimental design

The experiment included 80 male white rats (average weight 180-200 gr) distributed into 8 groups (10 in each groups). The rats were obtained from the laboratory of the University of Al-Qadisiyah, Iraq. Each group included 10 animals for a period of 21 days.

The experiment consisted of eight different treatment groups. The control group (C) received normal saline physiological solution daily for 21 days. The first treatment group (T1) received weekly injections of cisplatin at a concentration of 2 mg/kg of body weight for 21 days. The second treatment group (T2) received the same cisplatin injections and a daily dose of Vitamin D3 at a concentration of 5000 IU for 21 days. In the third treatment group (T3), animals received cisplatin injections along with a daily dose of Vitamin D3 at a concentration of 10,000 IU for 21 days. The fourth treatment group (T4) received cisplatin injections and a daily dose of Vitamin D3 at a concentration of 15,000 IU for 21 days. The fifth treatment group (T5) solely received a daily dose of Vitamin D3 at 5000 IU of body weight for 21 days. The sixth treatment group (T6) received a daily dose of Vitamin D3 at 10,000 IU of body weight for 21 days. Lastly, the seventh treatment group (T7) received a daily dose of Vitamin D3 at 15,000 IU of body weight for 21 days.

Cisplatin dosage

Cisplatin was obtained from drug stores (Iraq) in the form of a liquid bottle with a concentration of (50 mg/100 ml) and the dose was prepared as described by Florea and Büsselberg (2011) at a concentration of 2 mg/kg of body weight by dissolving the required concentration depending on the average body weight of the animal. Inject each animal weekly under the peritoneum for 21 days.

Serum interleukin-12

The level of interleukin-12 in the serum was determined using the ELISA test and the Direct ELISA Sandwich method according to the instructions contained in the examination kit supplied by the Chinese company BT Lab (Florea and Büsselberg, 2011).

Serum C-reactive protein

The CRB-Latex assay is a rapid-slide stacking assay based on the modification of the latex fixation method and was used for the direct detection of C-reactive protein (CRP) and its semi-quantitative estimation in serum (Desoize and Madoulet, 2002).

Platelets, total and differential numbers of white blood cells

Platelets, total and differential numbers of white blood cells were examined using Auto Blood Analyzer Sysmex-XP300 (Germany) according to instruction of the device (Desoize and Madoulet, 2002).

Statistical analysis

After data collection and tabulation, statistical analysis program SPSS version 25 (USA) was used. Where the data were statistically analyzed according to the one-way ANOVA test, and the Least Significant Difference (LSD) was used for the posthoc test at the 0.05 level of significance (Daniel and Cross, 2018). Mean data are expressed with standard deviation (SD).

RESULTS AND DISCUSSION

Table 1 presents the interleukin-12, TNF-α, C-reactive protein, and platelet count concentrations in different treatment groups. In the first treatment (T1), there was a significant increase in the concentration of interleukin-12 compared to the

other groups ($p < 0.05$). Regarding TNF-α, the T1 group showed a significant increase compared to the control and other treatments ($p < 0.05$).

The elevated levels of TNF-α observed could potentially be linked to immune cells present within the tumor microenvironment, including Kupffer cells and macrophages (Titov et al., 2022). The findings align with prior researches of Florea and Büsselberg (2011), Ito et al. (2012), and Erbas et al. (2014) which emphasized the existence of diverse receptor types, such as TNF-α, IL-6, and IL-12 in hepatocytes.

One of the important effects of high concentration of TNF-α is to stimulate the accumulation of reactive oxygen species (ROS) in the epithelial cells, and this accumulation causes damage to the DNA of the epithelial cell and cause mutation in the cells (Laird et al., 2014).

The improvement was observed in the patients diagnosed with hepatic steatosis that administered with Vitamin D3 in their treatment regimen (Ito et al., 2012). It was demonstrated that Vitamin D3 possesses the capacity to mitigate the inflammatory process through various mechanisms. These mechanism is due to diminish the T1 helper 1 (Th1) cell response while augmenting the Th2 response, resulting in reduced levels of TNF-α and interleukin-1. Furthermore, Vitamin D3 was found to decreases the concentration of interleukin-12 by impacting both monocytes and B cells, as indicated in studies by Mirhosseini et al. (2017) and Mohammed et al. (2019).

The platelet count indicated a significant reduction in group T1 compared to the other treatments ($p < 0.05$). The cisplatin binds with the DNA of bone marrow cells, which leads to the destruction of the bone marrow and thus reduces the production of platelets (Mu et al., 2005; Perry, 2008).

Vitamin D3 demonstrated positive effects on the blood platelet count, which is consistent with findings from a previous study by Papapostoli et al. (2016). The results of current study indicated that vitamin D may influence the process of megakaryocytopoiesis, and the formation of platelet precursor cells. This process involves calcium-dependent events mediated by the non-genomic activity of Vitamin D receptors (VDR) within mitochondria (Weir et al., 2011). Moreover, the relationship between platelet count and oxidative stress is closely linked, highlighting the role of vitamin D as a well-known antioxidant (Wilson et al., 2007). Furthermore, vitamin D demonstrates anticoagulant and anti-inflammatory properties, which additionally enhance its positive effects on platelet function.

The data depicted in Table 1 regarding C-reactive protein revealed an increase in group T1 compared to the control group and other treatment regimens ($p < 0.05$). These results were agreed with the study by Wu et al. (2014). C-reactive protein is an inflammatory biomarker and a strong indicator of kidney abnormalities and functions in humans and animals (Stuveling et al., 2003). C-reactive protein production is assumed to be restricted by the liver, but a recent study suggested that the kidney may be a second site for C-reactive protein formation (Zoair, 2021). The observed effect of Vitamin D3 on platelet count can be attributed to its anti-inflammatory properties. Several studies including Mohammed and Qasim (2021), Abolhasani Zadeh et al. (2022), and Huldani et al. (2022) have reported that Vitamin D3 supplementation can lead to reduced levels of inflammatory markers, including TNF-α and C-reactive protein in rats. Another study highlighted that decreased levels of Vitamin D3 in circulation were associated with increased inflammation, marked by elevated levels of IL-6 and C-reactive protein (Hafsan et al., 2022). The Vitamin D3 supplementation helps to reduce C-reactive protein levels and increase IL-10, which possesses potent anti-inflammatory effects in rats. IL-10 can inhibit monocyte activation and suppress the production of inflammatory mediators (Zhang et al., 2010; Zakharova et al., 2019; Ansari et al., 2022).

Table 1. The effects of different concentrations of Vitamin D3 on immune parameters of immunosuppressed rats with cisplatin

Group	IL-12 (pg/ml)	Tumor necrosis factor alpha (pg/ml)	Platelet count (x103/mm)	C-reactive protein (mg/L)
C	6.28±0.88^{B}	0.16±1.34^{B}	2.31±341.80^{A}	7.06±0.03^{B}
T1	1.10±11.63^{A}	0.68±3.36^{A}	4.22±263.40^{B}	8.27±0.07^{A}
T2	0.76±10.04^{B}	±2.930.28^{B}	2.83±309.50^{A}	7.51±0.08^{B}
T3	±8.160.75^{B}	±1.800.27^{B}	±320.402.96^{A}	7.45±0.08^{B}
T4	±7.610.71^{B}	±1.380.20^{B}	2.81±334.00^{A}	7.41±0.03^{B}
T5	±6.690.83^{B}	0.12±1.27^{B}	±336.402.44^{A}	7.08±0.04^{B}
T6	±6.970.8^{B}	1.310.16^{B}	3.13±335.80^{A}	7.15±0.04^{B}
T7	±7.200.83^{B}	±1.320.15^{B}	2.94±333.00^{A}	7.20±0.04^{B}

^{ABC} Different superscript letters indicate significant differences in the columns between the treatments ($p < 0.05$). IL-12: Interleukin 12. C: The control group that received the physiological saline solution for the duration of the experiment (21 days). T1: The first treatment represents a group of rats that were immunosuppressed with cisplatin at a concentration of 2 mg/kg bw. T2: The second treatment represented a group of rats that were immunosuppressed and dosed with Vitamin D3 at a concentration (5000 IU). T3: The third treatment represents a group of rats that were immunosuppressed and dosed with Vitamin D3 at a concentration of (10,000 IU). T4: The fourth treatment represents a group of rats that were immunosuppressed and dosed with Vitamin D3 at a concentration (15,000 IU). T5: The fifth treatment represents the group of rats that received Vitamin D3 at a concentration (5000 IU). T6: The fifth treatment represents the group of rats that were dosed with Vitamin D3 at a concentration of (10,000 IU). T7: The fifth treatment represents the group of rats that were dosed with Vitamin D3 at a concentration of (15,000 IU)

Table 2 presents the results of the total number of white blood cells and the percentage of lymphocytes, neutrophils, monocytes, and eosinophils in different treatment groups. In group T1, there was a significant decrease in the total number of white blood cells, compared to the control group and other treatments ($p < 0.05$). Regarding the percentage of lymphocytes, group T1 displayed a significant increase, compared to the control group and other treatments ($p < 0.05$).

The results of the current study indicated a significant decrease in the average percentage of neutrophils in group T1, compared to the control and other treatment groups ($p < 0.05$). The results showed a significant increase in the percentage of monocyte cells in group T1, compared with the control and other treatment groups ($p < 0.05$). The results indicated a significant increase in the average percentage of eosinophils in the treatment group 1 compared to the control group and other treatment groups ($p < 0.05$).

The reduction in white blood cell count was similar to the study of Mackall et al. (1994). The reason for the decrease in the white blood cells in treatment 1 is attributed to the fact that cisplatin causes side effects when used, including the decrease of white blood cells, and it is associated with immune suppression. These effects may lead to a significant decrease in white blood cells in peripheral blood. Additionally, cisplatin affects T and B lymphocytes in the spleen and lymph nodes (Florea and Busselberg, 2011). Chemotherapy is contributed to decline in white blood cell, by influencing the liver, and kidneys (Ito et al., 2012; Jhaveri et al., 2013). According to a study by Zhang et al. (2010), chemotherapy-induced reduction in white blood cell and it could be due to its impact on bone marrow, and it is reducing the ability of bone marrow to produce cells and compromising the immune system, thereby reducing overall body protection. This could be the results of an increase in the levels of IL-10, known for its immunosuppressive properties, and inhibiting IL-10 could potentially restore immunity function (Florea and Büsselberg, 2011). IL-10 is used therapeutically to inhibit the proliferation and cytokine production of Th1 lymphocytes (Nguyen et al., 2021). As a consequence of using cisplatin, there was a decrease in the levels of neutrophils, those results in weakening the body's defense mechanisms, and causing a deficiency of macrophages.

The expressing vitamin D receptors and 1α-hydroxylase, leading to anti-inflammatory effects (Ao et al., 2021). Vitamin D3 reduces the differentiation and secretion of inflammatory cytokines (IL-2, IFNγ, and TNF-α) by Th1 cells while enhancing the differentiation and secretion of anti-inflammatory cytokines (IL-4, IL-5, and IL-10) by Th2 cells. Furthermore, Vitamin D3 enhances T-cell differentiation and regulation, preventing an exaggerated stress response (Florea and Büsselberg, 2011).

Chemotherapy-induced bone weakening and immune system defects result in increased IL-12 levels, while Vitamin D3's role in immune regulation helps to counteract inflammation and maintain immune balance. The results of current study indicated that vitamin D supplementation can increase the level of immune cells such as monocytes, lymphocytes, and eosinophils.

Table 2. The effects of different concentrations of Vitamin D3 on the differential number of white blood cells in rats immunosuppressed with cisplatin.

Group	W.B.C Count	LYM (%)	NEU (%)	MONO (%)	Eosino (%)
C	9.96 ± 0.06^{A}	65.99 ± 3.11^{B}	25.00 ± 1.92^{A}	5.29 ± 0.22^{BC}	3.90 ± 0.16^{B}
T1	4.76 ± 0.04^{C}	74.04 ± 2.16^{A}	11.89 ± 0.98^{B}	7.22 ± 0.30^{A}	7.01 ± 0.26^{A}
T2	6.33 ± 0.19^{B}	63.64 ± 1.88^{B}	23.44 ± 0.57^{A}	6.42 ± 0.21^{B}	4.52 ± 0.21^{B}
T3	6.59 ± 0.27^{B}	68.76 ± 1.61^{B}	20.10 ± 0.74^{A}	6.11 ± 0.09^{B}	4.17 ± 0.17^{B}
T4	8.12 ± 0.13^{A}	67.99 ± 1.80^{B}	19.73 ± 2.21^{A}	5.98 ± 0.33^{B}	4.2 ± 0.18^{B}
T5	8.96 ± 0.13^{A}	66.34 ± 2.31^{B}	24.18 ± 1.16^{A}	5.26 ± 0.20^{BC}	3.90 ± 0.12^{B}
T6	8.10 ± 0.08^{A}	67.35 ± 2.07^{B}	23.01 ± 1.29^{A}	5.19 ± 0.25^{BC}	4.02 ± 0.10^{B}
T7	8.06 ± 0.09^{A}	68.51 ± 1.14^{B}	22.64 ± 1.19^{A}	5.84 ± 0.19^{B}	4.01 ± 0.21^{B}

^{ABC} Different superscript letters indicate significant differences in the columns between the treatments ($p < 0.05$). C: The control group that received the physiological saline solution for the duration of the experiment (21 days). T1: The first treatment represents a group of rats that were immunosuppressed with cisplatin at a concentration of 2 mg/kg bw. T2: The second treatment represented a group of rats that were immunosuppressed and dosed with vitamin D3 at a concentration (5000 IU). T3: The third treatment represents a group of rats that were immunosuppressed and dosed with vitamin D3 at a concentration of (10000 IU). T4: The fourth treatment represents a group of rats that were immunosuppressed and dosed with vitamin D3 at a concentration (15,000 IU). T5: The fifth treatment represents the group of rats that received vitamin D3 at a concentration (5000 IU). T6: The fifth treatment represents the group of rats that were dosed with vitamin D3 at a concentration of (10,000 IU). T7: The fifth treatment represents the group of rats that were dosed with vitamin D3 at a concentration of (15,000 IU). WBC: White blood cells, LYM: Lymphocyte, NEU: Neutrophile, MONO: Monocyte, EOSINO: Eosinophile.

CONCLUSION

It can be concluded that different levels of Vitamin D3 (5000-15,000 IU) have positive influences on immunological parameters in immunosuppressed rats. There is a need to evaluate the effects of Vitamin D supplementation at other different doses on the other immunosuppressed animal species and human.

DECLARATIONS

Competing interests

The authors declare that they have no conflict of interest.

Authors' contribution

All authors contributed to the conceptualization and design of the study. Material preparation, data collection, and analysis were performed by Safa Masser Kmosh and Ahmed J. Al-Naely. The first draft was written by Safa Masser Kmosh. The analysis of data was conducted by Ahmed J. Al-Naely. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Data from the study are available according to a reasonable request.

Ethical considerations
The study was conducted originally and all analyzed data are prepared based on the experiment results. The text of the article is written originally without any unpermitted used from other published articles.

REFERENCES

Abdel-Daim MM, Abushouk AI, Donia T, Alarifi S, Alkahtani S, Aleya L, and Bungau SG (2019). The nephroprotective effects of allicin and ascorbic acid against cisplatin-induced toxicity in rats. Environmental Science and Pollution Research, 26: 13502. DOI: https://www.doi.org/10.1007/s11356-019-04780-4

Abolhasani Zadeh F, Bokov DO, Salahdin OD, Abdelbasset WK, Jawad MA, Kadhim MM, Qasim MT, Kzar HH, Al-Gazally ME, Mustafa YE et al. (2022). Cytotoxicity evaluation of environmentally friendly synthesis Copper/Zinc bimetallic nanoparticles on MCF-7 cancer cells. Rendiconti Lincei. Scienze Fisiche e Naturali, 33: 441-447. DOI: https://www.doi.org/10.1007/s12210-022-01064-x

Abdul Aziz AS, Al-Sharifi ZAR, and Kadhem HK (2020). Impact of vitamin D on male Iraqi patients with infertility. Annals of Tropical Medicine and Public Health, 23(S20): SP232240.

Ambrosio DD, Cippitelli M, Cocciolo MG, Mazzeo D, Di Lucia P, Lang R, Sinigaglia F, and Panina-Bordignon P (1998). Inhibition of IL-12 production by 1;25-dihydroxyvitamin D3. Involvement of NF-kappaB downregulation in transcriptional repression of the p40 gene. The Journal of Clinical Investigation, 101(1): 252-262. DOI: https://www.doi.org/10.1172/JCI1050

Ansari MJ, Jasim SA, Taban TZ, Bokov DO, Shalaby MN, Al-Gazally ME, Kzar HH, Qasim MT, Mustafa YF, and Khatami M (2022). Anticancer drug-loading capacity of green synthesized porous magnetic iron nanocarrier and cytotoxic effects against human cancer cell line. Journal of Cluster Science, 34: 467-477. DOI: https://www.doi.org/10.1007/s10876-022-02235-4

Ao T, Kikuta J, and Ishii M (2021). The effects of vitamin D on immune system and inflammatory diseases. Biomolecules, 11(11): 1624. DOI: https://www.doi.org/10.3390/biom11111624

Balasa B, Yun R, Belmar NA, Fox M, Chao DT, Robbins MD, Starling GC, and Rice AG (2014). Elotuzumab enhances natural killer cell activation and myeloma cell killing through interleukin‐2 and TNF‐α pathways. Cancer Immunology Immunotherapy, 64: 61-73. DOI: https://www.doi.org/10.1007/s00262-014-1610-3

Desoize B and Madoulet C (2002). Particular aspects of platinum compounds used at present in cancer treatment. Critical Reviews in Oncology/Hematology, 42(3): 317-325. DOI: https://www.doi.org/10.1016/S1040-8428(01)00219-0

Erbas O, Anil KH, Oltulu F, Aktug H, Yavasoglu A, Akman L, Solmaz V, and Taskiran D (2014). Oxytocin alleviates cisplatin-induced renal damage in rats. Iranian journal of basic medical sciences, 17(10): 747-752. PMID: https://pubmed.ncbi.nlm.nih.gov/25729542

Florea A and Büsselberg D (2011). Cisplatin as an anti-tumor drug: Cellular mechanisms of activity, drug resistance and induced side effects. Cancers, 3(1): 1352-1370. DOI: https://www.doi.org/10.3390/cancers3011351

Hafsan H, Bokov D, Abdelbasset WK, Kadhim MM, Suksatan W, Majdi HS, Widjaja G, Jalil AT, Qasim MT, and Balvardi M (2022). Dietary Dracocephalum kotschyi essential oil improved growth, haematology, immunity and resistance to Aeromonas hydrophila in rainbow trout (Oncorhynchus mykiss). Aquaculture Research, 53(8): 3164-3175. DOI: https://www.doi.org/10.1111/are.15829

Huldani H, Jasim SA, Bokov DO, Abdelbasset WK, Shalaby MN, Thangavelu L, Margiana R, and Qasim MT (2022). Application of extracellular vesicles derived from mesenchymal stem cells as potential therapeutic tools in autoimmune and rheumatic diseases. International Immunopharmacology, 106: 108634. DOI: https://www.doi.org/10.1016/j.intimp.2022.108634

Ito I, Ito Y, Mizuno M, Suzuki Y, Yasuda K, Ozaki T, Kosugi T, Yasuda Y, Sato W, Tsuboi N et al. (2012). A rare case of acute kidney injury associated with autoimmune hemolytic anemia and thrombocytopenia after long-term usage of oxaliplatin. Clinical and Experimental Nephrology, 16: 490-494. DOI: https://www.doi.org/10.1007/s10157-012-0620-8

Laird E, McNulty H, Ward M, Hoey L, McSorley E, Wallace J, Carson E, Molloy A, Healy M, Casey M et al. (2014). Vitamin D deficiency is associated with inflammation in older Irish adults. The Journal of Clinical Endocrinology & Metabolism, 99(5): 1807-1815. DOI: https://www.doi.org/10.1210/jc.2013-3507

Mackall CL, Fleisher TA, Brown MR, Margaret IT, Shad AT, Horowitz ME, Wexler LH, Adde MA, McClure LL, and Gress RE (1994). Lymphocyte depletion during treatment with intensive chemotherapy for cancer. Blood, 84 (7): 2221-2228. DOI: https://www.doi.org/10.1182/blood.V84.7.2221.2221

Mirhosseini N, Vatanparast H, Mazidi M, and Kimball SM (2017). The effect of improved serum 25-Hydroxyvitamin D status on glycemic control in diabetic patients: A meta-analysis. The Journal of Clinical Endocrinology & Metabolism, 102(9): 3097-3110. DOI: https://www.doi.org/10.1210/jc.2017-01024

Mohammed ZI and Qasim MT (2021). Hormonal profile of men during infertility. Biochemical and Cellular Archives, 21(Supplement 1): 2895-2898. Available at: https://go.rovedar.com/a55

Mohammed NA, El-Malkey NF, Ibrahim AA, and Abdullah DM (2019). Vitamin D3 supplementation ameliorates ovariectomy-induced cardiac apoptotic and structural changes in adult albino rats. Canadian Journal of Physiology and Pharmacology, 97: 647-654. DOI: https://www.doi.org/10.1139/cjpp-2018-0674

Mu W, Ouyang X, Agarwal A, Zhang L, Long DA, Cruz PE, Roncal CA, Glushakova OY, Chiodo VA, Atkinson MA et al. (2005). IL-10 suppresses chemokines; inflammation;and fibrosis in a model of chronic renal disease. Journal of the American Society of Nephrology, 16(12): 3651-3660. DOI: https://www.doi.org/10.1681/ASN.2005030297

Nasiri M, Farhangi H, Badiee Z, Ghasemi A, Golsorkhi M, and Ravanshad Y, and Azarfar A (2020). The effect of vitamin E on cisplatin induced nephrotoxicity: A clinical trial study. International journal of pediatrics, 8(1): 10767-773. DOI: https://www.doi.org/10.22038/ijp.2019.42813.3656

Nguyen HD, Aljamaei HM, Stadnyk AW(2021). The production and function of endogenous interleukin-10 in intestinal epithelial cells and gut homeostasis. Cell Mol Gastroenterol Hepatol 12(4):1343–52. doi: 10.1016/j.jcmgh.2021.07.005

Perry MC (2008). The chemotherapy source book. Lippincott William and Wilkins., Colombia, 351-360.

Papapostoli I, Lammert F, and Stokes CS (2016). Effect of short-term vitamin D correction on hepatic steatosis as quantified by controlled attenuation parameter (CAP). Journal of Gastrointestinal Liver Disease, 25(2): 175-181. DOI: https://www.doi.org/10.15403/jgld.2014.1121.252.cap

Richardson ML and Gangolli S (1993). Cisplatin. The dictionary of substances and their effects. Cambridge., Royal Society of Chemistry, UK, pp. 524-7.

Sun CY, Zhang QY, Zheng GJ, and Feng B (2019). Phytochemicals: Current strategy to sensitize cancer cells to cisplatin. Biomedicine & Pharmacotherapy, 110: 518-527. DOI: https://www.doi.org/10.1016/j.biopha.2018.12.010

Titov, A.; Kaminskiy, Y.; Ganeeva, I.; Zmievskaya, E.; Valiullina, A.; Rakhmatullina, A.; Petukhov, A.; Miftakhova, R.; Rizvanov, A.; Bulatov, E(2022). Knowns and Unknowns about CAR-T Cell Dysfunction. *Cancers* , *14*, 1078.

Weir GM, Liwski RS, and Marc M (2011). Immune modulation by chemotherapy or immunotherapy to enhance cancer vaccines. Cancers, 3(3): 3114-3142. DOI: https://www.doi.org/10.3390/cancers3033114

Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, Bayliss S, Moss P, Stanworth S, and Hyde CA (2007). A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anemia associated with cancer, especially that attributable to cancer treatment. Health Technology Assessment, 11(13): 1-202. DOI: https://www.doi.org/10.3310/hta11130

Wu Y, Ding Y, Tanaka Y, and Zhang W (2014). Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. International Journal of Medical Sciences, 11(11): 1185-1200. DOI: https://www.doi.org/10.7150/ijms.10001

Zoair MA (2021). Effect of per-treated and treated vitamin D on insulin resistance, lipid profile and platelet indices in adult diabetic male albino rats. Al-Azhar Medical Journal, 50(1): 809-820. DOI: https://www.doi.org/10.21608/amj.2021.151093

Zakharova I, Klimov L, Kuryaninova V, Nikitina I, Malyavskaya S, Dolbnya S, Kasyanova A, Atanesyan R, Stoyan M, Todieva A et al. (2019). Vitamin D insufficiency in overweight and obese children and adolescents. Frontiers in Endocrinology, 10: 103. DOI: https://www.doi.org/10.3389/fendo.2019.00103

Zhang Z, Baliga R, Baliga M, Ueda N, and Shah SV (2010). Role of cytochrome P-450 as a source of catalytic iron in cisplatininduced nephrotoxicity. Kidney International, 54(5): 1562-1569. DOI: https://www.doi.org/10.1046/j.1523-1755.1998.00161.x