Asian Journal of Plant Sciences

ISSN 1682-3974

science alert

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OPEN ACCESS Asian Journal of Plant Sciences

ISSN 1682-3974
DOI: 10.3923/ajps.2021.355.362

Research Article
Ameliorative Effects of *Taraxacum officinale* Crude Extracts on Paclitaxel Induced-Haematological Toxicity and Oxidative Stress

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Abstract

Background and Objective: Paclitaxel (PTX) is an effective anticancer agent but in the same fashion, has a major dose-limiting haematological toxicity. Taraxacum officinale (TXO) crude extract has been used in the treatment of anaemia in herbal remedies. Here, this study evaluated the possible attenuation of PTX-induced haematological adverse effects and lipid peroxidation with coadministration of TXO crude extract. **Materials and Methods:** The whole plant of TXO was soaked in water for 24 hrs, filtered, and evaporated to dryness with rotary evaporator. Five groups of 6 adult rats weighing between 150-160 g were used. Normal saline was administered to control group 1, group 2 was given 30 mg kg^{-1} of PTX alone intraperitoneally. Group 3 and 4 were given PTX 30 mg kg^{-1} followed by 200 and 400 mg kg^{-1} TXO respectively. The fifth group received 200 mg kg^{-1} TXO alone. Drug administration lasted for 10 days after which animals were sacrificed and blood collected for differential analysis. Significant ($p<0.001$) weight losses in PTX treated group and were attenuated by coadministration of TXO. **Results:** Group treated with TXO alone showed a significant ($p<0.001$) weight gain. Non-significant decreases in RBC counts, haemoglobin and haematocrit were observed with PTX alone, which were increased with the addition of TXO. Results also showed significant ($p<0.05$) decreases in WBC, neutrophil and platelet counts by PTX were also attenuated by co-administration with TXO. Increased lipid peroxidation by PTX was significantly reduced as well. **Conclusion:** This study has demonstrated that TXO crude extract has the potential to attenuate PTX-induced haematological adverse effects in rats, an anticancer drug frequently used in the treatment of many cancers.

Key words: *Taraxacum officinale*, paclitaxel, white blood cell, neutrophils, red blood cells

Citation: Emeka, P.M., H.M. Almofarfesh, S.A. Alsahlawi and H.A.H. Mohammad, 2021. Ameliorative effects of *Taraxacum officinale* crude extracts on paclitaxel induced-haematological toxicity and oxidative stress. Asian J. Plant Sci., 20: 355-362.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Chemotherapy has been documented to decrease the production of erythropoietin and also to moderate responsiveness of bone marrow to erythropoietin[1]. In addition invasive tumour is known to trigger immune responses and which consequently cause the production of different types of cytokines that, subsequently impede bone marrow functions, affecting haematopoietic precursors and shorten blood cell survival. Several haematological toxic effects of anticancer agents have been documented. These effects are associated with either direct interactions with blood cell elements or unintended actions due to generation of oxidative radicals during metabolism of these drugs. These phenomena could perhaps be the most probable explanations of anticancer drug-related haematological toxicity. Haematological adverse effects include leukopenia/neutropenia, thrombocytopenia and anaemia[2,3]. Paclitaxel (PTX) is a highly effective anticancer agent that is widely used to treat different types of solid tumours, including prostate, breast and ovarian cancers[4]. It enhances polymerisation of tubulin and the protein subunit of spindle microtubules by promoting assembly of microtubule[5,6]. *In vitro* studies have shown that paclitaxel can evoke and cause oxidative stress and consequently produce DNA oxidative adducts via the formation of hydrogen peroxide[7]. Hence, these actions are associated with paclitaxel cytotoxicity as reported in its use in breast cancer treatment[8]. Evidence showed that cancer patients treated with paclitaxel show instantaneous systemic oxidative stress with significant leukopenia as side effect[9], thus becoming its major dose-limiting haematologic adverse effect[2]. Leukopenia is described as an abnormal decrease in circulating White Blood Cells (WBC) in particularly, neutrophils as a result of myelosuppression which is evident in low total WBC counts. These reductions in leukocyte counts could also be due to the destruction or suppression of their production. The consequence of this reduction is linked to an increased risk of systemic infection and could be life threatening[10]. There is therefore a need to alleviate these adverse effects to improve the treatment efficacy of PTX for better cancer management. In the time past, herbal treatments employed in the management of several diseases and their health benefits have been known in human civilizations for centuries. Various studies have documented the efficacy of herbal products like TXO (*Taraxacum officinale*) that they have significant effects on treatment of diseases. TXO is of the family Asteraceae[11], reported growing in temperate zones of the northern hemisphere[12]. It is rich in vitamins A and C along with minerals such as iron and calcium more than most plants[13]. The traditional medicinal properties of TXO have been documented in Asia, Europe, Middle East and North America. Chinese, Indian and Russian folk medicines have recognized the medicinal potential of this plant in the treatment of liver disease. Traditionally, the Chinese use the plant in combination with other herbs for hepatitis[14]. Documented evidence showed that TXO can enhance immunity and treat respiratory tract infections[15] In addition, TXO is given as a tonic in anaemic patients as traditional herbal remedy[15]. Modaresi and Resalatpour[16] reported that it is effective in promoting blood formed elements and factors, in a dose-dependent fashion. The aim of this study therefore, was to examine the effectiveness of coadministration of crude extract of TXO in attenuating PTX- induced haematological adverse effects and lipid peroxidation in rats.

MATERIALS AND METHODS

Study area: This study was carried out from November, 2019 to March, 2020, including the period of plant drying, extraction and animals acclimatization.

Extract preparation: The whole plant of TXO excluding the roots were washed with distilled water to remove extraneous matters. The washed plant materials were then air dried for one week and turning regularly to avoid fungal growth. They were then pulverized using a milling machine, out of which 500 g of the dried powdered plant were soaked in 500 mL of distilled water in a 1000 mL conical flask. The content was vigorously shaken for about 10 min and allowed to stand for 24 hrs. The mixture was then filtered using cotton wool and re-filtered using Whatman No. 42 (125 mm) filter paper. A rotary evaporator was used to concentrate the extract. The obtained powder was stored in a dry container at room temperature until use.

Animal protocol: Sprague Dawley rats bred by the College Medicine Animal house of King Faisal University were used for this study. Animals were allowed to acclimatise after grouping them in different cages. They were allowed standard rat chow and tap water *ad libitum* during the period of acclimatization and duration of the experiment. Their cages were kept in the animal room with controlled temperature (21-24°C) and humidity (50-65) and a 12 hrs light/dark cycle. The study was approved by the Deanship for Scientific Research (DSR), King Faisal University, Hofuf, Saudi Arabia. Animal care and experimental procedures were performed in accordance with Animal Research Ethics as recommended DSR and The Governance of Animal Care and Use for Scientific Purposes in Africa and the Middle East[17].

Experimental design: Animals were acclimatized for 1 (one) week and were divided into five groups, each consisting of six animals. Group I (negative control group) received normal saline throughout the study. Group II received 30 mg kg^{-1} i.p of paclitaxel every two days for 10 days. Group III was with injected with paclitaxel (30 mg kg^{-1} i.p) as in group II but was followed by per oral administration of 200 mg kg^{-1} TXO. Similarly, group IV was administered with paclitaxel (30 mg kg^{-1} i.p) followed by per oral administration of 400 mg kg^{-1} TXO. Group V was administered with 200 mg kg^{-1} TXO alone. All the experimentations were for 10 days.

Haematological and biochemical investigation: Blood samples were collected from all groups on the 10th day of the experiment by retro-orbital puncture into clean EDTA bottles and haematological parameters analyzed for Red Blood Cells (RBC) counts, haemoglobin (Hb%) and associated differentials, total White Blood Counts (WBC) and all the differentials including neutrophils and lymphocytes counts. Also platelets (PLT), counts and associated parameters. Liver samples were harvested as well.

Malondialdehyde (MDA) assay: Lipid peroxidation was determined from liver homogenates by measuring the formation of Thiobarbituric Acid-reactive Substances (TBARS), as previously described by Hassoun *et al.*[18] and Ohakwa *et al.*[19]. Each sample for analysis contains the homogenates, phosphoric acid (1% w/v solution) and a volume of thiobarbituric acid and incubated 95°C for 1 hr. The subsequent TBARS concentration were measured at spectrophotometrically at 535 nm.

Statistical analysis: Data was analysed with a GraphPad Prism statistical software (Version 8.2, San Diego California, USA) and values were expressed as mean±SEM and differences between the groups were statistically determined by two-way analysis of variance (ANOVA) followed by Dunnett's test. Statistical significant level were considered at p<0.05/0.001.

RESULTS

Effects on animal weights: There were significant weight losses (<0.001) in PTX alone treated group (29.3±6.56 g, loss in weight) compared with the control (2.67±0.53 g gain in weight) given in Fig. 1. However, coadministration with TXO crude extract reduced these weight losses in a dose dependent manner (13.83±3.7 and 4.5±0.54 g weight loss). In addition, TXO crude extract alone showed weight gains among the group but was not significant compared with the control. Figure 2 showed percentage weight gain/loss in all treated groups. It describes percentage weight losses/gains, indicating that the losses observed in PTX only group were statistically significant (p<0.001) with 19.15% weight loss and in PTX plus TXO crude extract (200 mg kg^{-1}) group a weight loss of 9% compared with the control was observed.

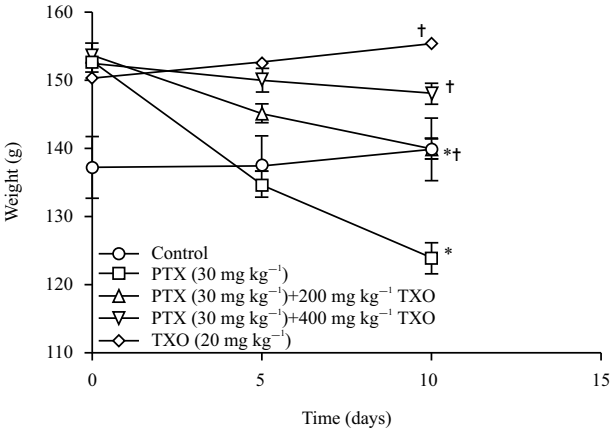

Fig. 1: Group mean weight changes (g) observed in different treatment groups

*Statistical significant p<0.001 in weight changes between the control with PTX and other treatment groups. † Significant difference between PTX alone and other treatment groups. PTX: Paclitaxel, TXO: *T. officinale*

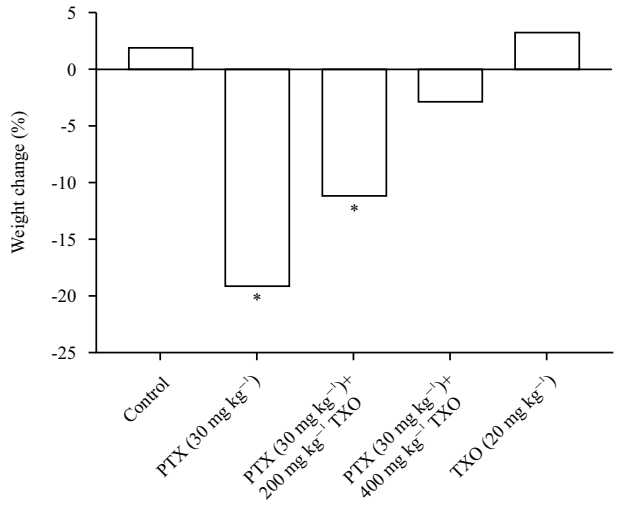

Fig. 2: Percentage weight change among different treatment groups

*Statistical significance (p<0.001) in percentage weight loss with PTX treated groups compared with the control. PTX: Paclitaxel, TXO: *T. officinale*

Table 1: Effects of PTX and doses of TXO crude extract on erythrocytic parameters of rats

Parameters	Control	PTX (30 mg kg^{-1})	PTX+TXO (200 mg kg^{-1})	PTX+TXO (400 mg kg^{-1})	TXO (200 mg kg^{-1})
Red blood cell ($\times 10^6$ µL)	7.04±1.3	6.66±0.55	6.31±0.8	6.7±1.37	8.34±0.5
Hb (g dL^{-1})	12.75±2.2	11.5±0.73	11.9±0.57	12.1±1.97	15.5±0.99
Hematocrit (%)	39.75±7.0	35.16±3.12	33.80±1.7	36.55±8.7	44.15±0.78
MCV (fL)	56.5±0.14	52.82±2.8	54.00±4.24	54.35±1.91	55.7±0.71
MCH (Pg)	18.15±0.7	18.12±0.65	19.00±1.56	18.15±0.78	18.25±0.21
MCHC (g dL^{-1})	32.1±0.14	34.3±1.63	35.35±0.07	33.4±2.54	33.15±1.62
RDW (%)	7.04±1.3	11.76±1.36	10.65±1.1	12.55±1.3	11.5±0.28

PTX: Paclitaxel, TXO: *T. officinale.* MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, MCH: Mean corpuscular hemoglobin, RDW: Red cell distribution width

Table 2: Effects of PTX and doses of TXO crude extract on White blood cells and their differentials in rats

Parameters	Control	PTX (30 mg kg^{-1})	PTX+TXO (200 mg kg^{-1})	PTX+TXO (400 mg kg^{-1})	TXO (200 mg kg^{-1})
WBC ($\times 10^3$ µL^{-1})	11.66±8.5	2.49±0.78*	9.85±1.2	8.36±1.92	10.00±2.12
Neutrophils (%)	17.75±0.63	5.8±3.69*	7.9±1.83*	10.4±3.34	15.65±1.5
Lymphocytes (%)	75.95±0.66	86.58±3.98*	85.00±3*	77.65±17.2	73.75±2.5
Monocytes (%)	1.7±0.24	5.2±2.82*	4.15±2.3*	4.1±0.35*	1.5±1.06
Eosinophils (%)	4.4±0.42	1.9±2.77*	2.45±2.62	2.15±0.21	4.25±0.21
Basophils (%)	0.2±0.11	0.55±0.58	0.52±0.1	0.25±0.07	0.3±0.22

PTX: Paclitaxel, TXO*: T. Officinale,* * p<0.05

Table 3: Effects of PTX and doses of TXO crude extract on platelets and associated parameters in rats

Parameters	Control	PTX (30 mg kg^{-1})	PTX+TXO (200 mg kg^{-1})	PTX+TXO (400 mg kg^{-1})	TXO (200 mg kg^{-1})
Platelets (10^3 mm^{-3})	482.5±10.6	401.4±38.36*	447.00±11.4*	326.00±102*	488.00±2.82
Plateletcrit (%)	0.4±0.56	0.29±0.24	0.326±0.02	0.35±0.04	0.33±0.22
MPV (fL)	3.75±5.3	8.94±2.9*	7.3±0.52*	3.6±5.1	5.2±0.57
PDW (%)	4.0±5.7	9.8±0.53*	6.47±11.4	5.95±12.8	6.32±2.1

PTX: Paclitaxel, TXO*: T. officinale*, *p<0.001. MVP: Mean platelet volume, PDW: Platelet distribution width

Haematological parameters: Results here showed a reduction in RBC counts among the group administered with PTX alone with a count of 6.66±0.5 compared to the control RBC count of 7.04±1.3×10^6 µL. In addition, PTX plus TXO 200 mg kg^{-1} displayed no significant difference in RBC count as well as PTX plus TXO 400 mg kg^{-1} giving 6.31±0.8 and 6.7±1.37 counts respectively. It therefore indicates that PTX had no significant effect on healthy rats RBC count used in this study. However, administering TXO alone produced a rise in RBC count (8.33±.05), compared to all the groups, but with no significant difference. The same pattern was reflected in the haematocrit, MCV, MCH, MCHC and RDW (%) counts, affirming that not significant effects of PTX on erythrocytic parameters were observed given in Table 1.

The PTX effects on WBC counts and associated parameters produced a significant (p<0.05) reduction in WBC with a count of 2.49±0.78 compared with control (11.66±8.5) given in Table 2. However, coadministration with TXO crude extract attenuated these reductions. The effect of PTX on neutrophils was equally drastically reduced, from 17.75±0.63-5.8±3.69%. As observed in this study, TXO co-administration attenuated these effects in a dose-dependent manner, giving 7.9±1.83 and 10.4±3.3 for 200 and 400 mg kg^{-1}, respectively. Furthermore, monocyte counts were increased by PTX administration, giving a count of 5.2±2.8 compared with the control (1.7±0.42). This effect appeared to be statistically significant (p<0.05) and was mitigated by coadministering TXO crude extract (Table 2).

Results showing the effects of PTX and crude extracts of TXO on platelets and associated parameters are presented on Table 3. It shows that PTX administered alone significantly reduced platelet counts in healthy rats. Also, the effects of co-administration with TXO (200 mg kg^{-1}) crude extract were observed to mitigate this effect. Furthermore, TXO crude extract alone produced an increase in platelet counts, showing that it possesses the potential to protect the platelets from the effects of PTX as observed in this study. In addition, as presented on Table 3, observed similar trends in action by the administration of PTX alone on Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW).

Table 4 showed the effects of PTX and TXO crude extract, including their co-administration on lipid peroxidation in the liver. These observations were made in all the treatment groups and control. Results showed that PTX 30 mg kg^{-1} produced a significant (p<0.001) increase in MDA, 3.56±1.1 compared to control 1.02±0.2. Coadministration of TXO crude extract with PTX decreased MDA levels significantly (p<0.001) in a dose-dependent manner, from 3.56±1.1-2.45±0.78 (for

Table 4: Effect of paclitaxel and *T. officinale* crude extract on lipid peroxidation in the liver of control and experimental animals

Parameters	Control	PTX (30 mg kg^{-1})	PTX+TXO (200 mg kg^{-1})	PTX+TXO (400 mg kg^{-1})	TXO (200 mg kg^{-1})
Malondialdehyde (MDA)	1.02±0.2	3.56±1.1*	2.45±0.78*	2.1.7±0.41*	1.1±0.15

PTX: Paclitaxel, TXO: *T. officinale*, *p<0.001

200 mg kg^{-1}) and 2.1±0.41 (for 400 mg kg^{-1}) respectively also compared with the control. 400 mg kg^{-1}). TXO alone had no significant effect on MDA level compared with the control.

DISCUSSION

Haematological toxicities maybe as a result of myelosuppression by chemotherapeutic agent like PTX. Usually, it becomes a limiting factor to their use. Neutropenia is documented to be the main adverse effect of PTX and treatment available for this toxic effects has been reported to cause leukopenia in patients[20]. Roesnberg *et al.*[21] and Shao *et al.*[22] reported that the use of Granulocyte Colony-stimulating Factor (G-CSF) for patients receiving PTX, were observed to develop leukaemia. Therefore, a safe alternative with minimal side effects profile is desired, because treatment of malignancies usually takes a long period. In this study, the effect of crude extract of TXO on PTX induced haematological adverse effects was investigated. TXO has been reported previously to enhance RBC counts, Hb and WBC count significantly in mice[16]. Current findings showed that, while investigating the effect on the whole blood picture, the administration of PTX to healthy rats, produced significant weight losses. However, in groups given PTX plus TXO observed that this effect was reversed in a dose dependent manner. In addition, with TXO given alone, there was an increase in body weight. This observation is similar to the study conducted by Tahtamouni *et al.*[23] and Oh *et al.*[24] They reported body weight gains in rats administered with crude extract of TXO, which is consistent with current observation in this study. It was observed that the effect of PTX on erythrocytic parameters, showed a non-significant reduction in RBC counts, Hb and haematocrit as well as in other related erythrocytic parameters. These findings are comparable to the reports of Panis *et al.*[8] However, Demers *et al.*[25] studies, did not support these results, as they reported that PTX produced no observable changes in erythrocytic parameters in mice. Interestingly, TXO co-administration did not significantly change RBC counts or Hb, but administering TXO alone, was found to increase RBC counts, Hb and haematocrit in current experimental rats. Supporting this finding is the work of done by Modaresi and Resalatpour[16] who also reported similar observations in mice. The use of TXO as a remedy for anaemia has been documented by various studies[15]. In the present study, PTX significantly reduced WBC counts and out of which the neutrophils were markedly diminished. Documented evidence show that PTX toxicities included neutropenia.[26] Also previous reports by Rowinsky *et al.*[27] indicated that neutropenia is the principal toxicity associated with the clinical use of PTX. Coadministartion of TXO crude extract, showed that these effects were attenuated in dose dependent manner. The mitigation of the effects of PTX-induced reduced WBC counts and indeed of neutropenia can be attributed to the fact that TXO crude extract showed the potential to enhance haematological parameters as reported by Modaresi and Resalatpour[16]. Current study therefore, supports this view as neutrophils are enhanced in the presence of infections and reduced amount is reported to increase patients' vulnerability to serious infections. Numerous studies have also shown that the Chinese, European herbalists and Arabian communities use TXO traditionally to treat various diseases[28,29]. Therefore, reports regarding the use of aqueous extract of TXO in oxidative stress, inflammation and cancers have been documented[28-30]. In this investigation however, current results showed a significant increase in lymphocytes counts. The current observation regarding this finding was comparable to the work of Branham *et al.*[31] who reported that PTX administered to healthy human adults had increased lymphocytes counts. In their report, they showed that DNA damage by PTX induced increased lymphocytes production associated with DNA repair. In the present study, healthy experimental rats were used and as well observed a significant increase in lymphocytes counts. On the contrary, studies of PTX on cancer models, reported reduced lymphocytes counts[32]. The findings in this study also showed an increase in monocytes counts in the presence of PTX. A high monocytes count is known to stimulate interleukins secretions. Interleukins in turn potentiates lymphocytes activities like T and B cells[33]. This correlates with increased lymphocytes observed with PTX in this study. Also, low eosinophils counts is reflected in low WBC counts caused by PTX, an observation made in this study as well. As Pavan-Kumar[34] observed, PTX causes the release of basophils, which is reported to be responsible for the hypersensitivity reactions observed in patients administered PTX, an observation also made by Gao *et al.*[35] Basophils release histamine and by so doing promote inflammation[36]. In the present study, an increase in basophils counts in healthy rats administered with PTX reported.

Significant decrease in platelets counts and associated parameters were also reported. Similar findings have been documented, reporting the effects of PTX on blood formed elements[25]. Accordingly, evidence show that PTX causes drug-induced thrombocytopenia by destroying platelets and this adverse effect is seen in 4-20% of patients[37]. However, this is contrary to the observation and reports of Kim *et al.*[38] who demonstrated an increase in platelet counts in mice. Lipid peroxidation analysis in liver revealed an elevation of MDA, which is regarded as an oxidative maker implicated in oxidative stress by PTX. Current findings demonstrated consistency with the work of Panis *et al.*[39] In this investigation, coadministration of TXO crude extract with PTX, decreased the level of MDA, indicating that it can potentially influence drug-induced oxidative stress. This observation is very well collaborated by the report of Choi *et al.*[40]. They also found a reduced liver MDA in rabbits fed with crude extracts of TXO. Altogether, current findings have shown that TXO crude extract, administered to rats in combination with PTX exhibited the potential to attenuate haematological adverse effects of this anticancer agent and this will indeed improve its tolerability.

CONCLUSION

In conclusion, this study revealed that PTX (paclitaxel) produced significant neutropenia evidenced by the reduction in WBC and neutrophils in experimental rats, which was effectively attenuated by the coadministration of TXO crude extract. This is contrary to some reported studies where they observed anaemia and neutropenia. Also, this study reported increased liver lipid peroxidation, attenuated also by coadminstration of TXO crude extract with PTX. Therefore, this plant crude extract appears to possess the potential to attenuate PTX-induced haematological toxicity.

SIGNIFICANCE STATEMENT

Taraxacum officinale (TXO) extracts have been used in traditional medicine as herbal remedies by many civilizations dating back to 500 BC. The paper comes in the wake of continuous search for efficacious and cheap ways of managing the chemotherapeutic adverse effects. The results of this study have shown the efficacy of TXO crude extract in attenuating the haematologic toxic effects of anticancer agent, paclitaxel in animal model. It could potentially be a complementary treatment or even supplemented with anticancer agents that cause haematological adverse effects, to improve treatment outcome.

ACKNOWLEDGMENT

The authors would like to thank the Deanship for Scientific Research, at King Faisal University (Research number 185005) for supporting this study and the University for their Continued Contribution to scientific knowledge. The authors would also like to appreciate the efforts of Mr. Tameem M Alyahian and Sami S Algami for their technical assistance in completing this study.

REFERENCES

1. Sankaran, V.G. and M.J. Weiss, 2015. Anemia: Progress in molecular mechanisms and therapies. Nat. Med., 21: 221-230.
2. Xin, D.S., L. Zhou, C.Z. Li, S.Q. Zhang and H.Q. Huang *et al.*, 2018. TC > 0.05 as a pharmacokinetic parameter of paclitaxel for therapeutic efficacy and toxicity in cancer patients. Recent. Pat. Anticancer. Drug. Discov., 13: 341-347.
3. Lee, C.K., H. Gurney, C. Brown, R. Sorio and N. Donadello *et al.*, 2011. Carboplatin–paclitaxel-induced leukopenia and neuropathy predict progression-free survival in recurrent ovarian cancer. Br. J. Cancer, 105: 360-365.
4. Zhang, D., J.R. Wu, X.J. Duan, K.H. Wang and Y. Zhao *et al.*, 2019. A bayesian network meta-analysis for identifying the optimal taxane-based chemotherapy regimens for treating gastric cancer. Front. Pharmacol., Vol. 10. 10.3389/fphar.2019.00717.
5. Wang, P., H. Wang, Q. Huang, C. Peng and L. Yao *et al.*, 2019. Exosomes from M1-polarized macrophages enhance paclitaxel antitumor activity by activating macrophages-mediated inflammation. Theranostics, 9: 1714-1727.
6. Hadzic, T., N. Aykin-Burns, Y. Zhu, M.C. Coleman and K. Leick, G.M. Jacobson and D.R. Spitz, 2010. Paclitaxel combined with inhibitors of glucose and hydroperoxide metabolism enhances breast cancer cell killing via H_2O_2-mediated oxidative stress. Free Radic. Biol. Med., 48: 1024-1033.
7. Ramanathan, B., K.Y. Jan, C.H. Chen, T.C. Hour, H.J. Yu and Y.S. Pu, 2005. Resistance to paclitaxel is proportional to cellular total antioxidant capacity. Cancer Res., 65: 8455-8460.
8. Panis, C., A.C.S.A. Herrera, V.J. Victorino, F.C. Campos and L.F. Freitas *et al.*, 2012. Oxidative stress and hematological profiles of advanced breast cancer patients subjected to paclitaxel or doxorubicin chemotherapy. Breast Cancer Res. Treat., 133: 89-97.
9. Li, Y., X. Sui, Z. Su, C. Yu and X. Shi *et al.*, 2020. Meta-analysis of paclitaxel-based chemotherapy combined with traditional Chinese medicines for gastric cancer treatment. Front. Pharmacol., Vol. 11. 10.3389/fphar.2020.00132.
10. Lima, S.S., M.S. França, C.C. Godoi, G.H. Martinho, L.A. de Jesus, R.M. Romanelli and W.T. Clemente, 2013. Neutropenic patients and their infectious complications at a university hospital. Rev. Bras. Hematol. Hemoter., 35: 18-22.

11. Astafieva, A.A., E.A. Rogozhin, T.I. Odintsova, N.V. Khadeeva, E.V. Grishin and T.A. Egorov, 2012. Discovery of novel antimicrobial peptides with unusual cysteine motifs in dandelion *Taraxacum officinale* Wigg. flowers. Peptides, 36: 266-271.
12. Schutz, K., R. Carle and A. Schieber, 2006. Taraxacum: A review on its phytochemical and pharmacological profile. J. Ethnopharmacol., 107: 313-323.
13. Abdel-Magied, N., S.M. Abdel Fattah and A.A. Elkady, 2019. Differential effect of *Taraxacum officinale* L. (dandelion) root extract on hepatic and testicular tissues of rats exposed to ionizing radiation. Mol. Biol. Rep., 46: 4893-4907.
14. Modaresi, M., 2012. A comparative analysis of the effects of garlic, elderberry and black seed extract on the immune system in mice. J. Anim. Vet. Adv., 11: 458-461.
15. Mahesh, A., R. Jeyachandran, L. Cindrella,D. Thangadurai, V.P. Veerapur and D.M. Rao, 2010. Hepatocurative potential of sesquiterpene lactones of *Taraxacum officinale* on carbon tetrachloride induced liver toxicity in mice. Acta Biol. Hung., 61: 175-190.
16. Modaresi, M. and N. Resalatpour, 2012. The effect of *Taraxacum officinale* hydroalcoholic extract on blood cells in mice. Adv. Hematol., 10.1155/2012/653412.
17. Mohr, B.J., F.A. Fakoya, J. Hau, O. Souilem and L. Anestidou, 2017. The governance of animal care and use for scientific purposes in Africa and the middle east. ILAR J., 57: 333-346.
18. Hassoun, E.A., S.C. Wilt, M.J. Devito, A. Van Bergelen, N.Z. Alsharif, L.S. Birnbaum and S.J. Stohs, 1998. Induction of oxidative stress in the brain tissues of mice after subchronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Sci., 42: 23-27.
19. Ohkawa, H., N. Ohishi and K. Yagi, 1979. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal. Biochem., 95: 351-358.
20. Link, D.C., 2019. Mechanisms of leukemic transformation in congenital neutropenia. Curr. Opin. Hematol., 26: 34-40.
21. Rosenberg, P.S., B.P. Alter, A.A. Bolyard, M.A. Bonilla and L.A. Boxer *et al*., 2006. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. Blood, 107: 4628-4635.
22. Shao, Y.Q. and Y.Z. Zheng, 2017. A report of periodic neutral granulocyte reduction and literature review. Chinese J. Hematol., 38: 889-892.
23. Tahtamouni, L.H., R.A. Al-Khateeb, R.N. Abdellatif, Z.A. Al-Mazaydeh, S.R. Yasin, S. Al-Gharabli and A.Z. Elkarmi, 2016. Anti-spermatogenic activities of *Taraxacum officinale* whole plant and leaves aqueous extracts. Vet. Res. Forum., 7: 89-97.
24. Oh, S.M., H.R. Kim, Y.J. Park, H. Lee and K.H. Chung, 2015. Ethanolic extract of dandelion (*Taraxacum mongolicum*) induces estrogenic activity in MCF-7 cells and immature rats. Chin. J. Nat. Med., 13: 808-814.
25. Demers, M., B. Ho-Tin-Noé, D. Schatzberg, J.J. Yang and D.D. Wagner, 2011. Increased efficacy of breast cancer chemotherapy in thrombocytopenic mice. Cancer Res., 71: 1540-1549.
26. Alsharedi, M., T. Gress, J. Dotson, N. Elmsherghi and M.T. Tirona, 2016. Comparison of toxicity profile and tolerability between two standard of care paclitaxel-based adjuvant chemotherapy regimens in breast cancer. Med. Onco., Vol. 33. 10.1007/s12032-016-0740-1.
27. Rowinsky, E.K., E.A. Eisenhauer, V. Chaudhry, S.G. Arbuck and R.C. Donehower, 1993. Clinical toxicities encountered with paclitaxel (Taxol). Semin. Oncol., 20: 1-15.
28. Sigstedt, S.C., C.J. Hooten, M.C. Callewaert, A.R. Jenkins and A.E. Romero *et al*., 2008. Evaluation of aqueous extracts of Taraxacum officinale on growth and invasion of breast and prostate cancer cells. Int. J. Oncol., 32: 1085-1090.
29. You, Y., S. Yoo, H.G. Yoon, J. Park and Y.H. Lee *et al*., 2010. *In vitro* and *in vivo* hepatoprotective effects of the aqueous extract from *Taraxacum officinale* (dandelion) root against alcohol-induced oxidative stress. Food Chem. Toxicol., 48: 1632-1637.
30. Kim, J., K. Noh, M. Cho, J. Jang and Y. Song, 2007. Anti-oxidative, anti-inflammatory and anti-atherogenic effects of Dandelion (*Taraxacum officinale*) extracts in C57BL/6 mice fed atherogenic diet. Faseb. J., 21: A1122-A1122.
31. Branham, M.T., S.B. Nadin, L.M. Vargas-Roig and D.R. Ciocca, 2004. DNA damage induced by paclitaxel and DNA repair capability of peripheral blood lymphocytes as evaluated by the alkaline comet assay. Mutat. Res. Genet. Toxicol. Environ. Mutagen., 560: 11-17.
32. Tustumi, F., F.R. Takeda, A.A.G.S. Brandão, R.A.A. Sallum, U.R. Junior and I. Cecconello, 2019. Lymphocyte count and platelet volume predicts postoperative complications in esophagectomy for cancer: A cohort study. Arq. Gastroenterol., 56: 377-385.
33. Blumenreich, M.S., 1990. The White Blood Cell and Differential Count. In: Clinical Methods: The History, Physical, and Laboratory Examinations, Walker, H.K., W.D. Hall and J.W. Hurst (Eds.)., Butterworths, Boston, pp: 724-727.
34. Kumar, K.A.P., 2020. Paclitaxel hypersensitivity. Cancer Res. Stat. Treat., 3: 419-420.
35. Gao, W., Y. Zan, Z.J. Wang, X.Y. Hu and F. Huang, 2016. Quercetin ameliorates paclitaxel-induced neuropathic pain by stabilizing mast cells, and subsequently blocking PKCε-dependent activation of TRPV1. Acta Pharmacol. Sin., 37: 1166-1177.
36. Bax, H.J., J. Chauhan, C. Stavraka, A. Khiabany and M. Nakamura, 2020. Basophils from cancer patients respond to immune stimuli and predict clinical outcome. Cells, Vol. 9. 10.3390/cells9071631.

37. Üyetürk, Ü., Ş.H. Arslan, M. Kurt-Yüksel and F. Altuntaş, 2011. Paclitaxel therapy and immune thrombocytopenic purpura: Coincidence or association? Turk J. Hematol., 28: 151-152.
38. Kim, J.Y., S. Lee, Y. Kim, E.J. Jeong and I.H. Lee *et al*., 2019. Subacute toxicity and toxicokinetics study of DHP107, an oral paclitaxel formulation with once-weekly dosing in mice. Regul. Toxicol. Pharmacol., 103: 196-204.
39. Panis, C., R. Binato, S. Correa, V.J. Victorino and V. Dias-Alves *et al*., 2017. Short infusion of paclitaxel imbalances plasmatic lipid metabolism and correlates with cardiac markers of acute damage in patients with breast cancer. Cancer Chemother. Pharmacol., 80: 469-478.
40. Choi, U.K., O.H. Lee, J.H. Yim, C.W. Cho, Y.K. Rhee, S.I. Lim and Y.C. Kim, 2010. Hypolipidemic and antioxidant effects of dandelion (*Taraxacum officinale*) Root and Leaf on Cholesterol-Fed Rabbits. Int. J. Mol. Sci., 11: 67-78.