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Antidote to Cyclophosphamide-Induced Myelosuppression: The Vitex doniana leaf Effect

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Abstract: *Myelosuppression is a common side effect with the use of cyclophosphamide in the treatment of several malignancies. It results in anaemia, leukopenia, thromobcytopenia and decrease in other blood parameters. This has a limiting effect on use of cyclophosphamide, as fesolate has not been able to overcome this problem. And many clinicians now result to blood transfusion to help bring the blood parameters to an acceptable level before cyclophosphamide is used. Twenty (20) Wistar rats were used for this experiment. The rats were divided into 5 groups, with 4 rats in each group. Group 1 was control; groups 2-5 were treated with 100mg/Kg of cyclophosphamide; group 3 and 4 also received 250mg/Kg and 500mg/Kg of extract, respectively, while group 5 received 400mg/Kg of fesolate. There was significant decrease (P<0.05) in the packed cell volume and white blood cell count and number of multinucleated cells in the bone marrow in group 2 when compared with group 1. Group 3, 4 and 5 showed increases in the packed cell volume, white blood cell count and number of multinucleated cells in the bone marrow. This increase was statistically significant (P<0.05)in group 4. Vitex doniana leaf extract has shown to increase the haematological parameters, such as packed cell volume and white blood cell count and number of multinucleated cells in the bone marrow in the presence of cyclophosphamide. This leaf extract can be utilized in clinical practice to prevent the bone marrow suppression and anaemia that follows the administration of cyclophosphamide for treatment of malignancies.*

Keywords:*cyclophosphamide, myelosuppression, vitex doniana, bone marrow, chemotherapy*

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I. Introduction

Myelosuppression is a common side effect of chemotherapeutic agents, which is usually anticipated when these agents are used in the management of malignancies.[1] Myelosuppression may affect the production of neutrophils and platelets, thereby predisposing the patients to increased susceptibility to infection and easy bleeding. These life-threatening potentials of chemotherapeutic agents are seriously affecting their use in cancer therapies, as patients may die of complications of the treatment instead of the disease.

Cyclophosphamide is one of these chemotherapeutic agents. It can be administered as a single agent or used in combination with other therapeutic agents. And can be given orally or as an intravenous medication with a wide range of dosing regimens and usage protocols.[2] Cyclophosphamide can be used in treatment of a variety of malignancies such as leukaemias, lymphomas, breast cancer, multiple myeloma, ovarian cancers, retinoblastoma, neuroblastoma, mycosis fungoides, neuroblastoma.[2] Cyclophosphamide is excreted unchanged in urine and may cause haemorrhagic cystitis.[3] Other adverse effects seen with use of cyclophosphamide include nausea, vomiting, alopecia.[2] Cyclophosphamide and other chemotherapeutic agents are usually not given if the white blood cell count, platelet count and the haemoglobin concentration or packed cell volume are not optimal.[3]

There are several options available to help build up or improve the blood parameters before use of these chemotherapeutic agents. These options include use of haematinics such as Fesolate, Vitamin C and Vitamin E; and blood transfusion, which could be whole blood or blood fractions such as platelet concentrate, granulocyte colony stimulating factor, red cell concentrate and others. In urgent and severe cases of anaemia, these agents may not be able to get the blood level to the required level. They may also not be readily available in resource poor societies.[4] Some plants, such as *Vitex doniana* leaf, have been used traditionally for treatment of anaemia.[5] *Vitex doniana* leaf contains saponins, tannins and alkaloids which may be responsible for its haematinic effect.[6]

II. Materials and Method

Collection of plant material

Fresh leaves of *Vitexdoniana* were obtained from the *Vitexdoniana* tree in Udi, Enugu, Nigeria. It was authenticated by the department of botany, Enugu State University of Science and Technology, Enugu, Nigeria.

Preparation of extract

The leaves were washed with distilled water after removal of the stalks and air-dried under shade at room temperature. Then pulverized to fine powdered form using pestle and mortar. The powdered material was sieved using sieve with little pores to remove the ungrounded fibres.[7] One thousand grams (1000g) of the powdered leaves was extracted exhaustively, each time. The extract was filtered using Whatman No. 2 filter paper. And then concentrated with rotary evaporator at 40°C and stored in refrigerator at 4°C until use.[8]

Procurement of rats

Twenty(20) male Wistar rats with average weight of 200g were procured from the animal house of the Department of Anatomy, Enugu State University of Science and Technology. The rats were handled according to the guideline of the Committee for the purpose of control and supervision of experiments on Animals, India. The rats were grouped into 5 (1-5). Each group had 4 rats and was placed in separate clean cages in the animal house of the Department of Anatomy, Enugu State University of Science and Technology. They were allowed to acclimatize for two (2) weeks. During this period, they had free access to rat chow and water.

Administration of extract

Group 1 was negative control and was given 1ml Normal saline throughout the period of the experiment.
Group 2 was given cyclophosphamide 100mg/Kg from day 12-14 of the experiment.
Group 3 was given 250mg/Kg of *Vitex doniana* leaf extract from day 1-14 of the experiment.
Group 4 was given 500mg/Kg of *Vitex doniana* leaf extract from day 1-14 of the experiment.
Group 5 was positive control and was give Fesolate tablet at dose of 400mg/Kg.
At the end of the experiment (day 15), the rats were anaesthetized by inhalation of chloroform. Blood samples were then collected from the ophthalmic vein through the medial canthus of the rats, in the entire group. The rats were then sacrificed and the bone marrow aspirated and slide smear made immediately and fixed before further analysis.

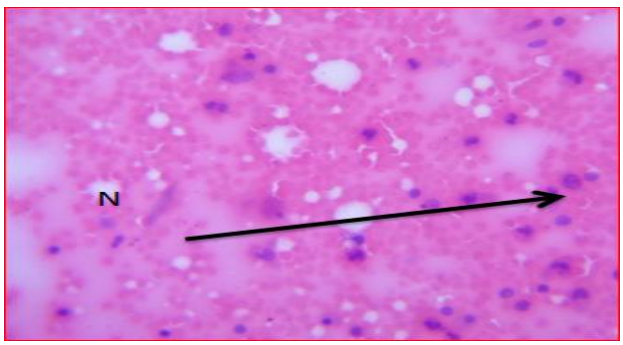
III. Results

Table 1: Result of full blood count

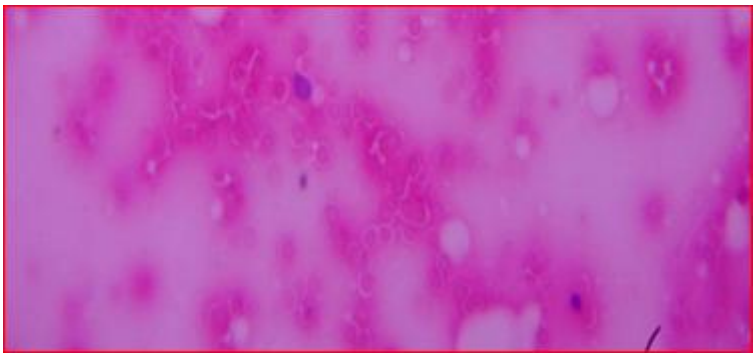
Groups	PCV(%)	WBC($x10^9$/L)	Neutrophils(%)
1	46.50±0.71	7.75±2.12	57.51±2.12
2	20.50±0.70^	4.20±0.00	51.00±.00
3	30.00±7.07^	6.25±1.76	43.50±13.34
4	34.50±0.70*	9.45±2.12*	48.51±9.19
5	36.00±0.00*	7.20±1.41	53.00±4.23

P=0.0039 P=0.0264 P=0.0511

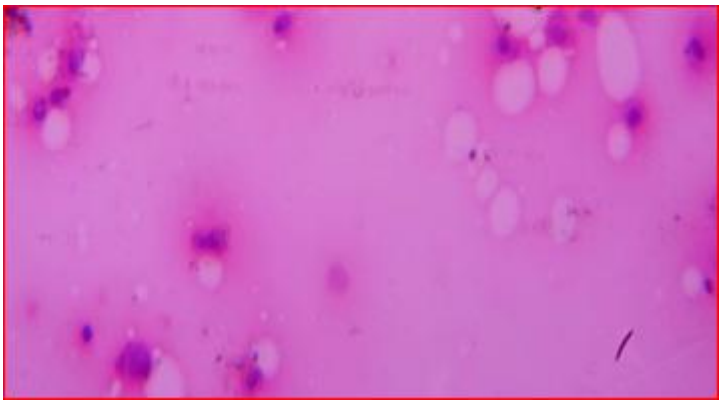
Values are expressed as Mean± SD. where ^P<0.05 showed a significant difference compared to group A and *P<0.05 showed a significant difference compared to groups B, C,F while values without superscript shows no significant difference (P>0.05) using One– way ANOVA with Tukey HSD test for multiple comparison



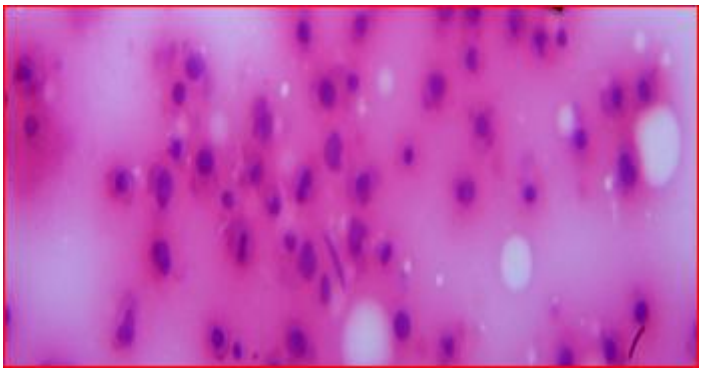
Group 1: received 1ml of normal saline



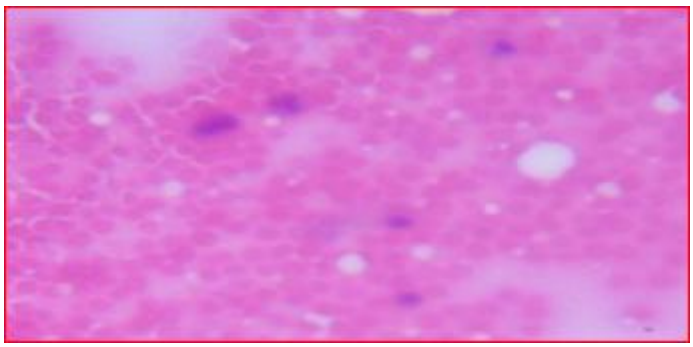
Group 2: treated with cyclophosphamide 100mg/Kg



Group 3: low dose Vitex doniana with cyclophosphamide



Group 4: high dose Vitex doniana with cyclophosphamide



Group 5: Fesolate with cyclophosphamide

IV. Discussion

This study buttressed the fact that cyclophosphamide causes bone marrow suppression[9] as evidenced by the reduction in the packed cell volume and white blood cell count of the experimental animals. Huyan et. al. and Tahoun et. al. also got similar results in their experiments.[10,11]The decreases in the packed cell volume and the white blood cell count were statistically significant ($P<0.05$). The bone marrow histology also showed reduction in the number of proliferating cells in the groups treated with cyclophosphamide only.

The aqueous leaf extract of *Vitex doniana* protected the bone marrow from the adverse effect of the cyclophosphamide. This is evident in the increasing amount of proliferating cells seen in the histology of the groups treated with graded doses of *Vitex doniana* and cyclophosphamide. The proliferating cells in the group treated with 500mg/Kg of leaf extract of *Vitex doniana* and cyclophosphamide were similar to that of the control.

There were also statistically significant increases in the packed cell volume and the white blood cell count in the groups treated with leaf extract of *Vitex doniana* and cyclophosphamide when compared to the group treated with cyclophosphamide alone. This increase is also significantly more when compared with the group treated with fesolate and cyclophosphamide.

V. Conclusion

Vitex doniana leaf extract has shown to improve the haematological parameters, such as packed cell volume and white blood cell count in the presence of cyclophosphamide. It also improved the number of proliferating cells in the bone marrow. These effects were better than that seen with fesolate. So*Vitex doniana* leaf extract can be utilized in clinical practice where anaemia is one of the factors that limit the effective use of cyclophosphamide in treatment of several organ malignancies.

CONFLICT OF INTEREST

No conflict of interest

References

[1]. Carey PJ. 2003. Drug-induced myelosuppression: diagnosis and management. Drug Saf. 26(10):691-706.

[2]. Hubbard RD, Fidanze S. 2007. Therapeutic areas II: cancer, infectious diseases, inflammation and immunology and dermatology. in Comprehensive Medicinal Chemistry II

[3]. Reynard J, Brewster S, Biers S.2003. Prostate cancer: management of advanced disease-castrate-resistant prostate cancer. Oxford handbook of urology. 3ed. Oxford university press. 358-363.

[4]. Liumbruno G, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. 2009. Recommendations for the transfusion of red blood cells. Blood transfusion. 7(1). 49-64.

[5]. Ukaejiofo EO, Ghasi SI, Okwuosa CN, Neboh EE, Ufelle SA. 2011. Myelo-protective activity of aqueous and methanolic leaf extracts of vitex doniana in cyclophosphamide-induced myelo-suppression in wistar rats. International Journal of Biological & Medical Research. 2(1): 409-414

[6]. Agbafor KN, Nwachukwu N. Phytochemical Analysis and Antioxidant Property of Leaf Extracts of Vitex doniana and Mucunapruriens. 2011. Biochemistry research journal. Volume 11.

[7]. Auwal U, Olanitola SO, Lawan FD, Muhammad A. 2018. Antibacterial Activity of Fractionated Extracts of Carica papaya Leaves and Stem Bark against Clinical Isolates of Methicillin Resistant Staphylococcus aureus (MRSA). Modern application in pharmacy and pharmacology. 1(5): 520-525.

[8]. Alabi OA, Haruna MT, Anokwuru CP, Jegede T, Abia H, Okegbe VU, Babatunde EE. 2012. Comparative studies on antimicrobial properties of extracts of fresh and dried leaves of Carica papaya on clinical bacterial and fungal isolates. Advances in Applied Science Research. 3(5): 3107-3114.

[9]. Lee J, Lim KT. 2013. Protection against cyclophosphamide-induced myelosuppression by ZPDC glycoprotein (24 kDa). Immunol Invest. 42(1):61-80.

[10]. Huyan XH, Lin YP, Gao T, Chen RY, Fan YM. 2011. Immunosuppressive effect of cyclophosphamide on white blood cells and lymphocyte subpopulations from peripheral blood of Balb/cmic. IntImmunopharmacol. 11(9):1293-7.

[11]. Tahoun EA, El- Borai NB, Khalifa HK and El- Gendy H. 2019. Contribution of garlic for improving the cytoprotective effect of mesna against cyclophosphamide toxicity in rats. GSC Biological and Pharmaceutical Sciences, 7(3), 08-20.