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PROTECTIVE EFFECT OF D-PINITOL ISOLATED FROM AERIAL PARTS OF SOYBEAN PLANTS ON HAEMATOLOGICAL PROFILE AGAINST DOXORUBICIN-INDUCED CYTO-TOXICITY IN MICE

Murugesan Sudha [*1] and Thangarasu Vetrichelvan [2]

Department of Pharmacology [1], Department of Pharmaceutical Analysis [2], Adhiparasakthi College of Pharmacy, Melmaruvathur - 603319, Tamil Nadu, India.

Keywords:

D-Pinitol, Doxorubicin, Haematological parameters, Antioxidant effect, Free radical scavenging activity

Correspondence to Author:
Murugesan Sudha

M. Pharm., Ph.D,
Assistant Professor,
Department of Pharmacology,
Adhiparasakthi College of Pharmacy,
Cheyyur Taluk, Kancheepuram District, Kesavarayanpettai,
Melmaruvathur - 603319, Tamil Nadu, India.

E-mail: kaviyasudha7@gmail.com

ABSTRACT: The aim of this research was to examine the protective effect of D-Pinitol on haematological profile against Doxorubicin-induced cytotoxicityin mice. Doxorubicin is a chemotherapeutic agent valuable in treating various cancers regardless of its toxicity to normal cells, including hematopoietic suppression. Oxidative stress and generation of reactive oxygen species appear to be the reason for Doxorubicin-induced cytotoxicity in bone marrow cells. D-Pinitol is a richly available carbohydrate in Soybean plants and it has been shown to possess free radical scavenging activity and antioxidant effect in previous researches. Sixty Swiss Albino mice were divided into ten groups: Control, Doxorubicin (5 mg/kg), D-Pinitol (100 mg/kg, 200 mg/kg, 300 mg/kg and 400 mg/kg) and D-Pinitol (100 mg/kg, 200 mg/kg, 300 mg/kg and 400 mg/kg) + Doxorubicin (5 mg/kg). Blood samples were taken from the mice to determine the blood levels of haematological parameters such as white blood cells, lymphocytes, monocytes, red blood cells, hemoglobin, hematocrit and platelets. The D-Pinitol-only treated groups reported no significant variations in haematological parameters compared to the control group. Theblood levels of haematological parameters were decreased significantly in Doxorubicin alone treated group compared to the control group. In the Doxorubicin and D-Pinitol co-treated groups, D-Pinitol significantly elevated the blood levels of haemato-logical parameters in a dose-dependent manner compared to the Doxorubicin group. Our findings suggested that the D-Pinitolco-treatment with Doxorubicin could effectively alleviate the accompanying Doxorubicin-induced cytotoxicity in bone marrow cells by attenuating oxidative stress and reactive oxygen species production through its antioxidant effect and free radical scavenging activity.

INTRODUCTION: Doxorubicin (DOX) is widely accepted as a potent broad-spectrum chemo-therapeutic agent against different types of tumors. Its medicinal use was restricted because of its potential toxicities, including myelosuppression and cardiac toxicity [1, 2].

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In bone marrow (hematopoietic) cells, the sub-sequent generation of reactive oxygen species (ROS) and the deterioration of endogenous anti-oxidants due to DOX administration can activate the intrinsic apoptotic pathway.

Oxidative stress also tends to play a major role in DOX-induced cytotoxicity in bone marrow cells. Harmful effects of DOX produced due to ROS production and oxidative stress could be alleviated with the usage of antioxidants and free radical scavengers. Antioxidants and free radical scavengers may protect hematopoietic cells by directly inactivating ROS or regulating ROS

signaling involved in genetic expression and attenuating oxidative stress [1, 3]. Hence the treatment of cancer patients can be improved by a novel therapeutic strategy in which one compound having an antioxidant effect and free radical scavenging activity is used to improve DOX's antitumor efficacy while minimizing severe side effects [1, 4]. D-Pinitol is present as a primary carbohydrate in *Glycine max* L. Merr (Soybean) plants [5, 6].

It creates tremendous interest in the worldwide scientific community because of its documented therapeutic benefits such as anti-neoplastic[7], anti-inflammatory [8], anti-diabetic [9], hepatoprotective [10], renal protective [11], immuno-modulatory, preventive of osteoporosis [5] and Alzheimer's disease ameliorative [12], *etc.*

Earlier literature indicated that D-Pinitol is efficient in scavenging free radicals and has antioxidant properties [13, 14]. Nevertheless, its role in the alleviation of complications associated with DOX chemotherapy is not studied.

Since, previous studies indicated that concomitant administration of antioxidant and free radicals scavenger with DOX could reduce the side effects of DOX [15, 16], this study was intended to determine the impact of D-Pinitol on reducing the cytotoxic effect of DOX in bone marrow cells. An Automated hematology analyzer has been used in our study since it has been widely used as an easy, fast and reliable diagnostic method for humans and animals [17].

MATERIALS AND METHODS:

Ethics Statement: The experimental protocol was approved by Institutional Animal Ethics Committee (IAEC), Adhiparasakthi College of Pharmacy (Reg. No. 409/PO/Re/S/01/CPCSEA), and the approval number was APCP/IAEC/2019-2020/1.

Statistical Analysis: Statistical analysis was performed by one way ANOVA method. Values were expressed as mean and for n = 6. All data were analyzed with the GraphPad Prism 8.0.1 software. $P < 0.05$ was considered statistically significant.

Materials Required: Doxorubicin HCL (TCI chemicals, India), D-Pinitol isolated from aerial parts of Soybean (*Glycine max* L. Merr.,) plants, Mindray BC-3000 Auto Hematology Analyzer (Mindray Medical India Private Limited, India), Diluting fluid (CELLPACK DCL, Sysmex, India).

Methodology: Swiss Albino Mice (Sex: Male and Female; Weight: 25–30 g) were housed in cages and were kept on a 12 h light/dark cycle. Before the commencement of the study, the animals were acclimatized in cages maintained in a clean and controlled environment based on CPCSEA guidelines [18].

Treatment: Ten groups of animals, each comprised of six mice, were taken for the study. Animals were treated with D-Pinitol for fifteen consecutive days and Doxorubicin for three days (on 1st day, 8th day and 15th day) [21] as per the treatment protocol. Haematological parameters (white blood cells, lymphocytes, monocytes, red blood cells, hemoglobin, hematocrit and platelets) were analysed before the treatment (day 1) and following the treatment (day 15) in an Automated Hematology Analyzer. 20 µl of blood sample was taken from the tail vein of each mouse by making a slight incision in the tail with the scalpel blade. Then blood was poured into an EDTA coated tube and was mixed gently. Then, 500 µl of diluents was added to the 20 µl of well-mixed whole blood sample. The blood was thoroughly mixed with diluting fluid using a pipette.

TABLE 1: TREATMENT PROTOCOL

Groups	Treatment
I	0.5 ml of 0.9% normal saline daily (Vehicle Control)
II	Doxorubicin (5 mg/kg), i.p. on 1st, 8thand 15th days (Positive Control)
III	D-Pinitol (100 mg/kg), p.o. daily
IV	D-Pinitol (200 mg/kg), p.o. daily
V	D-Pinitol (300 mg/kg), p.o. daily
VI	D-Pinitol (400 mg/kg), p.o. daily
VII	Doxorubicin (5 mg/kg), i.p. on 1st, 8thand 15th days +D-Pinitol (100 mg/kg), p.o. daily
VIII	Doxorubicin (5 mg/kg), i.p. on 1st, 8thand 15th days +D-Pinitol (200 mg/kg), p.o. daily
IX	Doxorubicin (5 mg/kg), i.p. on 1st, 8thand 15th days +D-Pinitol (300 mg/kg), p.o. daily
X	Doxorubicin (5 mg/kg), i.p. on 1st, 8thand 15th days +D-Pinitol (400 mg/kg), p.o. daily

Selection of doses of Doxorubicin and D-Pinitol were based on Hajra *et al.,* and Navarro *et al.,* respectively.

The analyzer was set ready for analysis of the blood. Pre-dilution mode was selected in the analyzer. The tube was set to the sample probe. The start button was switched on.

After the buzzer sound heard and the screen of the analyzer displayed 'analysing', the tube was removed from the probe. When the screen showed 'Ready', the next sample was prepared, and the same procedure was repeated. The samples should be run within 30 minutes of dilution; otherwise, the samples will be clumped and lead to erroneous results [22].

RESULTS AND DISCUSSION: The effects of D-Pinitol pretreatment on the haematological parameters (white blood cells, lymphocytes, monocytes, red blood cells, hemoglobin, hematocrit and platelets) of mice after exposure to DOX were represented in the tables and figures **Table 2, 3, 4, 5, 6, 7** & **8** and **Fig. 1, 2, 3, 4, 5, 6** & **7**). All groups of animals expressed normal values for all haematological parameters on day 1 (before treatment).

TABLE 2: PROTECTIVE EFFECT OF D-PINITOL ON WHITE BLOOD CELLS OF DIFFERENT GROUPS OF MICE EXPOSED TO DOX

Day	White Blood Cells (10^3/µl)									
	Group I (Control-0.9% Normal saline)	Dose in mg/kg								
		Group II (DOX 5)	Group III (D-P 100)	Group IV (D-P200)	Group V (D-P 300)	Group VI (D-P 400)	Group VII (DOX 5+ D-P 100)	GroupVII (DOX5+D-P 200)	Group IX(DOX 5+ D-P 300)	Group X (DOX 5+ D-P 400)
Day 1	8.5± 0.103	8.7± 0.063	8.317± 0.204	8.65± 0.327	8.417± 0.162	8.783± 0.236	8.267± 0.178	8.833± 0.23	8.85± 0.067	8.817± 0.168
Day 15	9.217± 0.174	2.717± 0.26 ^{a*}	9.067± 0.173^{aNS}	8.95± 0.169^{aNS}	8.883± 0.232^{aNS}	8.617± 0.158^{aNS}	3.55± 0.159$^{a*b@}$	5.383± 0.185^{a*b*}	6.717± 0.218 ^{a*b*}	8.133± 0.105 $^{a\#b*}$

Abbreviation: DOX – Doxorubicin; D-P – D-Pinitol. Mean ± SEM, n=6, where, a- Group II, III, IV, V, VI, VII, VIII, IX & X compared with Group I. b- Group VII, VIII, IX & X compared with Group II. * P < 0.001, # P < 0.01 &@ P < 0.05.

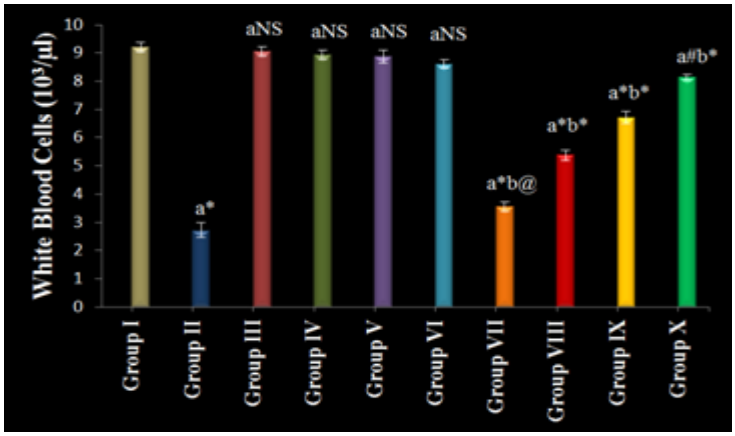

FIG. 1: HISTOGRAM - PROTECTIVE EFFECT OF D-PINITOL ON WBC OF MICE EXPOSED TO DOX

TABLE 3: PROTECTIVE EFFECT OF D-PINITOL ON LYMPHOCYTES OF DIFFERENT GROUPS OF MICE EXPOSED TO DOX

Day	Lymphocytes (10^3/µl)									
	Group I (Control-0.9% Normal saline)	Dose in mg/kg								
		Group II (DOX 5)	Group III (D-P 100)	Group IV (D-P 200)	Group V (D-P 300)	Group VI (D-P 400)	Group VII (DOX 5+D-P 100)	Group VIII (DOX 5+ D-P 200)	Group IX(DOX 5+D-P 300)	Group X (DOX 5+ D-P 400)
Day 1	6.717± 0.185	6.683± 0.114	6.533± 0.223	6.683± 0.196	6.567± 0.186	6.117± 0.182	6.717± 0.221	6.6± 0.248	6.733± 0.163	6.58± 0.221
Day 15	5.833± 0.171	1.8± 0.058 ^{a*}	5.9± 0.285 ^{aNS}	6.067± 0.461 ^{aNS}	6.267± 0.38 ^{aNS}	6.233± 0.131 ^{aNS}	2.633± 0.163 $^{a*b\#}$	3.433± 0.263 ^{a*b*}	4.483± 0.192 ^{a*b*}	4.933± 0.184 $^{a\#b*}$

Abbreviation: DOX – Doxorubicin; D-P – D-Pinitol. Mean ± SEM, n=6, where, a- Group II, III, IV, V, VI, VII, VIII, IX & X compared with Group I. b- Group VII, VIII, IX & X compared with Group II. * P < 0.001, # P < 0.01 &@ P < 0.05.

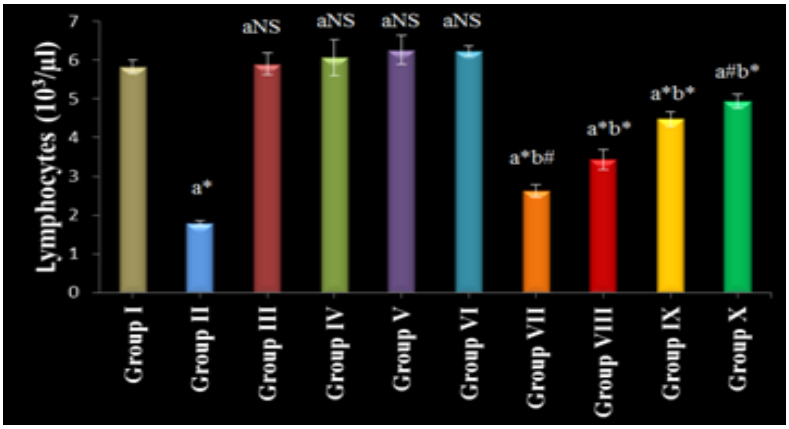

FIG. 2: HISTOGRAM-PROTECTIVE EFFECT OF D-PINITOL ON LYMPHOCYTES OF MICE EXPOSED TO DOX

TABLE 4: PROTECTIVE EFFECT OF D-PINITOL ON MONOCYTES OF DIFFERENT GROUPS OF MICE EXPOSED TO DOX

Day	Monocytes (10^3/µl)									
	Group I (Control-0.9% Normal saline)	Dose in mg/kg								
		Group II (DOX 5)	Group III (D-P 100)	Group IV (D-P 200)	Group V (D-P 300)	Group VI (D-P 400)	GroupVII (DOX 5+ D-P 100)	Group VIII (DOX 5+D-P 200)	Group IX(DOX 5+ D-P 300)	Group X (DOX 5+ D-P 400)
Day 1	0.74± 0.019	0.69± 0.024	0.68± 0.015	0.71± 0.018	0.73± 0.017	0.69± 0.026	0.72± 0.025	0.66± 0.015	0.74± 0.022	0.683± 0.031
Day 15	0.578± 0.023	0.178± 0.01 ^{a*}	0.565± 0.038 ^{aNS}	0.553± 0.014 ^{aNS}	0.557± 0.028 ^{aNS}	0.542± 0.028 ^{aNS}	0.247± 0.014 $^{a*b@}$	0.347± 0.014 ^{a*b*}	0.433± 0.014 ^{a*b*}	0.507± 0.016 $^{a@b*}$

Abbreviation: DOX – Doxorubicin; D-P – D-Pinitol. Mean ± SEM, n=6, where, a- Group II, III, IV, V, VI, VII, VIII, IX & X compared with Group I. b- Group VII, VIII, IX & X compared with Group II. * P < 0.001, # P < 0.01 &@ P < 0.05.

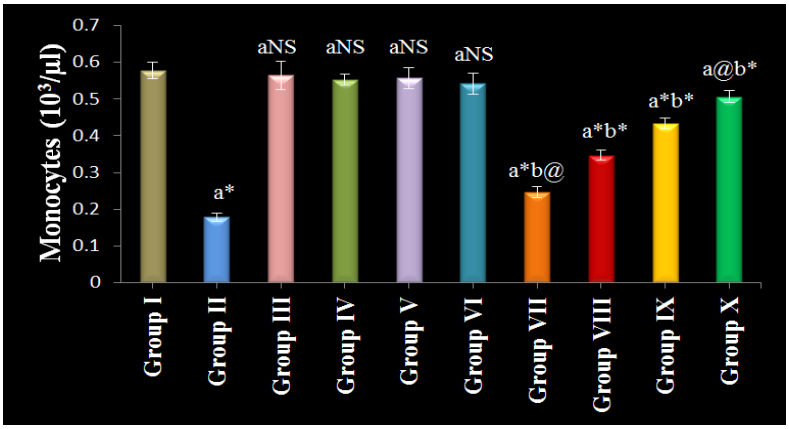

FIG. 3: HISTOGRAM - PROTECTIVE EFFECT OF D-PINITOL ON MONOCYTES OF MICE EXPOSED TO DOX

TABLE 5: PROTECTIVE EFFECT OF D-PINITOL ON RED BLOOD CELLS OF DIFFERENT GROUPS OF MICE EXPOSED TO DOX

Day	Red Blood Cells (10^6/µl)									
	Group I (Control-0.9% Normal saline)	Dose in mg/kg								
		Group II (DOX 5)	Group III (D-P 100)	Group IV (D-P 200)	Group V (D-P 300)	Group VI (D-P 400)	Group VII (DOX 5+D-P 100)	Group VIII (DOX 5+D-P 200)	Group IX (DOX 5+ D-P 300)	Group X (DOX 5+ D-P 400)
Day 1	7.21± 0.082	7.575± 0.323	7.033± 0.136	7.217± 0.318	7.875± 0.25	7.217± 0.098	7.35± 0.043	7.8± 0.271	7.717± 0.209	7.783± 0.229
Day 15	7.25± 0.096	4.817± 0.151 ^{a*}	7.167± 0.178 ^{aNS}	7.383± 0.343 ^{aNS}	7.217± 0.122 ^{aNS}	7.117± 0.13 ^{aNS}	5.65± 0.188 $^{a*b\#}$	6.533± 0.238 $^{a@b*}$	7.017± 0.178 ^{aNSb*}	7.133± 0.131 ^{aNSb*}

Abbreviation: DOX – Doxorubicin; D-P – D-Pinitol. Mean ± SEM, n=6, where, a- Group II, III, IV, V, VI, VII, VIII, IX & X compared with Group I. b- Group VII, VIII, IX & X compared with Group II. * P < 0.001, # P < 0.01 &@ P < 0.05.

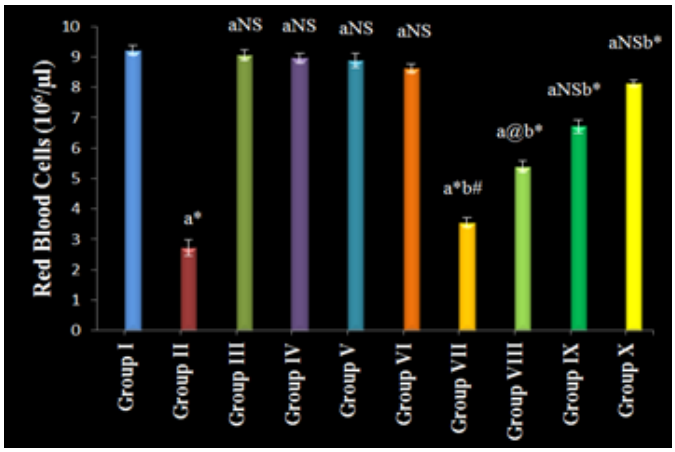

FIG. 4: HISTOGRAM - PROTECTIVE EFFECT OF D-PINITOL ON RBC OF MICE EXPOSED TO DOX

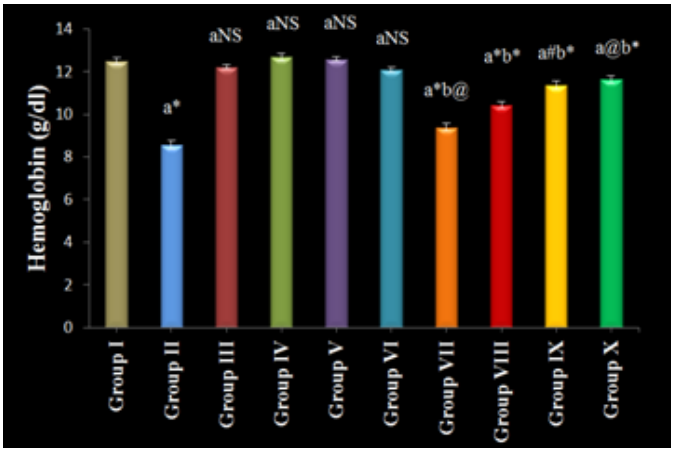

FIG. 5: HISTOGRAM - PROTECTIVE EFFECT OF D-PINITOL ON HEMOGLOBIN OF MICE EXPOSED TO DOX

TABLE 6: PROTECTIVE EFFECT OF D-PINITOL ON HEMOGLOBIN OF DIFFERENT GROUPS OF MICE EXPOSED TO DOX

Day	Hemoglobin (G/Dl)									
	Group I (Control-0.9% Normal saline)	Dose in mg/kg								
		Group II (DOX 5)	Group III (D-P 100)	Group IV (D-P 200)	Group V (D-P 300)	Group VI (D-P 400)	Group VII (DOX 5+D-P 100)	Group VIII (DOX 5+ D-P 200)	Group IX (DOX 5+D-P 300)	Group X (DOX 5+D-P 400)
Day 1	12.1± 0.106	12.48± 0.152	11.58± 0.176	12.6± 0.171	12.35± 0.118	12.15± 0.141	12.17± 0.273	13.08± 0.164	13± 0.086	13.12± 0.146
Day 15	12.48± 0.154	8.567± 0.198 a*	12.23± 0.115 aNS	12.68± 0.178 aNS	12.6± 0.106 aNS	12.08± 0.122 aNS	9.4± 0.186 a*b@	10.42± 0.158 a*b*	11.35± 0.193 a#b*	11.63± 0.189 a@b*

Abbreviation: DOX – Doxorubicin; D-P – D-Pinitol. Mean ± SEM, n=6, where, a- Group II, III, IV, V, VI, VII, VIII, IX & X compared with Group I. b- Group VII, VIII, IX & X compared with Group II. * P < 0.001, # P < 0.01 &@ P < 0.05.

TABLE 7: PROTECTIVE EFFECT OF D-PINITOL ON HEMATOCRIT (HCT) OF DIFFERENT GROUPS OF MICE EXPOSED TO DOX

Day	HCT %								
	Group I (Control-0.9% Normal saline)	Dose in mg/kg							
		Group II (DOX 5)	Group III (D-P 100)	Group IV (D-P 200)	Group V (D-P 300)	Group VI (D-P 400)	Group VII (DOX 5+D-P 100)	Group VIII (DOX 5+D-P 200)	Group IX (DOX 5+ D-P 300)	Group X (DOX 5+D-P 400)
Day 1	39.27± 0.204	41.32± 0.375	38.18± 0.397	39.05± 0.148	40.08± 0.209	39.22± 0.328	39.68± 0.416	42.17± 0.33	41.82± 0.348	42.08± 0.151
Day 15	45.08± 0.335	26.32± 0.367 a*	45.57± 2.157 aNS	44.3± 1.751 aNS	44.53± 1.77 aNS	44.17± 1.922 aNS	29.03± 0.894 a*b@	33.17± 0.209 a*b*	35.33± 0.268 a*b*	37.4± 0.258 a*b*

Abbreviation: DOX – Doxorubicin; D-P – D-Pinitol. Mean ± SEM, n=6, where, a- Group II, III, IV, V, VI, VII, VIII, IX & X compared with Group I. b- Group VII, VIII, IX & X compared with Group II. * P < 0.001, # P < 0.01 &@ P < 0.05.

TABLE 8: PROTECTIVE EFFECT OF D-PINITOL ON PLATELETS OF DIFFERENT GROUPS OF MICE EXPOSED TO DOX

Day	Platelets (10^3/µl)									
	Group I (Control-0.9% Normal saline)	Dose in mg/kg								
		Group II (DOX 5)	Group III (D-P 100)	Group IV (D-P 200)	Group V (D-P 300)	Group VI (D-P 400)	Group VII (DOX 5+D-P 100)	Group VIII (DOX 5+D-P 200)	Group IX(DOX 5+D-P 300)	Group X (DOX 5+D-P 400)
Day 1	506.3± 7.645	499.5± 6.329	485± 7.933	510.5± 7.961	518.2± 12.72	501.5± 11.25	512.2± 10.53	496.5± 7.36	502.3± 13.65	506.7± 5.358
Day 15	525.7± 10.57	296.2± 5.907 a*	527.7± 16.04 aNS	523.8± 7.139 aNS	530.2± 7.812 aNS	527.2± 2.762 aNS	347.2± 8.412 a*b#	353.8± 7.613 a*b*	370.7± 9.175 a*b*	417.7± 10.56 a*b*

Abbreviation: DOX – Doxorubicin; D-P – D-Pinitol. Mean ± SEM, n=6, where, a- Group II, III, IV, V, VI, VII, VIII, IX & X compared with Group I. b- Group VII, VIII, IX & X compared with Group II. * P < 0.001, # P < 0.01 &@ P < 0.05.

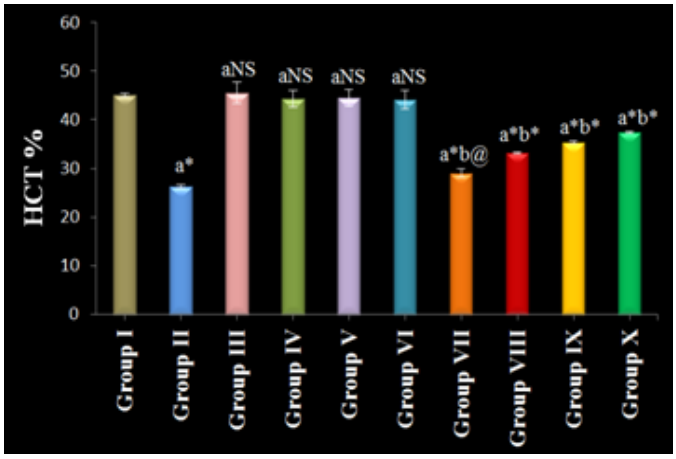

FIG. 6: HISTOGRAM - PROTECTIVE EFFECT OF D-PINITOL ON HEMATOCRIT OF MICE EXPOSED TO DOX

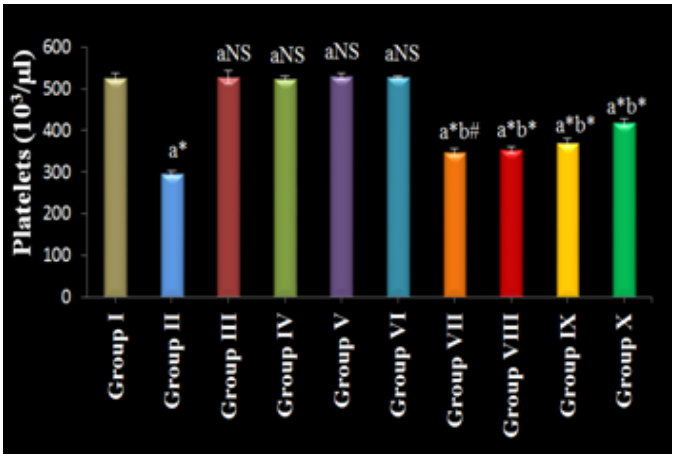

FIG. 7: HISTOGRAM - PROTECTIVE EFFECT OF D-PINITOL ON PLATELETS OF MICE EXPOSED TO DOX

Our findings showed that after 15 days of treatment, D-Pinitol had no marked effects on haematological parameters in the D-Pinitol-only treated groups compared to the control group. DOX (5 mg/kg) significantly ($p<0.001$) reduced the levels of the haematological parameters (white blood cells, lymphocytes, monocytes, red blood cells, hemoglobin, hematocrit and platelets) compared to the control animals. However, in the DOX and D-Pinitol co-treated groups, D-Pinitol (100 mg/kg, 200mg/kg, 300 mg/kg and 400 mg/kg) restored the blood levels of haematological parameters to a greater degree in a dose-dependent manner ($P<0.001$, compared with DOX group). Hence our results confirmed that DOX treatment caused an abnormal decrease in the blood levels of haematological parameters, but pretreatment of D-Pinitol with DOX resulted in a restoration of those levels to normal. In prior findings, it was concluded that DOX administration has resulted in recurrent and severe cardio toxicity and bone marrow suppression [1, 2].

Peripheral Cytopenia resulting from hematopoietic suppression is recurrent dose-limiting side effect of DOX. DOX-induced cytotoxicity in bone marrow cells inhibits the function of proliferating hematopoietic precursor cells, leading to deprivation of formed elements. These toxicities of DOX contribute to decreased patient's quality of life [23]. It is generally recognized that oxidative stress and the production of free radicals may serve as an essential role in the mechanism of DOX-induced cytotoxicity in bone marrowcells [1, 4]. As a result, a non-toxic 'regimen' having an antioxidant effect and free radical scavenging activity with improving the effectiveness of DOX without increasing its toxic effect is expected to enhance the treatment of cancer patients [15, 16]. Haemato-logical parameters were analysed in an Automated Hematology Analyzer using peripheral blood of mice to know the ability of D-Pinitol in the prevention of DOX-induced cytotoxicity in bone marrow cells. Our studies have confirmed the protective effect of D-Pinitol against DOX-induced cytotoxicity in bone marrow cells by restoring the abnormal blood levels of haematological parameters due to DOX to the normal levels. It could be correlated mainly with the role of D-Pinitol as a free radical scavenger and an antioxidant [13, 14]. The data revealed that the use of D-Pinitol with DOX could strengthen the therapeutic effect by reducing its cytotoxicity.

CONCLUSION: In this study, it was observed that D-Pinitol (100 mg/kg, 200 mg/kg, 300 mg/kg, and 400 mg/kg) co-treated with DOX (5 mg/kg) restoredthe suppressed blood levels of white blood cells, lymphocytes, monocytes, red blood cells, hemoglobin, hematocrit and platelets due to DOX administration to normal blood levels. The protective role of D-Pinitol may be due to its antioxidant effect and free radicals scavenging activity. The co-administration of D-Pinitol with DOX has the merits of enhancing the prognosis of DOX chemotherapy.

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