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Effects of *Trema orientalis* Leaves Extract on Hematological Parameters of Cadmium Induced Toxicity in Wistar Rats

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Abstract: *The effect of T. orientalis on the hematological parameters of cadmium induced toxicity in rats was investigated in order to ascertain the ameliorative potential of the extract on the toxic effect of cadmium on blood cells. One hundred and five male rats were randomly grouped into five (A, B, C, D and E) such that group A (control) was administered distilled water while 10 mg kg^{-1} body weight of cadmium was administered orally to group B. Rats in group C were given oral administration of the extract (100mg/kg body weight) while 10mg/kg body weight of cadmium was administered toboth D and E followed by orally administration of the plant extract at 100 mg kg^{-1}body weight to D and 200 mg kg^{-1} body weight to group E. Some hematological parameters of the experimental animals were evaluated after 3, 5, 10, 15 and 21 daily doses. Cadmium significantly decrease ($p < 0.05$) the hematological parameters (Hemoglobin, RBC, PCV, WBC, MCH, Platelet and MCV) evaluated in this study. The methanolic leaf extract of T. orientalis administered significantly ($p < 0.05$) increased the levels of hemoglobin, RBC, PCV, WBC, MCH, platelet and MCV as compared to cadmium untreated group. The levels of PCV, RBC and MCV was increased above the control value, whereas, hemoglobin, WBC, MCH and platelet were close to the control values. The co-administration of cadmium and the extract of T. orientalis at doses of 100 mg kg^{-1} and 200 mg kg^{-1} significantly ($p < 0.05$) increased the levels of the hematological parameters. The observed increase showed a concentration dependent trend. The hemato-protective property of this extract may be due to the phytochemical constituents of the leaves which consist of blood enriching minerals such as Fe, K, Na, P and Ca. Also Trema orientalis has a hematopoietic effect in rats administered with its extract.T. orientalis leaves possess both hematoprotective and hematopoietic property. These therefore support the established folkloric use of the plant in anemic conditions. Furthermore, the methanolic leaf extract of T. orientalis may be beneficial in the management of hematological conditions.*

Keyword: *Cadmium, T. orientalis, Toxicity, hematological parameters and Rats.*

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I. Introduction

Cadmium is a hazardous and toxic heavy metal that produces severe noxious health issues in humans (Jarup*et al*., 1998; ATSDR, 2008; Singh *et al*., 2010).Cadmium as non-essential heavy metal causes oxidative stress, and also was found to generate free radicals according to (Wang *et al*., 2014;Ojo*et al*., 2014). The atmospheric composition of Cd could be through mining and smelting operations, fuel combustion (Zhang *et al*., 2012; Chen *et al*., 2014), burning of wastes from municipal, sludge from sewage (Edwards *et al*., 2013), and the application of phosphate fertilizer (Gill *et al*., 2013). Humans can obtain Cd from crops, leaves of vegetables and tobacco (Fan *et al*., 2009; Garcı´a- Esquinas*et al*., 2014), soil (Guo and Zhou, 2006), and fruits and oily seeds (Schwarz *et al*., 2014). On exposure, Cadmium enters the blood where it binds to the erythrocytic membrane and stimulates the formation of metallothioneins and reactive oxygen species (ROS) leading to alterations in the antioxidant system and causing oxidative damage in red blood cells (RBCs). Therefore, cadmium is known to induce anemia, reduce the RBCs count, hematocrit value as well as hemoglobin concentration(McCarty, 2012). The most common strategies employed in the management of heavy metal toxicity is chelation therapy which improve metal excretion. However, it is reported that chelators for cadmium toxicity generate concerns bordering on side-effect and efficacy (McCarty, 2012). So far, there is no approved chelation therapy protocol for cadmium toxicity (McCarty, 2012). In the light of the above reasons there is an upsurge in research on the use of nutrients and phytochemicals in the management of heavy metal toxicity. *Trema orientalis* also known as Celtisorientalis Linn, Celtisguineensis or Sponiaorientalis Linn is of the family of Ulmacceae.The plant in Nigeria major native languages are known as Telemukwu by the Igbos, Ajeanaby the Hauses and Afefe by the Yorubas (Akin *et al*., 2014), and the Igalas in the North-Central part of Nigeria called it Afofo. The plant has common names such as pigeon wood, charcoal tree, Indian charcoal tree, gunpowder tree. It has a near universal distribution across the world. The aerial parts, flowers, bark, and seeds of *T. orientalis*

exhibit various pharmacologicalactivities including laxativity, hypoglycemic, anti-pyretic, analgesic, anti-microbial properties, anticonvulsant, and anti-plasmodial activity. These effects may be mainly due to the fact that it contains important biologically active compounds (Adinortey*et al*., 2013). Angasa*et al*., (2011) reported that the leaves contain flavonoid and as well possesses antiradical and iron chelating activities. The ameliorative effects of the extract on hematological indices in cadmium induced toxicity have not been reported. Considering the fact that on a daily bases man is exposed to a variety of dangerous chemicals that induce intoxication in the system, this study was designed to investigate the effects of methanol leaves extract of *Trema orientalis*on hematological parameters in rats exposed to cadmium.

II. Materials And Methods

Plant Materials

Fresh leaves of *Tremaorientalis* was collected from the premises of Kogi State University, Anyigba, Nigeria, and the plant was thereafter identified in the Department of Biological Sciences, Kogi State University and the voucher specimen was deposited in the department's herbarium with voucher no. 31,285.

Animals

One hundred and five (105) male Wistar rats weighing between 180 ± 10.00g were used in the experiment. The Wistar rats were purchased from the Breeding and Care Facility of the Kogi State University, Anyigba Nigeria: where this study took place. The animals were kept in standard aluminum cage at the animal house under a strict compliance with the guide for animal research, as detailed in NIH, (1992) Guidelines for the Care and Use of Laboratory Animals. Animals were fed ad libitum with commercially formulated pelletized rat feed (T.J Top Feed Ltd, Port Harcourt, Nigeria) and water under a natural light/dark cycle. The animals were allowed to acclimatize in the standard aluminum cage for 2 weeks before the commencement of the study as to allow for adaptation of life in the cage.

Chemicals

$CdCl_2$(source of cadmium) is product of Sigma-Aldrich (Germany) while Methanol is product of BDH (England). All other chemical used are of analytical grade.

Preparation of *Tremaorientalis*Leave Extract

The method described by Trono *et al*, (2016) was adopted. The leaves were cleaned; air dried at room temperature for three (3) weeks and was pulverised using blender (Super Master Co., Ltd, Osaka, Japan). The methanol extract of *Tremaorientalis*was prepared using235g of the powdered leaves soaked in 705ml of 80% (1:3 w/v) methanol for 72 hours while it was stirred intermittently. The combined extract was filtered through a vacuum filter using Whatman No.1 filter paper. The resulting solution was subjected to heat using water bath heater at 55°C to give 48.2g yield of the crude extract corresponding to a percentage yield of 20.5%.

Induction of Experimental Animals

Cadmium was dissolved in distilled water and orally given to the rats at a dose of 10 $mgkg^{-1}$ body weight (Al-Hashem*et al*., 2009). The *Tremaorientalis*extract administered orally was reconstituted in distilled water to give the desired doses of 100 and 200 mg kg^{-1} body weight used in the animal study. 1ml of both the chemical substance and extract were administered appropriately

Animal Grouping and Preparation of Blood Sample

One hundred and five(105) Wistar rats were completely randomized into 5 groups of A-E made up of the control (n = 5) group and four treatment groups (where n = 25 each). Animals in group A which served as the control group were orally administered distilled water, whereas 10 mg Cd/kg body weight was orally administered to group B, D and E followed by orally administration of methanol extract of *Tremaorientalis*leave to group C, D (100 mg kg^{-1} body weight) and group E (200 mg kg^{-1} body weight). Five rats each from group B, C, D and E were sacrificed 24 hours after 3, 5, 10, 15 and21 daily doses of administration. However, the remaining 5 rats in group A (control) were sacrificed 24hours after the last administration. For each day of the sacrifice the rats were placed in a glass jar containing cotton wool soaked in diethyl ether after which the jugular veins was cut with sharp sterile scalpel for blood collection. Blood was collected into dry clean bottles containing anticoagulant for haematological analysis.

Hematological Analysis

The method described by Baker and Silver, (1985) was used in the determination of the hematological parameters using Automated Hematologic Analyzer (Sysmex kox1: SysmexHaematology System, Model KX-21W, Corporation, Japan) to count the following hematological parameters: red blood cell (RBC), white blood

cell (WBC), packed cell volume (PCV), hemoglobin (Hb), the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and Platelet.

Statistical Analysis

The results are expressed as mean ±SEM, for each analysis significant differences was determined by Analysis of Variance (ANOVA) and Dunnett's Post Hoc test for multiple comparisons at 95% confidence level using SPSS software (SPSS Inc., Chicago, USA).

III. Results

There was significant decrease ($p < 0.05$) in the levels of hematological parameters in cadmium exposed animals as compared to the control **(Table 1).** However, no significant difference ($p > 0.05$) was observed between the control animals and extract treated animals. Across the days of administration progressive decrease of haemoglobin concentration was observed till the last day of the experimental period in the cadmium exposed group (Table 1).

The extract alone did not significantly ($p > 0.05$) affect the concentration of haemoglobin in the blood of the animals throughout administration as compared to the control animals (Table 1). Inversely, the combined administration of 10 mg kg^{-1} body weight of cadmium and the extract at the dosage of 100 mg kg^{-1} body weight showed significant difference ($p < 0.05$) following 3rd, 5th and 10th doses in comparison to the cadmium exposed group. However, following 15th and 21st doses of the administration the remedial effect of the extract had good result which compared well with the control. Similarly, at the administration of 10 mg kg^{-1} body weight of Cd and the extract at 200 mg kg^{-1} body weight, there was significant ($p < 0.05$) increase in the concentration of haemoglobin following the administration of the extract (Table 1).

Table 1. Effect of Methanol leaf extract of *T. orientalis*on haemoglobin concentration of Cadmium exposed Albino rats

Day	HGB (g/dL)				
	3	5	10	15	21
Group					
A	15.31± 0.39[a]	15.31± 0.39[a]	15.31± 0.39[a]	15.31± 0.39[a]	15.31± 0.39[a]
B	11.03 ± 0.05[b]	10.18 ± 0.39[b]	9.84 ± 0.40[c]	9.43 ± 0.11[c]	8.99 ± 0.55[c]
C	13.41 ± 0.39[a]	13.69 ± 0.58[a]	13.99 ± 1.47[a]	14.12 ± 0.69[a]	14.54 ± 0.46[a]
D	11.94 ± 0.41[b]	11.07 ± 0.67[b]	12.95 ± 1.46[b]	13.77 ± 1.02[a]	14.56 ± 0.46[a]
E	15.03 ± 0.95[a]	11.60 ± 0.42[b]	13.85 ± 0.71[a]	14.91 ± 0.36[a]	15.53 ± 0.49[a]

Data are mean ± SEM of five replicates. Test values with superscripts different from the control *a* for each parameter are significantly ($p < 0.05$) different.

The increase became manifested immediately after the 3rd dose of the extract, however, at 5th dose the haemoglobin concentration fluctuate in pattern but became consistent from 10th dose to the last day of the experimental period. Furthermore, the concentration of haemoglobin in the blood of extract dosed animals compared well with the control at the 21st dose (Table 1).

There was significant ($p < 0.05$) decrease in the RBC level following the exposure of the experimental animals to cadmium. This was observed from the very first exposure (Table 2), by which the RBC level had decreased by 50% as compare to the control group. There was a steady increase in the level of RBC in combined administration of cadmium with extract (100 mg kg^{-1} and 200 mg kg^{-1}) treated groups till the last day of the experiment when it compared favourablywith the control group (Table 2).

Similarly, significant ($p < 0.05$) decrease was observed in the level of PCV and WBC following the exposure of the experimental animals to cadmium, as compared to the control group. The effect manifest on the PCV immediately following the first exposure to cadmium, whereas, the effect manifest in the WBC after the 5th administration and the trends continued till the last day of experiment (Table 3 and 4). In contrast, the administration of extract (100 mg kg^{-1} and 200 mg kg^{-1} body weight) with cadmium, did not significantly ($p > 0.05$) alter PCV level at first dose compared to cadmium exposed group, but in subsequent doses effect of extract was manifested in the significant ($p > 0.05$) increase of PCVlevel, with the extract group comparing well with the control at the end of the experimental period (Table 3).

There was no significantdifference ($p > 0.05$) in the level of MCH in the cadmium exposed rats until after the 15th dose (Table 5). The exposure to cadmium as well as the administration of extract (100 mg kg^{-1} and 200 mg kg^{-1} body weight) showed its effect immediately after administration, and the trend of significant ($p < 0.05$) increase continues to the end of the experimental period (Table 5).

Table 2. Effect of Methanol leaf extract of *T. orientalis*on Red Blood Cell of Cadmium exposed Albino rats

RBC ($x10^6/\mu L$)					
Day	**3**	**5**	**10**	**15**	**21**
Group					
A	5.65 ± 0.31^a	5.65 ± 0.31^a	5.65 ± 0.31^a	5.65 ± 0.31^a	5.65 ± 0.31^a
B	2.72 ± 0.21^c	2.55 ± 0.59^c	2.27 ± 0.23^c	2.21 ± 0.11^c	1.99 ± 0.07^c
C	4.77 ± 0.25^a	4.67 ± 0.13^a	4.67 ± 0.29^a	5.76 ± 0.39^a	5.67 ± 0.31^a
D	3.92 ± 0.30^b	3.40 ± 0.34^b	3.99 ± 0.41^b	3.86 ± 0.73^b	4.88 ± 0.31^a
E	4.83 ± 0.57^a	4.37 ± 0.06^b	4.61 ± 0.45^a	4.55 ± 0.06^a	4.93 ± 0.09^a

Data are mean ± SEM of five replicates. Test values with superscripts different from the control *a* for each parameter are significantly ($p < 0.05$) different.

Also, at first exposure to cadmium the MCV and platelet counts of the experimental animals significantly ($p < 0.05$) decrease compared with the control group, and the trend continues to the last dose of exposure (Table 6 and 7).

Table 3. Effect of Methanol leaf extract of *T. orientalis*on Packed Cell Volume of Cadmiumexposed Albino rats

PCV (%)					
Day	**3**	**5**	**10**	**15**	**21**
Group					
A	43.21 ± 4.67^a	43.21 ± 4.67^a	43.21 ± 4.67^a	43.21 ± 4.67^a	43.21 ± 4.67^a
B	35.43 ± 0.75^c	33.17 ± 2.25^c	32.81 ± 0.45^c	31.68 ± 1.51^c	30.39 ± 0.75^c
C	35.00 ± 1.73^b	42.38 ± 1.07^a	41.50 ± 3.96^a	46.08 ± 2.49^a	44.76 ± 0.44^a
D	32.67 ± 10.7^c	37.60 ± 2.86^b	39.73 ± 5.40^b	41.28 ± 0.78^a	43.48 ± 0.83^a
E	33.17 ± 3.01^c	40.93 ± 0.78^a	41.17 ± 2.67^a	43.36 ± 0.90^a	44.79 ± 0.51^a

Data are mean ± SEM of five replicates. Test values with superscripts different from the control *a* for each parameter are significantly ($p<0.05$) different.

The exposure to cadmium alongside the administration of extract at varying doses (100 mg kg^{-1} and 200 mg kg^{-1} body weight) manifest generally in significant ($p < 0.05$) decreases in the platelet counts. Though not consistent, the values of the platelet counts kept increasing through the period of 10thand 15th administrationsup to the end of the experiment when the value becomes close to the control value (Table 6)

Table 4. Effect of Methanol leaf extract of *T. orientalis*on White Blood Cell count of Cadmiumexposed Albino rats

WBC ($x10^3/\mu L$)					
Day	**3**	**5**	**10**	**15**	**21**
Group					
A	8.97 ± 0.50^a	8.97 ± 0.50^a	8.97 ± 0.50^a	8.97 ± 0.50^a	8.97 ± 0.50^a
B	8.50 ± 1.00^a	5.37 ± 1.11^b	4.93 ± 2.08^b	4.24 ± 0.49^b	3.99 ± 0.21^c
C	9.01 ± 3.25^a	7.67 ± 3.22^a	7.60 ± 1.42^a	8.30 ± 0.99^a	8.40 ± 0.63^a
D	8.63 ± 4.15^a	6.11 ± 0.59^b	5.69 ± 0.43^b	6.24 ± 0.13^b	7.28 ± 0.34^a
E	8.78 ± 2.33^a	6.82 ± 2.01^b	7.01 ± 1.81^a	7.28 ± 1.84^a	7.57 ± 1.84^a

Data are mean ± SEM of five replicates. Test values with superscripts different from the control *a* for each parameter are significantly ($p<0.05$) different.

Meanwhile, significant ($p < 0.05$) increase was observed in MCV level after first exposure to cadmium alongside treatment with the extract (100 mg kg^{-1} and 200 mg kg^{-1} body weight). The effect of the extract manifested after the first administration and trend continues to the last dose of administration (Table 7).

Table 5. Effect of Methanol leaf extract of *T. orientalis*on Mean Corpuscular Haemoglobin ofCadmium exposed Albino rats

	MCH (Pg)				
Day **Group**	**3**	**5**	**10**	**15**	**21**
A	26.94 ± 1.11[a]	26.94 ± 1.11[a]	26.94 ± 1.11[a]	26.94 ± 1.11[a]	26.94 ± 1.11[a]
B	28.50 ± 2.29[a]	26.30 ±1.74[a]	24.30 ± 2.19[a]	19.79 ± 0.56[c]	18.82 ± 1.04[c]
C	27.87 ± 1.01[a]	26.79 ± 0.74[a]	27.56 ± 3.15[a]	25.37 ± 3.94[a]	26.25 ± 1.35[a]
D	27.30 ± 3.79[a]	24.43 ± 0.67[a]	26.43 ± 0.60[a]	23.57 ± 0.92[b]	24.55 ± 0.86[a]
E	27.37 ± 3.56[a]	25.09 ± 1.56[a]	26.23 ± 1.54[a]	25.45 ± 0.48[a]	25.62 ± 0.79[a]

Data are mean ± SEM of five replicates. Test values with superscripts different from the control *a* for each parameter are significantly ($p<0.05$) different.

Table 6. Effect of Methanol leaf extract of *T. orientalis*on Platelet counts of Cadmium exposedAlbino rats

PLT ($x10^3$/ µL)					
Day **Group**	**3**	**5**	**10**	**15**	**21**
A	265.4 ± 15.82[a]	265.4 ± 15.82[a]	265.4 ± 15.82[a]	265.4 ± 15.82[a]	265.4 ± 15.82[a]
B	187.0 ± 9.530[c]	237.3 ± 15.88[b]	200.7 ± 61.26[b]	188.0 ± 26.00[c]	185.3 ± 16.07[c]
C	203.7 ± 10.12[b]	235.0 ± 37.80[a]	245.7 ± 52.81[a]	266.7 ± 15.27[a]	259.0 ± 8.540[a]
D	299.0 ± 42.72[a]	217.0 ± 21.17[c]	203.0 ± 10.14[c]	230.3±33.71[b]	259.0 ± 10.15[a]
E	232.3 ± 6.030[b]	249.9 ± 1.640[a]	205.7 ± 55.90[c]	240.0± 10.00[b]	269.0 ± 6.550[a]

Data are mean ± SEM of five replicates. Test values with superscripts different from the control *a* for each parameter are significantly ($p<0.05$) different.

Table 7. Effect of Methanol leaf extract of *T. orientalis*on Mean Corpuscular Volume ofCadmium exposed Albino rats

MCV (fL)					
Day **Group**	**3**	**5**	**10**	**15**	**21**
A	77.21± 4.90[a]	77.21± 4.90[a]	77.21± 4.90[a]	77.21± 4.90[a]	77.21± 4.90[a]
B	75.37± 7.99[b]	74.07 ± 4.64[b]	70.73 ± 4.90[c]	70.86 ± 1.40[c]	69.37 ± 0.89[c]
C	78.63 ± 2.01[a]	77.62 ± 8.07[a]	83.73 ± 8.53[a]	77.28 ± 2.78[a]	78.48 ± 1.65[a]
D	72.96 ± 2.40[b]	74.31 ± 2.85[b]	74.56 ± 0.46[b]	78.03 ± 1.72[a]	80.33 ± 15.4[a]
E	72.73 ± 8.51[b]	74.77 ± 0.29[b]	75.91 ± 1.40[a]	77.33 ± 1.43[a]	81.03 ± 6.64[a]

Data are mean ± SEM of five replicates. Test values with superscripts different from the control *a* for each parameter are significantly ($p<0.05$) different.

IV. Discussion

The blood contains a very diverse cellular constituents and other metabolites that when their levels are determined as a result of administration of chemical compounds including natural products could provide medium for clinical investigation, nutritional status of individuals, toxic assessment and toxicity management (Vinodini, *et al*., 2019). Previous report has also suggested that blood is most important tissue in the body with reproducible metabolic alterations. Alterations in blood parameters are one of the most reliable toxicity markers of drugs and heavy metals (Vinodini, *et al*., 2019).

It is an established fact that blood cells are synthesized from bone marrow of animals: the decreased level in the several cellular blood components on exposure to cadmium as observed in this study is an indication that the bone marrow has been compromised in a way that the balance between synthesis and destruction of cells is distorted, favouring destruction/catabolism, hence, the decrease can be attributed to cadmium-induced toxicity (Ojo*et al*., 2014, Saliu*et al*., 2012 and Nurudeen*et al*., 2017). The toxic effects of cadmium were found to be annulled by the methanolic extract of *T. orientalis*.

Falke and Zwennis (1990) reported that lowered RBC count, decreased MCH and MCV are some of the hematological alterations associated with cadmium exposure. This is supported by findings from this study. Cadmium induced toxicity is credited to damage in the synthesis of erythropoietin, a hormone which promote the

formation of red blood cells. However, the reduction of RBC, PCV and haemoglobin levels in this study is similar to the report by Saliu*et al*., (2012). The reduction in RBC count, PCV and haemoglobin maybe associated with haemopoeisis, destruction and shrinkage of RBC (Ladokun*et al*., 2015). Furthermore, MCV and MCH determine the size of RBCs, concentrations as well as weight of haemoglobin in the RBCs (Ladokun*et al*., 2015). The decrease in the red blood cell count as observed in this study may also be a reflection of the decrease in the MCV and MCH as obtained in the present study. Similarly, the decrease in MCV maybe an indication that RBCs are abysmally small in size because of either the system inability to synthesize RBCs or a lack of available hemoglobin needed to complete the process of synthesizing RBCs (Ladokun*et al*., 2015). In view of the decreases in MCH and MCV, invariably there will be reductions in the levels of haemoglobin, RBC and PCV as observed in this study. Decrease in the white blood cell (WBC) of cadmium untreated group as observed in this study could be linked to weaken immunity, hence, posing inability to fight foreign substances. The present study also shows significant reduction in the platelet level on exposure of animals to cadmium. This justifies the poisonous effects of cadmium on blood components. Decrease in the platelet may lead to some severe hematological disorders like leukemia (Vinodini*et al*., 2019). It was also observed in the extract administered group that the PCV, RBC and MCV have increased significantly than the control group, so also heamoglobin, WBC, MCH and platelet. These results are in agreement with the report of Kasim *et al* (2015). The observed increase in MCV and MCH is synonymous with red blood cell hydration while the observed increase in WBC by the extract suggests that it might be immunoprotective (Kasim *et al*., 2015). On co-administration of cadmium and the extract (100 mg kg^{-1} and 200 mg kg^{-1}), the extract was able to increase the levels of the hematological parameters (haemoglobin, red blood cell count (RBC), packed cell volume (PCV), white blood cell (WBC), mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV) and platelet) as compared to cadmium untreated group. However, treatment with methanol leaf extract of *Tremaorientalis*was found to significantly improve the levels of all the haematological parameters. The hemato-protective and probably synthetic effect of this extract may be due to the phytochemical constituents of the leaves which consist of blood enriching minerals such as Fe, K, Na, P and Ca (Senga*et al*., 2016). Therefore,*Tremaorientalis*proved its hematopoietic effect in rats administered with its leaves extract .This can be beneficial and hence justifies the folkloric use of the plant as a blood booster in anemic conditions. Furthermore, the methanolic leaf extract of *T. orientalis* could be recommended in the management of hematological disorders arising basically from anemic condition.

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