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Protective measures of *Phyllanthus emblica* and Lycopodium 200C against cadmium induced nephrotoxicity and hepatotoxicity in *Mus musculus*

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Abstract
Enormous work has been done in the field of heavy metal toxicity till date. Maximum works were carried out to see the effects of arsenic and lead because of their huge applications by different industries. But, the factory effluents also contain some other metals including cadmium. Cadmium contaminates our environment not only through water but also through air and food. Works have already been performed to see the adverse effects of cadmium on environment as well as on different animal bodies; but, very few attempts were made to find remedies of such problems. Being carcinogenic, these metals can produce severe toxicity to various organs including liver, lung, kidney, testis etc. by interfering with normal cellular mechanisms. Remedies with different chemicals and radiotherapy treatments give some relives but add on different side effects. Research shows that the antioxidant pool present in some herbal extracts and homeopathic tinctures have anti-toxic, anti-oxidative and anti-carcinogenic properties which help them to fight against such toxic environment. the present study was undertaken to see the adverse effects of cadmium on different mammalian organs and the remedial effects of two common herbs, the *Phyllanthus emblica* (amla) extract and *Lycopodium clavatum* (club moss) in its homeopathic tincture form (Lycopodium 200C). To conduct this study *Swiss* albino mice were used as experimental model and different biomarker enzymes and biomonitoring protein molecules were selected to detect their total content as well as activities; these are serum alkaline phosphatase, serum lactate dehydrogenase, tissue metallothionein, serum urea nitrogen and creatinine etc. Results showed drastic changes with the applications of cadmium in different parameters which are again recovered by the applications of amla extract and Lycopodium 200C

Keywords: blood urea nitrogen, *mus musculus*, metallothionein, metal responsive element, nephrotoxicity, *phyllanthus emblica*

Introduction
Cadmium is well known for its nephrotoxic and hepatotoxic activities and causes severe damage to various organs including kidney and liver by producing free radicals. Heavy metals such as cadmium is shown to increase the metallothionein (MT) level in mammalian body by inducing the binding of some specific transcription factors to a region of MT gene known as metal responsive elements or MRE and thus induces transcription. Metallothionein is a special kind of cystein rich protein molecule which successfully binds with heavy metals (including cadmium) and transports it from other organs through blood stream to kidney from where it is then excreted out of the body. So an increase in metallothionein level can be seen in heavy metal induced organisms. Besides, blood urea nitrogen (BUN) and blood creatinine levels are also two important markers of kidney and liver injury whereas, alkaline phosphatase (ALP) is a well known marker for liver; an increase in alkaline phosphatase level indicates hepatic damages. The toxic effects of cadmium can be reduced by treating with extracts of Indian Gooseberry or *Phyllanthus emblica* (amla). Its active compounds include flavonoids like quercetin and many other antioxidants mainly different emblicanins, all of which have free radical scavenging activities and are active against heavy metal induced toxicity. The same kind of protective effects are seen in case of Lycopodium 200C which contains mainly lycopodine as its active compounds. The present study was undertaken to see the protective role of Indian Gooseberry along with the Lycopodium 200C on cadmium induced nephrotoxicity and hepatotoxicity in mice model. To conduct this study, *swiss* albino mice, i.e., *Mus musculus*, were used as experimental organisms and were divided into five sets; namely, SI or normal, SII or cadmium induced group, SIII or group administered with amla extracts along with cadmium, SIV or group administered with Lycopodium 200C along with cadmium and SV or group administered with both amla and Lycopodium 200C along with cadmium. After the treatment phase the mice were sacrificed and to test the effects of the treatment, ALP, BUN and blood creatinine level were estimated from blood samples and kidney metallothionein concentration was determined. Results showed an increase in metallothionein concentration in

both SII and SIII than that of normal (SI). These data indicates that the flavonoids and antioxidants present in amla and Lycopodium 200C reduce cadmium induced toxicity by increasing MT secretion. Again, BUN and the ratio of BUN-creatinine are higher in cadmium induced group (i.e., SII) than other groups (SI, SIII, SIV and SV). So, the present study shows protective measures of the active compounds of amla and Lycopodium 200C against cadmium induced hepato and nephrotoxicity.

Materials and Methods

The experiments were carried out in Genetics and Molecular Biology Research Unit of Department of Zoology, Vidyasagar University, Midnapore, West Bengal. The animals were handled and kept in normal laboratory condition of the concerned Department by maintaining all Animal Ethical Rules of UGC.

Animal Model and Experimental Sets

Swiss albino mice (~20gm each; 4 mice in each set) were used as experimental model and divided into different sets which are as follows:

1. One control set
2. Set administered with $CdCl_2$ for 80 days.
3. Set administered with $CdCl_2$ for 1st 40 days and experiments are performed after a 40 days post - incubation period.
4. Treatment series

There are total 6 types of set for 2 types of treatment series

A. Co-treatment for 80 days which includes introduction of both cadmium and herbal and homeopathic drugs alone and in combination resulting 3 different sets as mentioned below (Series I).
B. Post-treatment, i.e., after 40 days chronic exposure, CdCl2 is stopped and treatment series is carried out for 3 different combinations of drugs (Series II).

The 3 different sets for co-treatment and post-treatment are

1. $CdCl_2$+ Amla,
2. $CdCl_2$+Lycopodium 200
3. $CdCl_2$+ Amla + Lycopodium 200.

Drugs and Dosage

All the materials were collected from authorized dealer. Cadmium Chloride was used as the source of cadmium and purchased from Sigma-Aldrich and given with a high dose of 100 mg/kg body weight/mouse/day. To prepare amla juice fresh amla were collected from local market and then grinded and filtered to get a fresh juicy product and administered at a dose of 10 µl/20 gm body weight/ day. Lycopodium 200c was also collected from local homeopathic store and administered at a same dose with that of amla. The substrate for alkaline phosphatase, i.e., alkaline phosphate and fast blue RR salt were purchased from Sigma-Aldrich and other supportive materials were collected from Himedia.

Determining the Concentration of BUN and Creatinine, ALP and LDH Activities

To determine the concentration of Blood Urea Nitrogen and Blood Creatinine levels, ALP and LDH activities conventionally used biochemical assay kits from Himedia were used. To perform the assays the mice were sacrificed and the blood was collected by puncturing the heart. The blood samples from the consecutive sets were then centrifuged at 10,000 rpm for 10 minutes and serum were separated and stored at 40C. The assays were performed by following the methods provided with the assay kits.

Determining the Metallothionein Content

The metallothionein content was determined from mice kidney and liver by following the method of Linde & Gracia Vazquez (2006) [1]. Briefly, the tissues were collected from sacrificed mice and then homogenized in 3 volumes of buffer containing 0.5M sucrose, 20 mM Tris-HCl (pH 8.6) and 0.01% ß - mercaptoethanol. After centrifugation at 30,000 g for 20 minutes 1 ml of the supernatant was mixed with 1.05 ml chilled ethanol and 80 ml chloroform and again centrifuged at 6000 g for 10 minutes at 4°C. The collected supernatant then mixed with 3 volumes of chilled ethanol and incubated at -20°C for 1 hour. After another centrifugation at 6000 g for 10 minutes the pellets were washed in mixture containing ethanol, chloroform and homogenization buffer and centrifuged at same speed. Then the pellets were dried in freeze dryer and re-suspended in a buffer containing Tris-HCl and EDTA and added with the DTNB solution (Ellman's reagent). After 30 minutes incubation in room temperature the concentration of reduced sulfhydryl was calculated by comparing the absorbance at 412 nm with a standard curve of glutathione.

Statistical Analysis

To draw statistical interpretation, descriptive statistics, i.e., mean and standard error of mean along with the one way ANOVA were performed to test the presence of any significant differences between all the data at 0.05 level.

Results

Table 1: Values of Blood Urea Nitrogen, Serum Creatinine and BUN: CREATININE Ratio of 80 Days and 40+40 Days Treatment Series

	Values of 80 Days					Values of 40+40 Days			
SETS	**NC**	**CD**	**CD+A**	**CD+L**	**CD+A+L**	**CD**	**CD+A**	**CD+L**	**CD+A+L**
BUN	19.75± 0.617	14.84± 0.542*[a]	17.19± 0.469*[a, b]	14.95± 0.144*[a]	15.67± 0.175*[a]	33.81± 0.092*[a]	23.55± 0.092*[a, b]	18.73± 0.033*[a, b]	19.66± 0.183*[b]
CREATININE	0.85± 0.101	1.81± 0.506*[a]	1.25± 0.025*[b]	0.86± 0.007*[b]	0.81± 0.046*[b]	0.79± 0.025	0.9725±0.045	1.11± 0.446	0.92± 0.161
BUN: CREATININE RATIO	23.56± 2.037	8.67± 2.379*[a]	13.72± 0.267*[a, b]	17.09± 0.373*[a, b]	19.36± 0.905*[a, b]	42.69±1.291*[a]	24.26± 1.146*[b]	18.82± 6.303*[b]	21.76± 3.576*[b]

* Data significant at 0.05 levels. *a Significant with Normal Control group (NC). *b Significant with Cadmium induced group.

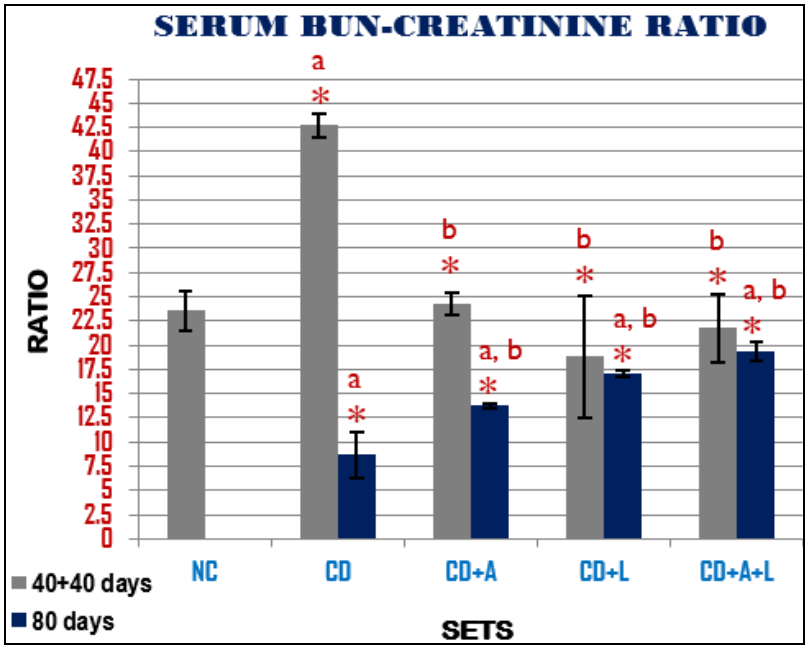

Fig 1: Diagrammatic representation of serum BUN & Creatinine ratio of mice from different sets of 80 and 40+40 days experimental series. Data are represented in mean±SEM and significant at 0.05 levels (*).*[a] Significant with Normal Control group (NC). *b Significant with Cadmium induced group (CD

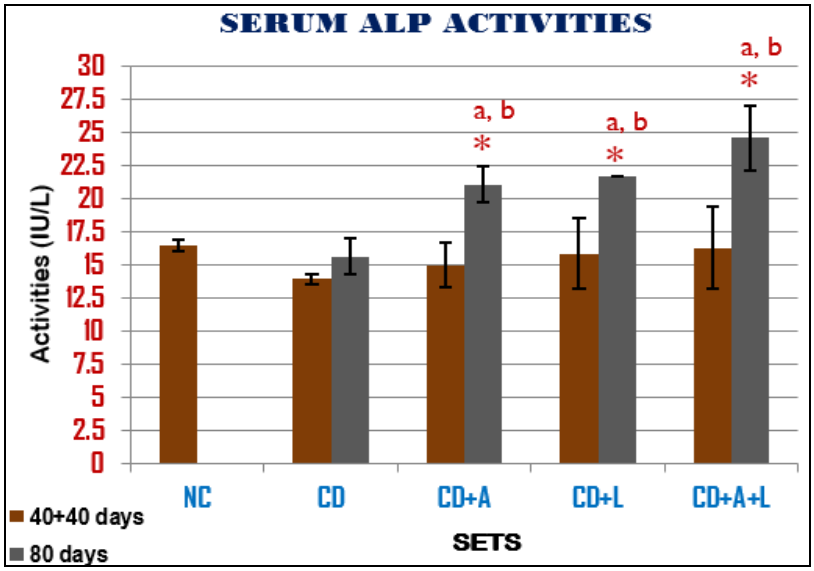

Fig 2: Bar diagram showing serum ALP activities of mice from the five sets of both 80 and 40+40 days treatment series. Data are represented in mean±SEM and significant at 0.05 levels (*).*[a] Significant with Normal Control group (NC). *b Significant with Cadmium induced group (CD)

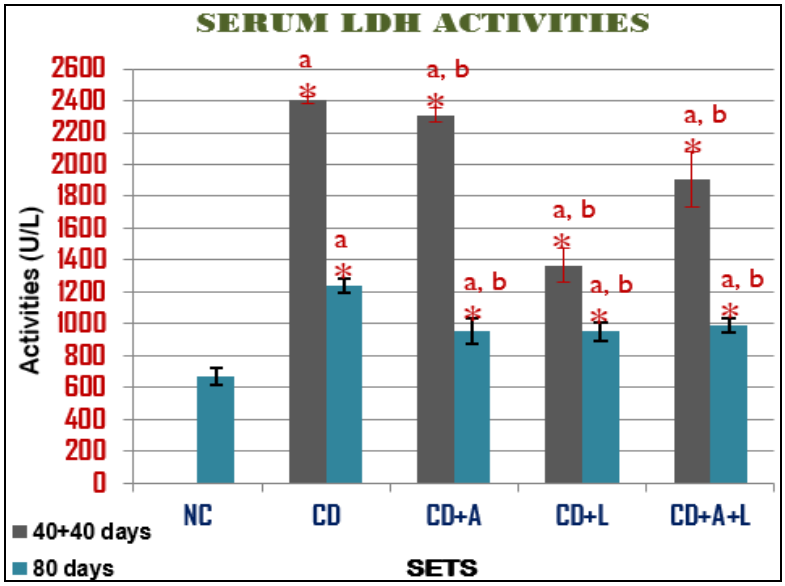

Fig 3: Diagrammatic representation of serum LDH activities of mice from different sets of 80 and 40+40 days experimental series. Data are represented in mean±SEM and significant at 0.05 levels (*).*[a] Significant with Normal Control group (NC). *b Significant with Cadmium induced group (CD)

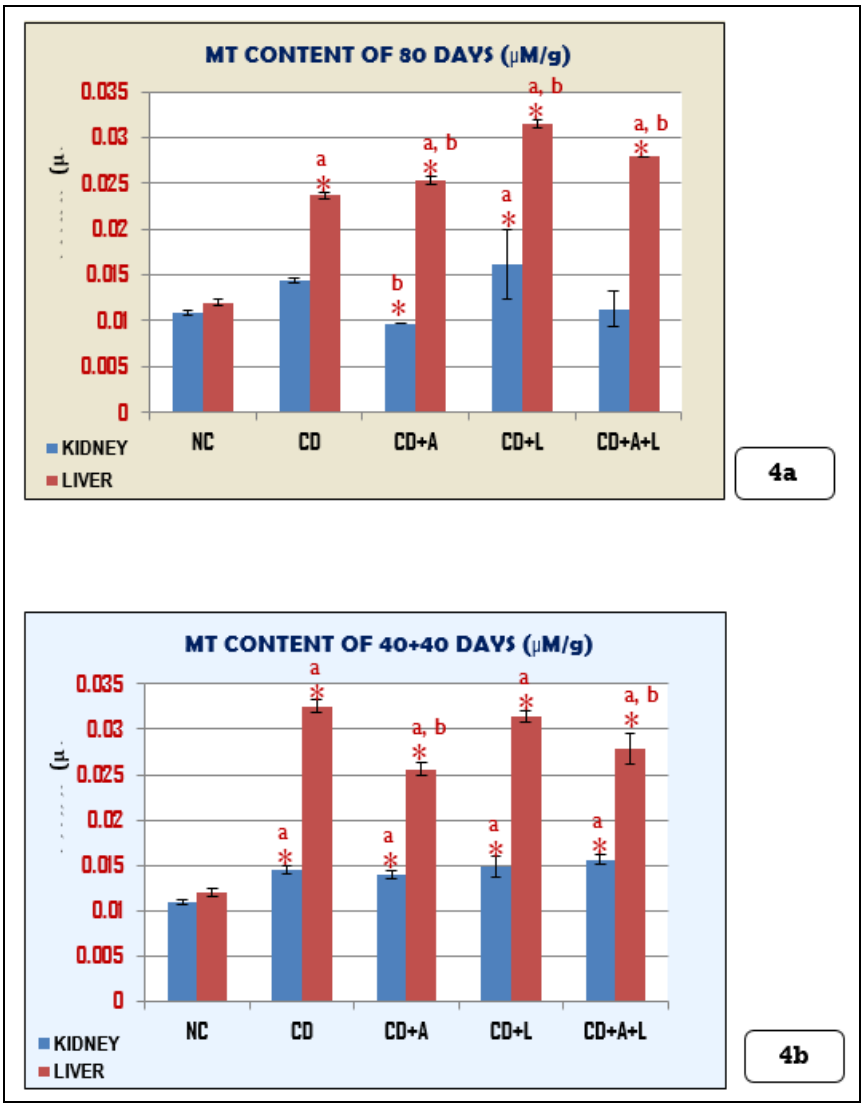

Fig 4: Diagrammatic representation of metallothionein content in kidney and liver of cadmium induced group and treated mice from 80 (4a) and 40+40 (4b) days experimental series. Data are represented in mean±SEM and significant at 0.05 levels. [a] Significant with Normal Control group (NC). [b] Significant with Cadmium induced group (CD)

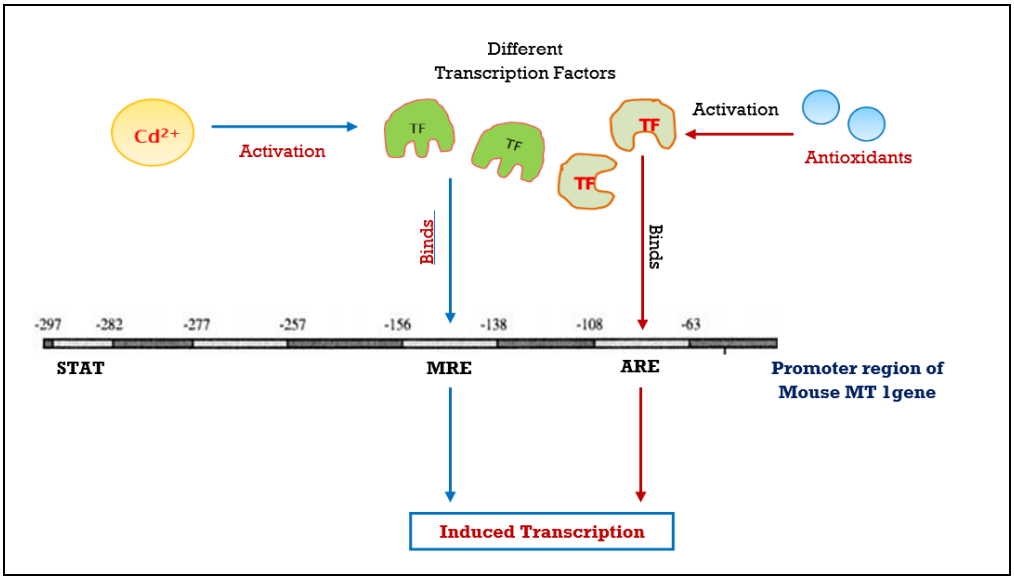

Fig 5: Proposed model representing the effects of metals like cadmium and antioxidant on the transcription of metallothionein gene

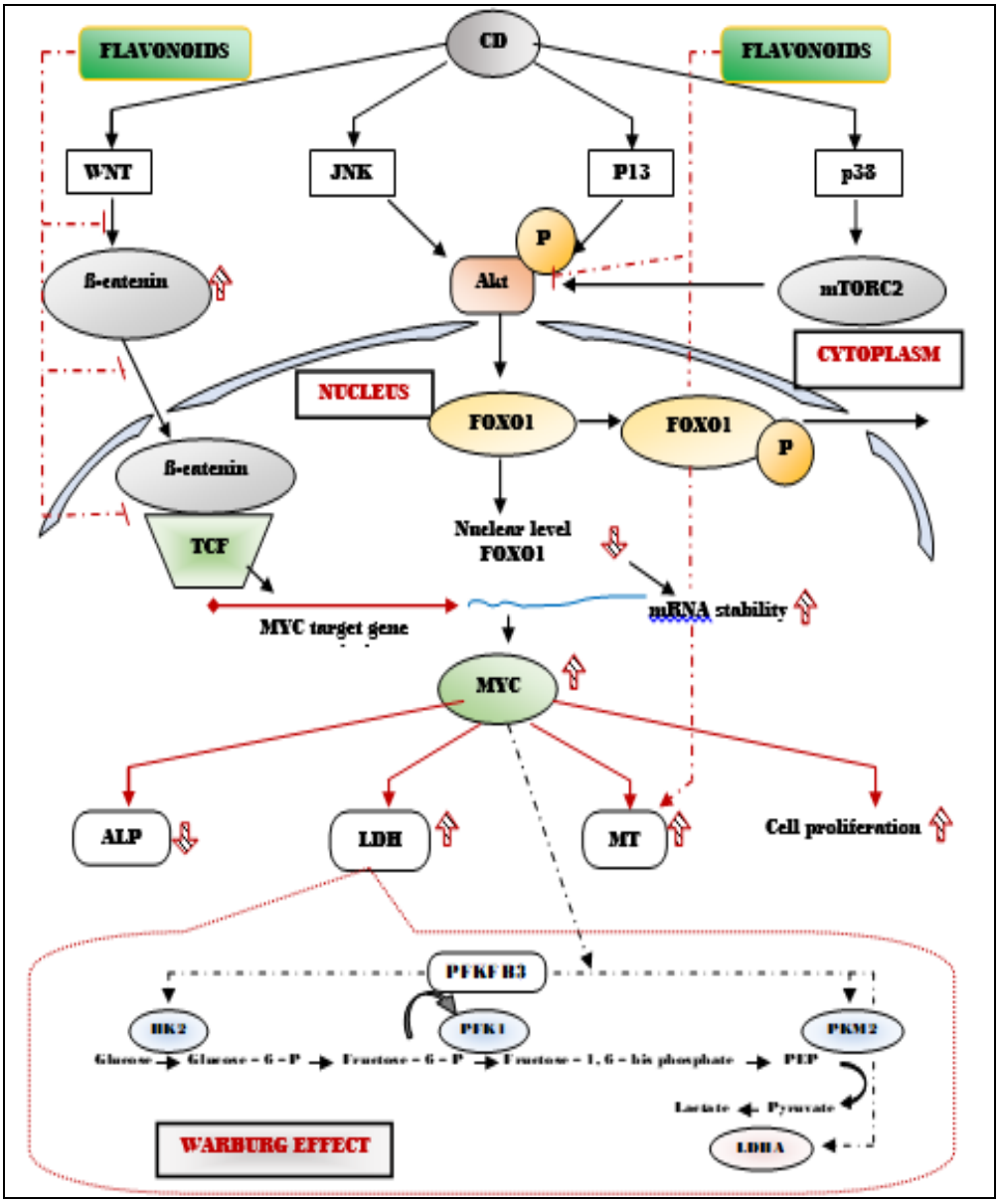

Fig 6: Signaling pathways controlling the entire experimental mechanism and results

Discussion

The blood urea nitrogen and blood creatinine levels are common parameters for liver and kidney injuries. The healthy liver produces ammonia which contains nitrogen; the break down product of protein used by the cell. The nitrogen then combines with many other elements like oxygen, carbon, hydrogen, thus produces urea. The urea is a chemical waste product which then travels from the liver to the kidney through blood stream. Healthy kidney filters the urea out of the body along with other waste products present in the blood. This filtered waste product then leaves the body as urine. The normal range of BUN present in the serum of a healthy human being ranges from 5 to 20 mg/dL. In the present study it is seen from Table 1 that the normal control (NC) group shows similar result where the BUN level is 19.75±0.617 mg/dL which is a normal range as with human. So, any elevated or low levels of BUN indicate renal or hepato-cellular injuries. Another waste product is creatinine which produced from creatine due to muscle metabolism. The creatine converted to creatinine every day in our body is approximately 2%. Creatinine is transported to the kidney through the blood stream and excreted out of the body through urine. Any change in creatinine level from that of its normal range implies severe kidney malfunctioning. Just like BUN the normal range of blood or serum creatinine level varies from 0.7 to 1.2 mg/dL. Again in Table 1 the creatinine level of NC group is 0.85±0.101 mg/dL which lies between the above said normal ranges. Another parameter to confirm the kidney and liver damage is the BUN:creatinine ratio shown by both Table 1 as well as Fig 1; the normal range lies between 10 to 20 which is the case in NC group of the present study. A higher ratio than 20 indicates pre-renal injuries where BUN disproportionately increased in serum relative to creatinine; whereas a ratio, lower than 10 implies intra-renal problems [2].

Keeping these facts in mind during judging the present data it is found that cadmium induced groups of both 80 and 40+40 days series show opposite results. In the 80 days series the cadmium induced group shows normal BUN level but elevated creatinine level thus lowering the ratio. As the elevated creatinine is the only marker for kidney injury the results imply that the kidney is more damaged than the liver in this group. Besides, in 40+40 days series the BUN level is much higher giving a normal range of creatinine level thus elevating the ratio; indicating liver is more damaged than kidney in this second series. This may be due to the short term exposure with cadmium and an incubation period of 40 days when no exposure was performed. In the meantime the body's defense system worked out to reveal the situation thus lowering the adverse effects of cadmium to some extent. The treatment phases showed significant differences with that of cadmium induced group. Both of the Indian Gooseberry and Lycopodium 200C worked hard to maintain the ratio in their normal range.

The serum alkaline phosphatase (ALP) is a key enzyme mostly used as biomarkers to detect renal and hepatic injuries. ALP are present in four isozymic forms in common human, whereas, two types of ALP isozymes are normally found in healthy mouse; these are liver, bone, kidney and placental ALP (L/B/K-ALP) and intestinal ALP. The level of ALP is normally changed from its normal level under stressful conditions, such as metal exposures, by either lowering or elevating the activity. Although lower levels of ALP activities are very few in research history the present study indicate a lower activity of ALP due to cadmium exposure in both of the 80 days and 40+40 days series and gradual increase are observed with treatment (Fig 2). More decreased activities are found in short term exposure than long term series. It is due to the effect of a cell signaling pathway where cadmium encourages a lower ALP secretion from its gene indirectly through the activation of some cell signaling molecules discussed latter. Besides, antioxidants and flavonoids present in the herbal extracts as well as homeopathic medicines can alter the situation by inhibiting particular molecules of the same cell signaling pathway followed by cadmium thus can be able to reversing the ALP activities. Long term treatments show much better effects than short term treatments to normalize the ALP activities. The treatment groups show the recovery of ALP activities altered by cadmium exposure in a mode where co-treatment shows highest potentialities and amla shows the lowest; the potentialities of different treatment groups can be expressed as co-treatment > Lycopodium 200C > amla.

Lactate dehydrogenase (LDH) is normally found in all living cells. Usually five isozymic forms of LDH can be found in mammalian body and all tissues contain various amounts of these five LDH isozymes. But, muscle, liver and red blood cells are the major sources of serum LDH activity levels3. LDH helps in glycolysis step of metabolism by converting the pyruvate to lactate in the absence of oxygen or vice versa in Cori cycle. Whereas, in tumor cells a cancer specific form of LDH, the LDH-A facilitates the above said procedure. The activity of LDH-A gene is controlled by *c-myc* and HIF-1 transcription factors. This elevated level of LDH-A activity further increases the production of lactate from pyruvate thus reducing the amount of pyruvate available to convert to acetyl Co-A. This phenomenon is known as Warburg effect [4].

The above information proves the fact seen in the bar diagrammatic representation of Fig 3. The elevated levels of serum LDH in cadmium induced groups of both series are thus due to the elevated level of LDH-A gene activities, which again induces cell proliferation thus destines the cells toward cancerous. Very little changes can be seen in 80 days treatment series than in 40+40 days. Drastic elevated activity level of about 2407.92±23.38 is found in cadmium exposed group of 40+40 days series. Treatment with Lycopodium 200C shows marked differences from other groups by lowering the activity to 1368.06±103.14. Other groups such as amla treated and co-treated groups also show significant differences but not like Lycopodium 200C. The effective potency of the treatment groups to minimizing the harsh effects of cadmium in this case thus go from Lycopodium 200C > Co-treatment > amla.

Approximately 3 to 10% of the ingested cadmium is normally absorbed by the gastrointestinal tract. The main organs that normally store cadmium are liver, kidney, lung, testis, spleen, heart, thymus, salivary gland, prostate

and epididymes. Among them approximately 50% of cadmium are found in liver and kidney due to their high metallothionein content (MT) and then found in lung. Being a metal chelator metallothionein binds with cadmium when it transported from plasma to red blood cells in blood. For its metal chelating nature MT plays important role in the excretion of cadmium through liver and kidney. From previous research it has been found that the promoter region of metallothionein gene normally contains a MRE (metal responsive element) region and an ARE (antioxidant responsive element) region. During metal flux the MRE region is activated through some specific MRE binding transcription factors like MTF-1; thus inducing the transcription of metallothionein in order to eliminate the entered metal particles from the body. A low level of MT content can be found in tumor cells because of the alteration of MT-zinc binding domain of P53 due to DNA methylation. Otherwise, a large production of metallothionein results to excrete out the foreign metals from the body in stressful condition or in toxic environment. Whereas, ARE region works by binding with transcription factors related to antioxidant responses. In other words, when antioxidants are present they activate some other series of transcription factors which again bind with the ARE region of the promoter of MT gene; thus inducing the transcription in order to release more cadmium out from the body. When both metal and antioxidants are present a large production of metallothionein can be found [5].

The present study showing in Fig 4 goes with the flow and gives a result where it can be seen that due to cadmium exposure a large amount of metallothionein was produced giving a large MT content in both series and for both the tissue types. Remarkable differences are seen in long term exposure, i.e., in 80 days series. Otherwise, a general pattern can be seen in both series. Cadmium increases the expression of MT which again increased by Lycopodium 200C treatment and also by co-treatment (Fig 5). But, in amla treated group both the series show low MT content in two tissues. This is due to the presence of quercetin in amla, which itself is a metal chelator; thus, binding with quercetin reduces the availability of metals to be bound with MRE binding transcription factors thus lowering the MT expression. But, it does not mean poor protective effects of Indian Gooseberry, because, in such condition quercetin itself helps to remove cadmium from the body by binding with it. Again comparing among tissues lung shows higher MT content following by testis in case of long term exposure (80 days), whereas, liver predominates following by kidney in short term exposure (40+40 days).

The results can be concluded by saying that cadmium obviously has a profound adverse effect on mammalian body which is clear from the abnormal conditions of different marker enzymes and biosensor proteins. The body defense system normally fights with the toxicological environment produced by cadmium by the increased production of metallothionein but is unable to eliminate the entire abnormalities in adverse condition. Also the higher MT content of liver follows by the kidney in short term exposure proves the presence of high cadmium concentration in these tissues; whereas, in case of long term exposure the lung becomes more affected followed by the testis. The Indian Gooseberry extract and homeopathic medicine Lycopodium 200C produced from the club moss or *Lycopodium clavatum* effectively reverse the adverse effects of cadmium; not only the herbal extracts and homeopathic medicines themselves but also they act their best in many places when applied in combination; such as, in case of ALP activities this combine treatment shows best results. Again, in many places Lycopodium follows the co-treatment by showing second best protection, such as BUN:Creatinine ratio and ALP activities. The remaining results show dominating activities of Lycopodium over that of others, which are, BUN, Creatinine, LDH activities, MT content and BUN:Creatinine ratio of 40+40 days. Although, a single place shows dominating amla activities over that of others which is the creatinine level, here the potencies goes down from amla to Lycopodium through co-treatment (A>C>L). So, the results show that Lycopodium and combined treatments are much better in reversing the adverse effects produced by cadmium at biochemical level.

To summarize the entire work we should focus on the major events occur within the cells which includes different signaling pathways described in Fig 6. The cadmium follows some signaling pathways which intern affects the other biological or enzymatic systems; thus damaging the body. The two possible pathways relevant to the present study are Wnt and MAPK (especially JNK, P13K and p38) pathways. These two signaling pathways work in combination to alter different enzymatic activities and even interfere with the tissue metallothionein content and cause cellular proliferation. In Wnt/ ß- catenin signaling the cadmium acts as the Wnt ligand. In the absence of Wnt ligand the ß- catenin normally binds with a multi-cellular complex including AXIN ½, GSK3, APC and CK1 which finally results in proteasomal degradation of the ß- catenin by phosphorylating the second one. When cadmium presents the ß- catenin becomes free from the other complex and migrates from cytoplasm to the nucleus where it again binds with some molecules such as TCF bound with the WRE region of its target gene, e.g., MYC target gene causing transcription and translation of MYC protein [6]. On the other hand the JNK, P13K and p38 pathway phosphorylate Akt. In connection with cadmium exposure the p38 activates the Akt via mTORC2 pathway; thus phosphorylates the Akt. The phosphorylated Akt then enters the nucleus and phosphorylates the FOXO1 which then exit out to the cytoplasm. In normal condition this FOXO1 hampers the MYC mRNA stability. Due to phosphorylation of FOXO1, its nuclear level becomes decreased and thus the MYC mRNA stability increases by elevating the MYC protein level [7]. This MYC protein produced by Wnt and MAPK pathways further interferes with other molecular activities by decreasing the alkaline phosphatase (ALP) activity level and increasing the LDH activity, metallothionein content; leading to cell proliferation [6, 8]. The increased LDH level thus interferes with the cori cycle in cancer cells. In these cells a special type of LDH, known as LDHA predominates. The elevated level of LDHA due to increased expression of C MYC in cancer cells the production of lactate increases with low availability of pyruvate entering the Kreb's cycle; thus the higher lactate level results in cell proliferation and damage (Warburg effect; Warburg

1956) [9]. The flavonoids and anti-oxidants, like those present in the Indian Gooseberry and club moss, on the other hand show potentials to inhibit these signaling pathways in many points; thus altering the effects of cadmium. One point is at the very beginning of the Wnt signaling pathway, where the flavonoids block the sides of Wnt ligand binding thus the ß- catenin remains bound with the multicellular complex which causes phosphorylation and degradation of the ß- catenin; thus preventing the further signal conduction. Another point is the binding with ß- catenin and TCF/ LEF complex at the nucleus; thus preventing it from binding with and inducing the transcription of its target genes. It can also block the ß- catenin before entering the nucleus causing ubiquitination and degradation of the second one. In MAPK pathway the flavonoids and anti-oxidants can block the activation of Akt; thus preventing the further transmission of signal [10]. In these mechanisms the active compounds present in herbal extracts and homeopathic medicines (made from herbal products) fights against cadmium induced toxic environment and reverses the adverse situations created by cadmium. However, in case of MT content the flavonoids and anti-oxidant can directly activates some transcription factors which can further bind with the ARE region of the metallothionein promoter and thus elevating the transcription of the gene. Allover a protective measure can be seen by using these two types of treatments. Both of the amla and club moss are proved to be effective in treating such kind of toxic damages in many extents.

Competing Interests
The authors declare no competing interests.

Author Contributions
Each author of this paper has some contributions toward the completion of this work. The entire work was performed by Dr. M. Chatterjee as a part of her Ph.D. research; under the joint supervision of Prof. J.K. Kundu of Vidyasagar University, Midnapore and Prof. G.C. Sadhukhan, Jadavpur University, Kolkata.

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