IJPSR (2017), Vol. 8, Issue 5 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 October, 2016; received in revised form, 05 February, 2017; accepted, 20 April, 2016; published 01 May, 2017

EFFECTS OF *GLYCOSMIS PENTAPHYLLA* LEAF POWDER AGAINST CHRONIC ARSENICOSIS IN RATS

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Keywords:

Arsenic, *Glycosmis pentaphylla*, Haemogram, Histopathology, Rats

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ABSTRACT: The present study was undertaken to evaluate the effects of *Glycosmis pentaphylla* (GP) leaf powder against sodium arsenite ($NaAsO_2$) induced toxicosis in adult albino rats. Forty eight albino rats having body weight 150-200 gm of either sex were randomly divided (equally) into four groups viz., I_0, I_1, I_2, I_3. Sodium arsenite was administered at 4mg/kg body weight daily in drinking water for 90 days to all rats of groups I_1, I_2 and I_3. The rats of group I_2 and I_3 were orally treated with leaf powder of *G. pentaphylla* at 500mg/kg and 250mg/kg ($1/10^{th}$ of and $1/20^{th}$ of LD_{50}) daily from 91^{st} day to 120^{th} day. Distilled water was given to rats of I_0 for 120 days and rats of I_1 for 91^{st} day to 120^{th} day. Blood samples were collected at different days for analysis of haemogram, biochemical parameters like ALT, AST, BUN and CRT. Tissue samples were collected to study activity of SOD, MDA, GSH, catalase and histopathology was conducted after completion of experiment. The results reveal that the *G. pentaphylla* leaf powder may mitigate the arsenicosis in rats at dose dependent manner and in future may be used to reduce or to prevent arsenic toxicity in human.

INTRODUCTION: Among all toxicants, arsenic ranks as an environmentally ubiquitous and epidemiologically important metalloid currently poisoning tens of millions of people worldwide [1, 2].

Chronic exposure to arsenic is associated with a wide range of toxic effects [1, 3]. Cancer of the skin, lung, kidney, liver and urinary bladder are the important cancers associated with these toxic effects [1, 3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(5).2287-97

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (5).2287-97

Higher level of arsenic in ground water are associated with sedimentary deposits derived from volcanic rocks, hence mineral teaching appears to be the source of arsenic concentration [4]. Liver and kidney are the organs mainly affected with arsenic intoxication [5]. Numerous biological materials have been listed for removal of toxic ions from aqueous solution over the last two decades.

Arsenic is mainly found in two forms, arsenite (the trivalent form, AS III) and arsenate (the pentavalent form ASV) of which trivalent arsenic has been considered to be more toxic than pentavalent arsenic [6].

Both arsenite and arsenate would have similar effects *in vivo*, as the absorbed arsenate is mostly reduced to arsenite in the body.

Pentavalent form of arsenic (arsenate) is reduced to trivalent form of arsenic (arsenite) in the body via methylation in the liver by the enzyme methyltransferase in the presence of S-adenosyl methionine as methyl donor and glutathione (GSH) as an essential co-factor, resulting in the formation of monomethyl arsonous (MMA) and dimethylarsinous (DMA) as end metabolites [7].

The World Health Organization has recommended 0.01 mg/l of arsenic in drinking water as an allowable range for human consumption.

Now a days, arsenic creates a serious public health issue in different developing countries, but chronic arsenic toxicity is a global health issue at present. It is also a major health problem of India and surrounding regions.

The specific curative treatment against arsenicosis is not yet recommended. Initial steps should be taken to stoppage of drinking arsenic contaminated water, improved diet, use of chelating agent [8].

A wide range of clinical features is common in persons exposed to chronic arsenic poisoning. Furthermore, the ubiquity of arsenic in the environment (*e.g.* soil, food, water or air), its biological toxicity and its redistribution are factors evoking public concern [9].

Despite a wealth of epidemiological and clinical data, the mechanisms by which different levels with different duration of arsenate cause body system dys-function are controversial. In addition, most of the studies for relationship between arsenic and body disorder have been conducted on trivalent inorganic arsenic (arsenite) and the role of arsenate (in AS V) is unsettled. More recent findings suggests that consumption of water with levels as low as 0.00017mg/l (0.17 ppb) over long period of time can still lead to arsenicosis (WHO 2001). Arsenic exerts its toxicity through the generation of reactive oxygen species ROS, which include hydrogen peroxide and free radicals such as superoxide anion. Free radicals have capable of damaging many cellular components such as DNA, proteins and lipids[10].

Use of medicinal plants possessing potent anti-oxidant properly can help to reduce oxidative stress and hepatotoxicity caused by heavy metals.

Glycosmis pentaphylla(Retz.) DC belongs to the family Rutaceae. The genus *Glycosmis* of the family Rutaceae is represented by nearly II species. *Glycosmis pentaphylla* (Retz), DC is a shrub or small (1.5 – 5 m) tree widely distributed from India. It is traditionally used for the treatment of fever liver complaints and certain other diseases. The stems are widely used as a brush for cleaning teeth [11].

Phytochemical researches of this species were mainly focused on hydrophobic alkaloids, including those of the quinolaone, quinazoline aridone and carbazole types of leaves, root and stems bark. Considering above, the present work was undertaken to examnine benefiacial effects of *G. pentaphylla* leaf powder in arsenicosis in rats if any.

MATERIAL AND METHODS:

Chemicals: All chemicals and kits used in this present study were obtained from Bangalore Geni (India), Congent (India), Merck (Germany), Rankem (India) and Sigma Chemicals (USA).

Experimental Animals: Forty eight white albino rats of either sexes having body weight 150-200 gm were procured from registered animal breeder. They were caged in polypropylene cages and were acclimatized in experimental animal room for seven days before starting the experiment. The animals were maintained with standard pallet feed and provided drinking water *ad libitum*. The Institutional Animal Ethics Committee approved the technical programme.

Preparation of *Glycosmis pentaphylla* leaf powder: The plant identification was made from BSI (Botanical Survey of India, Howrah, Kolkata) and specimen no. of GP was WBUAFS/Kol/1. Fresh plant leaves of *Glycosmis pentaphylla* were collected from local areas. Then the leaves were washed with distilled water, cut into pieces and room shade dried for 7 days. The dried leaves were pulverized into coarse powder in a grinding machine. The powder was dissolved in distilled water and administered to the experimental rats.

Determination of LD_{50} of *Glycosmis pentaphylla* leaf powder: Healthy albino rats (either sex) were used to determine LD_{50} of *G. pentaphylla* leaf powder as per the method of Ghosh [12] and it was

found to be 5000 mg/kg. Two dose levels i.e. 1/10th and 1/20th of LD_{50} of *Glycosmis pentaphylla* leaf powder were selected (500 and 250 mg/kg) for the present research work.

Experimental Design: Forty eight animals were randomly divided into four groups having twelve rats in each viz., I_0, I_1, I_2 and I_3. Rats in group I_0 were given feed and water *ad libitum*. Each rat in groups I_1, I_2 and I_3 were treated with sodium arsenite (4mg/kg) daily in drinking water for 90 days and leaf powder of *G. pentaphylla* was administered at 500 and 250 mg/kg dissolved in distilled water to animals of groups I_2 and I_3 respectively from 91 to 120 days. Animals of group I_1 were considered as experimental control/ untreated control group.

Collection of samples: Blood samples were collected on day 0, 14, 28, 42, 60, 90 and 120 from animals of each group. Tissue samples were collected on day 0, 90 and 120 after sacrificing four animals in each group.

Blood: Pooled blood samples were collected from the tail vein of 4 rats of each group according to procedure of Brown [13] and kept 1ml blood in EDTA treated test tube for haemogram and 2ml into pre-marked centrifuge glass test tubes immediately after collection and was kept at room temperature for 1hr without agitation to clot with a view to collect serum. The harvested sera were kept at -20 °C until used for biochemical parameters.

Tissue: The rats were sacrificed by maintaining standard protocol using higher dose of ketamine. Pieces of liver, kidney, heart, spleen, lung and intestine from each rat were collected and fixed in 10% buffered formalin for histopathological examination while some part of liver, kidney and heart were used for antioxidant status.

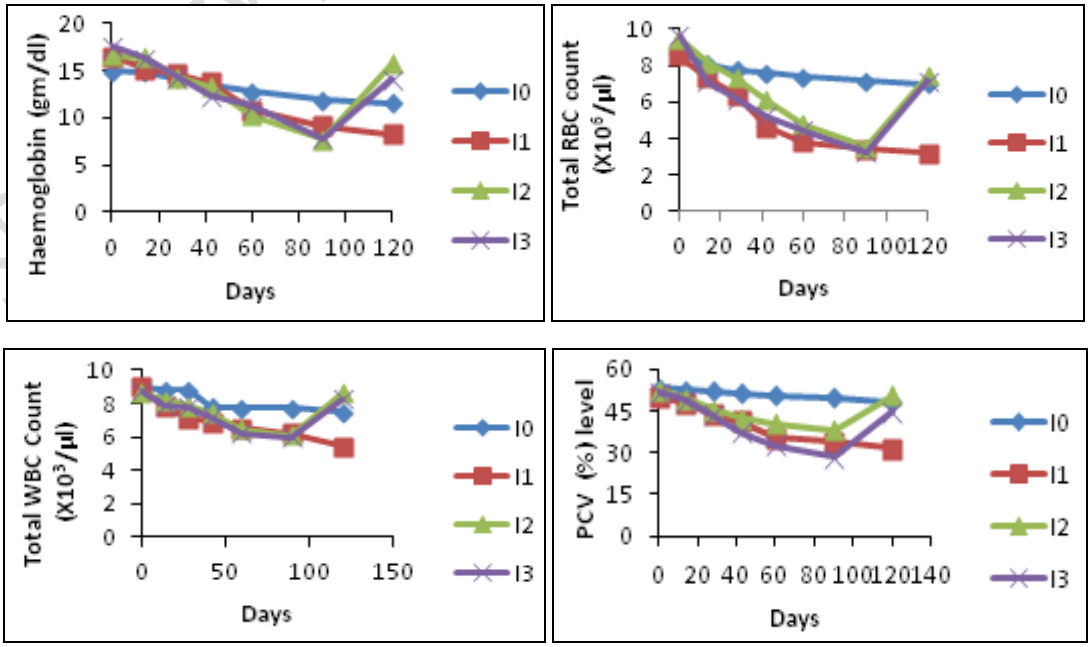
Haemogram: Haemoglobin, total RBC, total WBC, PCV and differential Count were determined as per standard method of coffin(1953) [14].

Biochemical Parameters: Serum AST and ALT activity was measured by the method of Reitman and Frankel (1957) [15] and CRT by Toro and Ackermann (1975) [16].

Tissue biochemical (Anti oxidant status): Reduced glutathione (GSH), Superoxide dismutase (SOD), MDA, Catalase activity in liver, kidney and heart tissues were determined as per Jollow *et al.*, 1974[17], Marklund S and Marklund G 1974[18], Ohkawa H *et al.*, 1979 [19] and Aebi 1984 [20] respectively.

Statistical Analysis: The results were expressed as Mean ± SE. the data were analysed statistically by using Univariant General Linear Model with two ways ANOVA in SPSS10 version of software.

RESULTS:



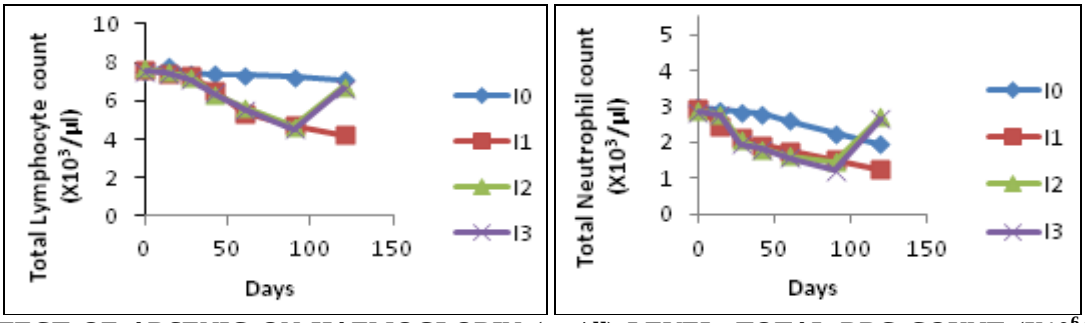


FIG. 1: EFFECT OF ARSENIC ON HAEMOGLOBIN (gm/dl) LEVEL, TOTAL RBC COUNT (X10^6/µl), TOTAL WBC COUNT (X10^3/µl), PCV(%) LEVEL, TOTAL LYMPHOCYTE COUNT (X10^3/µl), TOTAL NEUTROPHIL COUNT (X10^3/µl) IN RAT AFTER DAILY SINGLE ORAL ADMINISTRATION OF SODIUM ARSENITE AT 4mg/kg FOR CONSECUTIVE 90 DAYS AND AMELIORATIVE EFFECT BY *GLYCOSMIS PENTAPHYLLA* LEAF POWDER AFTER 90 DAYS ONWARDS

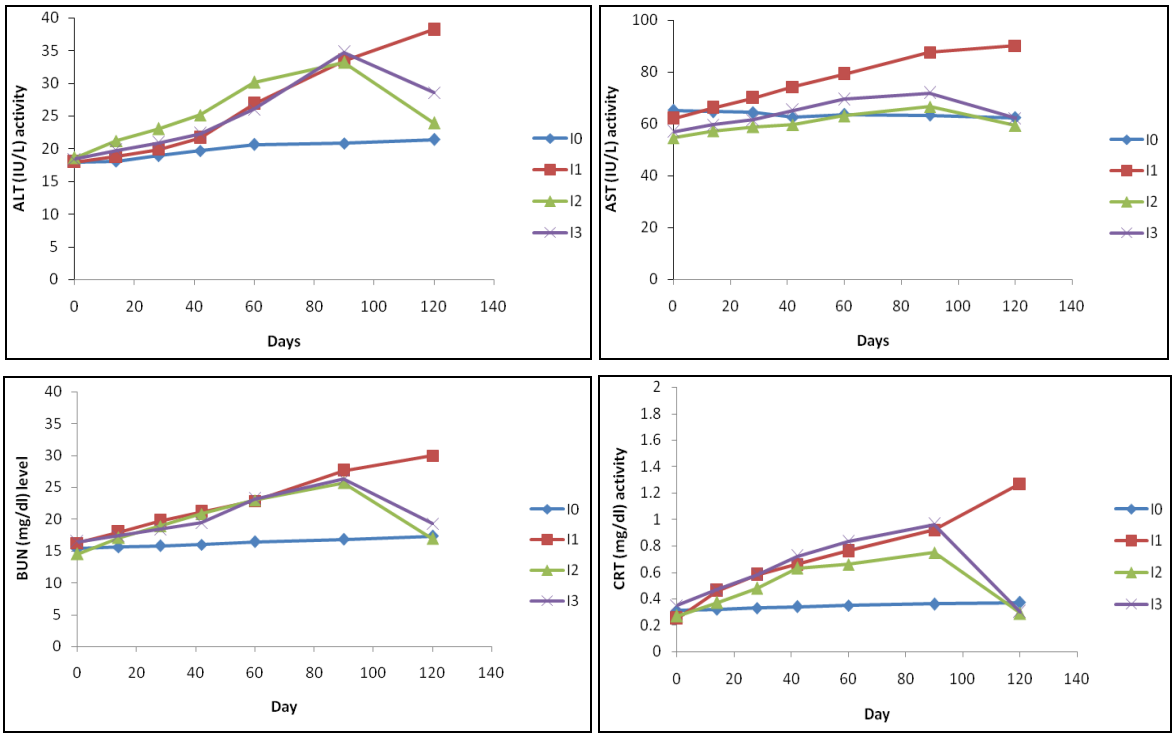
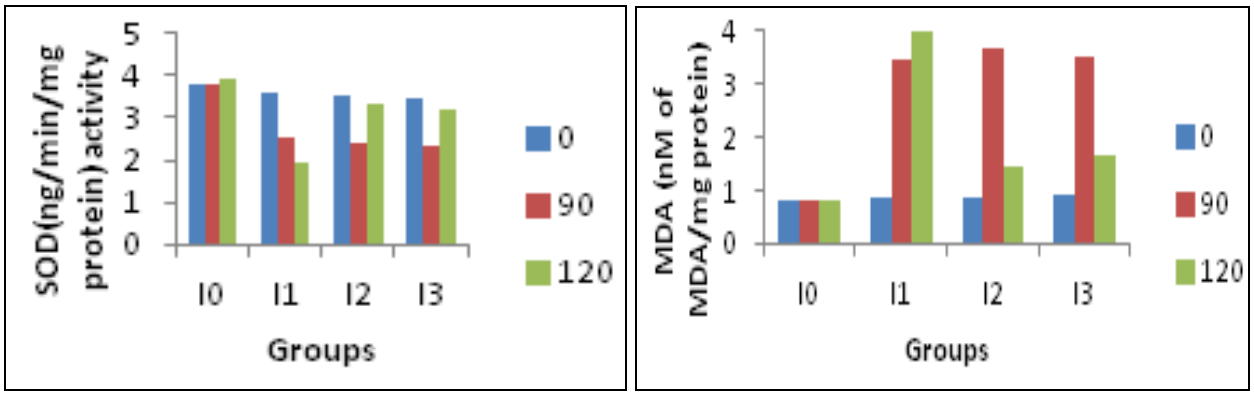


FIG. 2: EFFECT OF ARSENIC ON TOTAL ALT(IU/L) ACTIVITY TOTAL AST(IU/L) ACTIVITY, TOTAL BUN(mg/dl) LEVEL, TOTAL CRT (mg/dl) LEVEL IN RAT AFTER DAILY SINGLE ORAL ADMINISTRATION OF SODIUM ARSENITE AT 4 mg/kg FOR CONSECUTIVE 90 DAYS AND AMELIORATIVE EFFECT BY *GLYCOSMIS PENTAPHYLLA* LEAF POWDER AFTER 90 DAYS ONWARDS



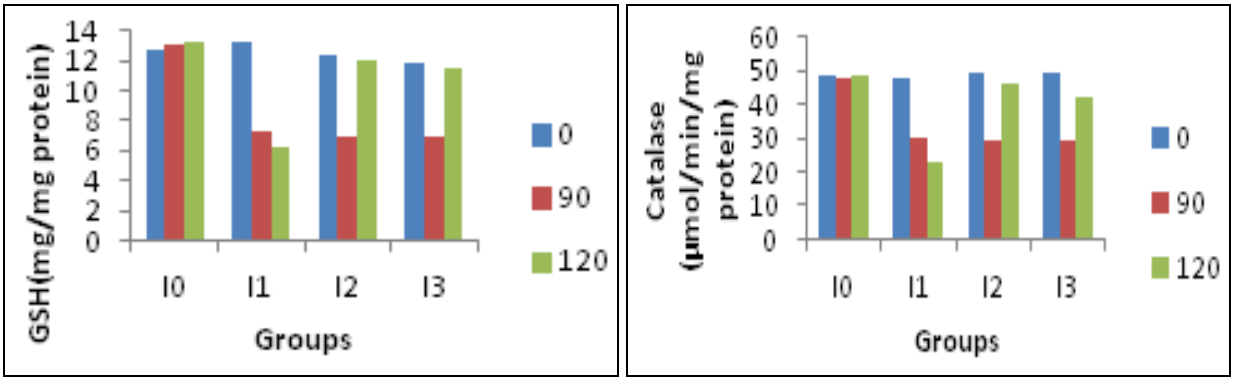


FIG. 3: EFFECT OF ARSENIC ON TOTAL SOD (ng/min/mg protein), TOTAL MDA (nM of MDA/mg protein), TOTAL GSH (mg/mg protein), TOTAL CATALASE (µmol/min/mg protein) IN HEART OF RAT AFTER DAILY SINGLE ORAL ADMINISTRATION OF SODIUM ARSENITE AT 4 mg/kg FOR CONSECUTIVE 90 DAYS AND AMELIORATIVE EFFECT BY *GLYCOSMIS PENTAPHYLLA* LEAF POWDER AFTER 90 DAYS ONWARDS

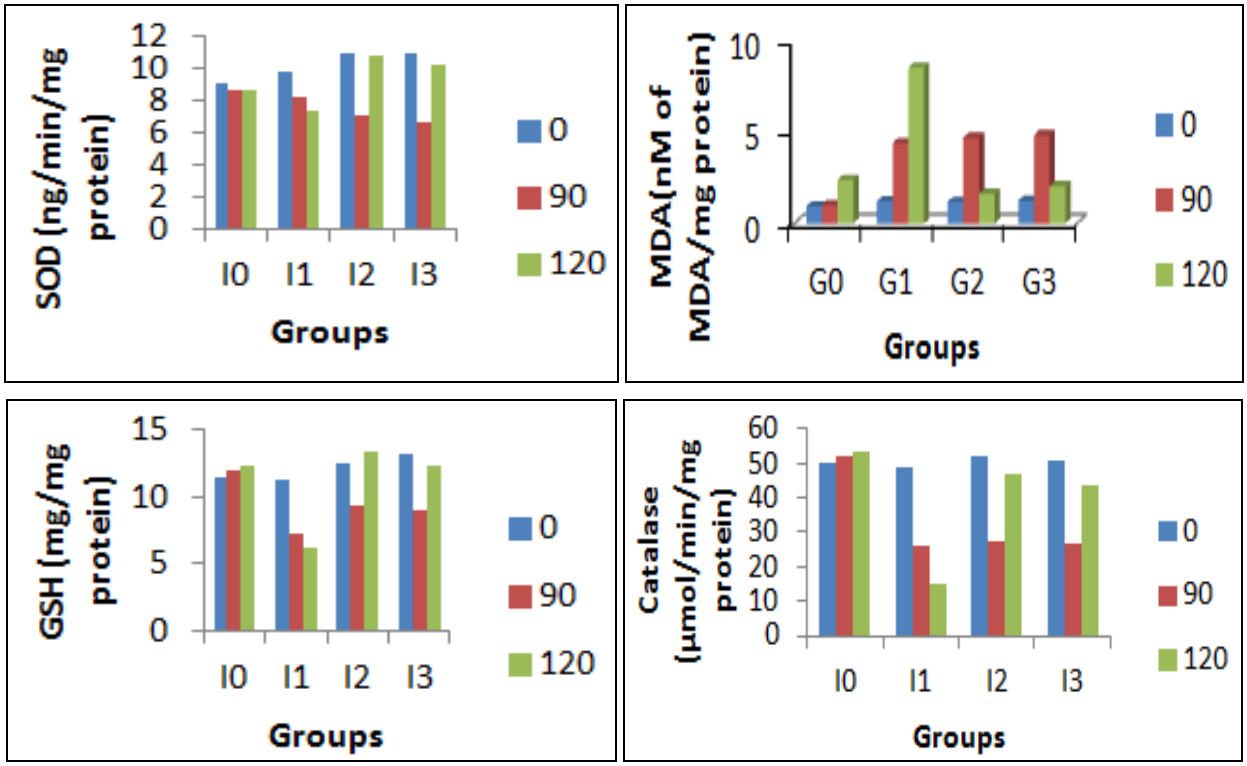
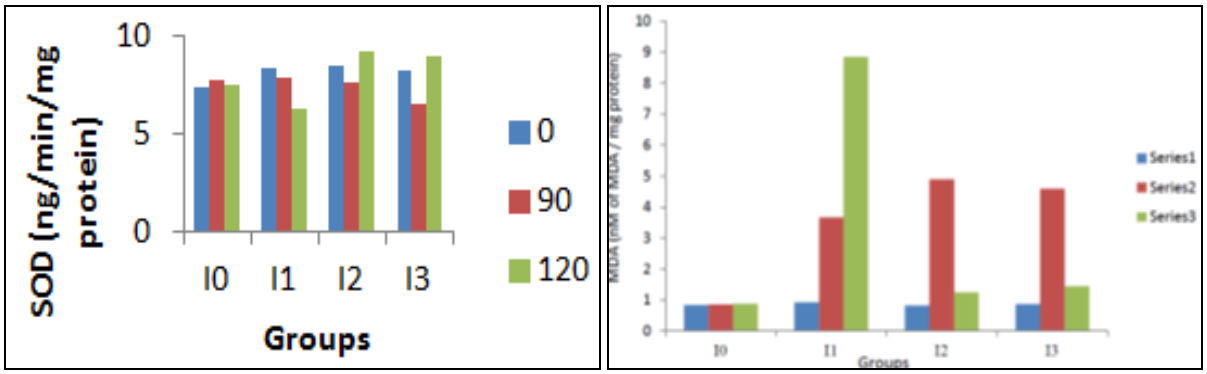


FIG. 4: EFFECT OF ARSENIC ON SOD ACTIVITY OF LIVER (SOD ng/min/mg protein), TOTAL MDA (nM OF MDA/mg protein), GSH (mg/mg protein), CATALASE (µmol/min/mg protein) OF RAT AFTER DAILY SINGLE ORAL ADMINISTRATION OF SODIUM ARSENITE AT 4 mg/kg FOR CONSECUTIVE 90 DAYS AND AMELIORATIVE EFFECT BY *GLYCOSMIS PENTAPHYLLA* LEAF POWDER AFTER 90 DAYS ONWARDS



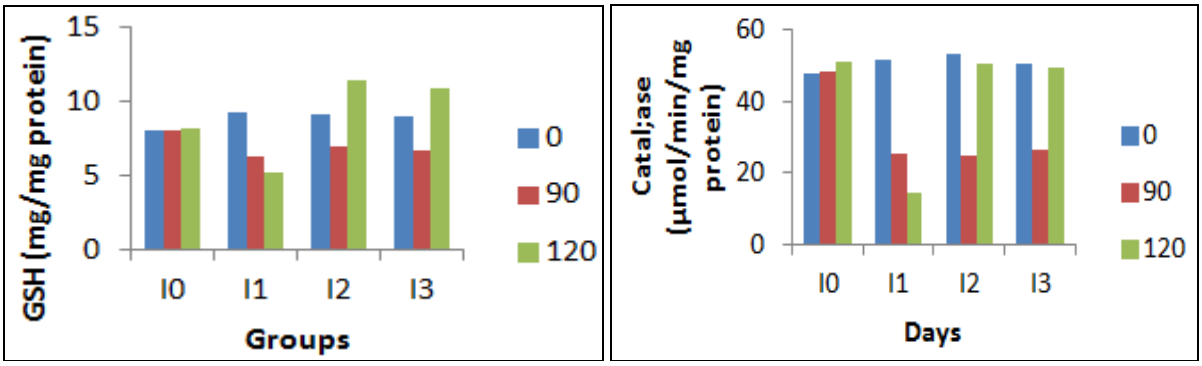


FIG 5: EFFECT OF ARSENIC ON TOTAL SOD (ng/min/mg protein), TOTAL MDA (nM of MDA/mg protein), TOTAL GSH (mg/mg protein), TOTAL CATALASE (µmol/min/mg protein) IN KIDNEY OF RAT AFTER DAILY SINGLE ORAL ADMINISTRATION OF SODIUM ARSENITE AT 4 mg/kg FOR CONSECUTIVE 90 DAYS AND AMELIORATIVE EFFECT BY *GLYCOSMIS PENTAPHYLLA* LEAF POWDER AFTER 90 DAYS ONWARDS

Histopathological findings:

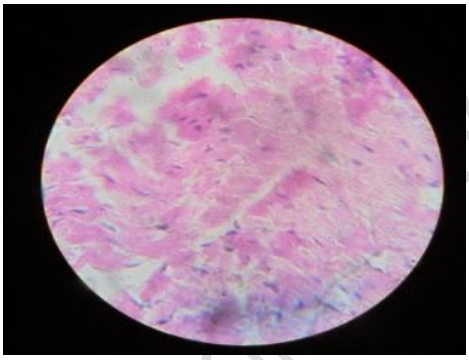


FIG. 6: CROSS SECTION OF HEART SHOWED CONGESTED BLOOD VESSELS IN THE MYOCARDIUM IN ARSENICOSIS INDUCED RATS(H & E 10X)

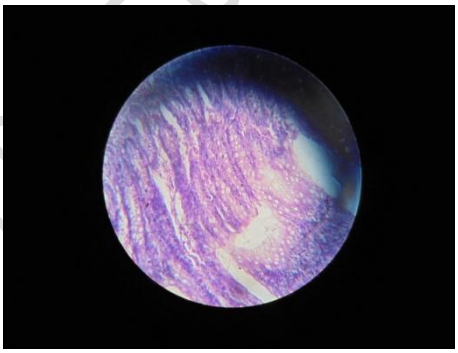


FIG. 7: CROSS SECTION OF INTESTINE SHOWED EXCESSIVE MUCOUS SECRETION IN ARSENICOSIS INDUCED RATS AND MASSIVE FATTY INFILTRATION IN EPITHELIAL CELLS OF THE VILLI. (H & E 40X)

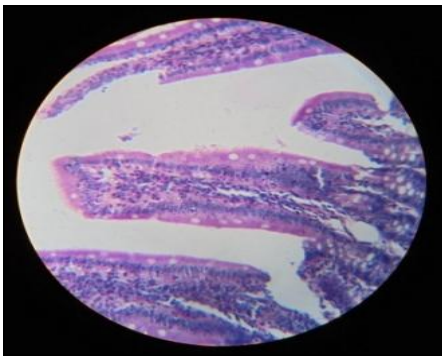


FIG. 8: CROSS SECTION OF INTESTINE SHOWED LESS SECRETION OF MUCOUS OF THE EPITHELIAL CELLS OF VILLI AFTER 30 DAYS ORAL TREATMENT WITH 500 mg/kg OF *G. PENTAPHYLLA* LEAF POWDER IN RATS (H & E 10 X)

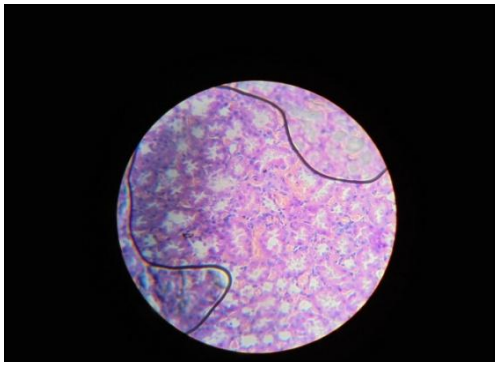


FIG. 9: CROSS SECTION OF KIDNEY SHOWED REDUCTION OF DEGENERATIVE CHANGES AFTER 30 DAYS ORAL TREATMENT WITH 250 mg/kg OF *G. PENTAPHYLLA* LEAF POWDER IN RATS (H & E 40 X)

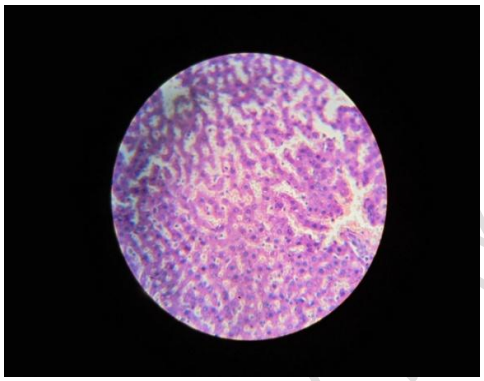


FIG. 10: CROSS SECTION OF LIVER SHOWED LESS FIBROSIS IN THE PORTAL AREA AFTER 30 DAYS ORAL TREATMENT WITH 500 mg/kg OF *G. PENTAPHYLLA* LEAF POWDER IN RATS (H & E 40 X)

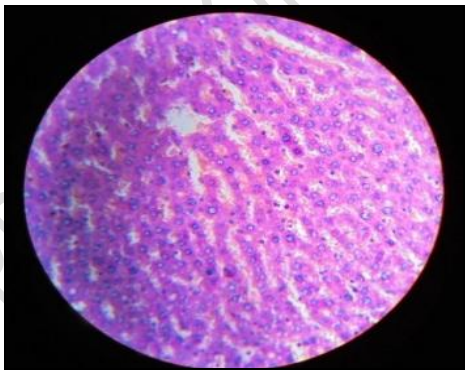


FIG. 11: CROSS SECTION OF LIVER SHOWED MILD FIBROSIS IN THE PORTAL AREA AFTER 30 DAYS ORAL TREATMENT WITH 250 mg/kg OF *G. PENTAPHYLLA* LEAF POWDER IN RATS (H & E 40 X)

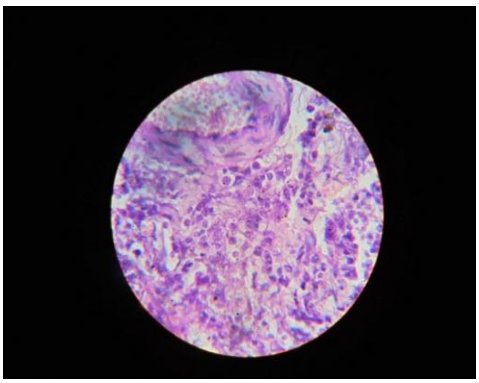


FIG. 12: CROSS SECTION OF LUNGS SHOWED LOCAL PNEUMONIC LESION AND FOCAL HAEMORRAGE IN THE LUNG ALVEOLI IN ARSENICOSIS INDUCED RATS (H & E 10X)

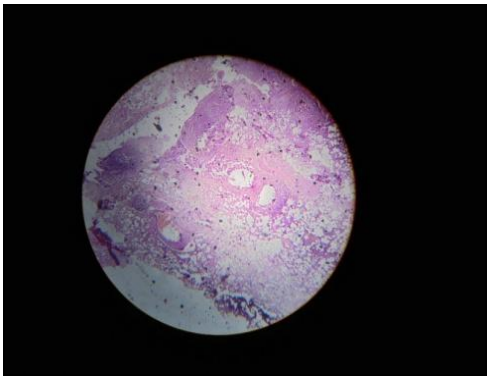


FIG. 13: CROSS SECTION OF LUNG SHOWED PLEURAL EDEMA WITH FOCAL PERI BRONCHIAL PNEUMONIC LESIONS AFTER 30 DAYS ORAL TREATMENT WITH 500 mg/kg OF *G. PENTAPHYLLA* LEAF POWDER IN RATS (H & E 40 X)

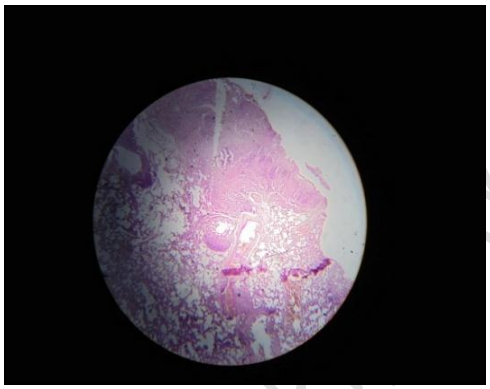


FIG. 14: CROSS SECTION OF LUNG SHOWED LESS CONGETION OF BLOOD VESSELS WITH FOCAL PNEUMONIC LESIONS AFTER 30 DAYS ORAL TREATMENT WITH 500 mg/kg OF *G. PENTAPHYLLA* LEAF POWDER IN RATS (H & E 40 X)

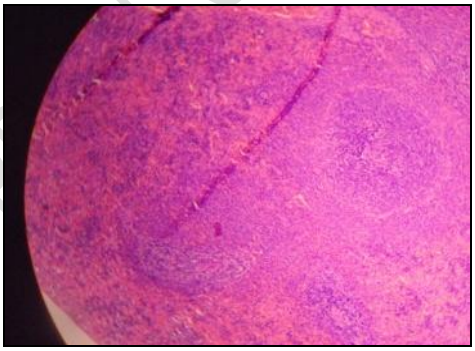


FIG. 15: CROSS SECTION OF SPLEEN SHOWED DEGENERATION OF THE LYMPHOCYTES IN THE GERMINAL FOCI IN THE RED PULP IN ARSENICOSIS INDUCED RATS (H & E 10X)

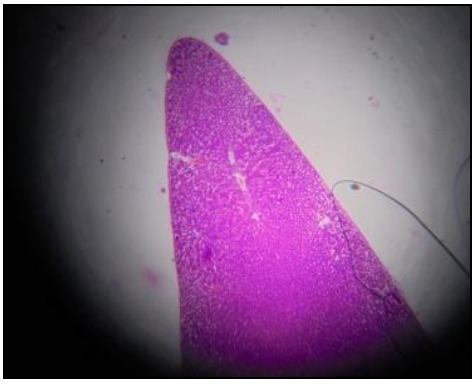


FIG. 16: CROSS SECTION OF LIVER SHOWED MASSIVE FATTY CHANGES AT THE PERIPHERY AND OF THE LOBULE IN ARSENICOSIS INDUCED RATS (H & E 10 X)

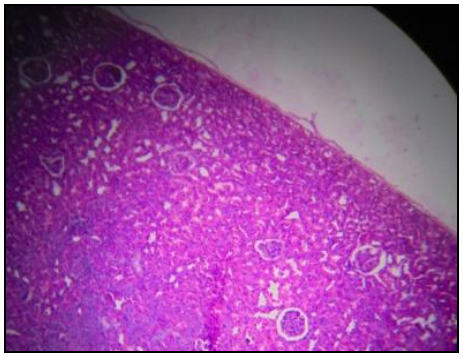


FIG. 17: CROSS SECTION OF KIDNEY SHOWED DAMAGED BOWMEN CAPSULE IN THE CORTEX IN ARSENIC INDUCED RATS (H & E 10 X)

The leaf powder of *G. pentaphylla* (500 & 250 mg/kg) significantly ($p<0.05$) increased level of haemoglobin, RBC, WBC, PCV, Lymphocyte, Neutrophil (**Fig. 1**) and decrease total ALT, AST, BUN and CRT (**Fig. 2**). Also *G. pentaphylla* leaf powder significantly increase activity SOD, GSH and Catalase of heart, liver and kidney (**Fig. 3, 4, 5**) and significantly decrease MDA of heart, liver and kidney (**Fig. 3, 4 5)**

DISCUSSION: The level of haemoglobin, total RBC count and PCV did not alter on respective days for group I_0 animals but the above values significantly ($p<0.05$) decreased till 90 days with respect to '0' day value in I_1, I_2 and I_3 groups of animals. The values significantly ($p<0.05$) decreased on day 120 in group I_1 but increased in I_2 and I_3 treated with *G. pentaphylla* leaf powder (**Fig. 1**). It is also evident from figure1that WBC, lymphocyte and neutrophil counts significantly decreased ($p<0.05$) till 90 day in I_1, I_2 and I_3 compared to '0' day but the value significantly ($p<0.05$) decreased on day 120 in group I_1 but increased in I_2 and I_3 treated with *G. pentaphylla* leaf powder. Arsenic is a toxic element for human and livestock causing serious health hazards biochemical and haemogram indices are the reliable parameters for assessment of the health status of humans and animals in arsenic toxicity [21, 22]. A significant increase in WBC count in arsenicosis rats has been observed in the present study which is in agreement with the findings of Charles 2014 [23].

It is observed from **Fig. 3, 4** and **5** that MDA of heart, liver and kidney did not alter significantly ($p<0.05$) in group I_1 at different days compared to its '0' day value. Again those values significantly ($p<0.05$) increased on day 90 for all I_1, I_2 and I_3 for group I_2 and I_3 animals and increased for group I_1 animals. It is also found from **Fig. 3, 4, 5** that SOD activity, catalase and GSH level of heart, liver, kidney did not alter significantly ($p<0.05$) in group I0 at different day compared to its day '0' value whilst the activity was decreased significantly ($p<0.05$) on day 90 and day 120 in arsenic treated animals (group I_1) but the activity was increased on day 120 in rats of groups I_2 and I_3 administered with leaf powder of *G. pentaphylla* at two dose levels. Arsenic causes toxicity through its inter action with sulphydryl groups of proteins and enzymes (to denature the proteins and enzymes within the cells) and also through an increase of ROS in the cells, consequently causing cell damage [23]. It has been reported that arsenic induced hematotoxicity is associated with As induced oxidative stress, imbalance of antioxidant system, increased lipid peroxidation resulting heme dysfunction through influencing heme biosysthesis pathway [24, 25, 26, 27].

The present results also express that exposure to arsenic significantly increase the oxidative stress which is supported with the increase level of lipid peroxidation and decreased level of non enzymic and enzymic antioxidants. But leaf powder of *G. pentaphylla* has significantly improved all these altered parameters in arsenic intoxicated rat.

Increased oxidative stress represents an imbalance between intracellular production of free radicals and the cellular defense mechanisms; notably, MDA is one of the most important markers of oxidative stress [23]. Extensive research demonstrated that arsenic causes oxidative stress in a dose and time-dependent manner [28] and increase the levels of MDA, deplete GSH and decrease activities of antioxidant enzymes such as SOD and CAT. The

leaf powder of *G. pentaphylla* was found to produce a significant less lipid peroxides than arsenic-treated rats. Section of heart of group I_1 animals revealed that blood vessels were congested in the myocardium with focal loss of striations of myocardial muscle and no neurotic changes were observed (**Fig. 6**). Section of heart of groups I_2 and I_3 animals did not reveal any significant changes apart from congestion of myocardial vessels following treatment with *G. pentaphylla* leaf powder at two dose levels.

Section of intestine of group I_1 animals showed a massive fatty infiltration in epithelial cells of the villi (**Fig. 7**). On the other hand lymphocytic proliferation in the different of focal of pairs patches is the prominent feature and increase in Globlet cells activity were indicative of local defence mechanism of the intestine following oral dose of *G. pentaphylla* leaf powder at 500mg/kg for 30 days in I_2 animals.

Expressive secretion of mucous of the epithelial cells of villi with moderate lucocytic infiltration of the lamina propria was seen in the cross section of intestine (**Fig. 8**) of group I_3 animals. Desquamation of alveolar epithelium and focal haemorrage in the lung alveoli was marked with haemosiderin pigment in the lungs of arsenic treated animals (I_1) (**Fig.12**) whilst mild pheumonic lesions were noticed in animals of group I_2 (**Fig. 13**). Mild local pneumonic lesions was noticed in the cross section of 1ung of I_3 animals (**Fig. 14**). Section of spleen of group I_1 animals showed lymphocytic proliferation infiltration in the red pulp (**Fig. 15)**. Section of spleen of group I_2 and I_3 animals showed moderate follicular lymphocytic proliferation infiltrating the red pulp. It may be observed that *G. pentaphylla* leaf powder acted as scavenger of superoxide and hydroxyl radical. The results also showed that arsenic exposure to rats caused a significant reduction in GSH level and decreased activities of SOD suggesting arsenic-induced oxidative stress. The treatment with *G. pentaphylla* leaf powder was able to restore the activities of SOD, catalase and increased GSH level.

Fig. 2 showed the activity of ALT, AST and level of BUN and CRT in different groups of animals. There values are higher till 90 days in arsenic treated animals suggesting some damage of both liver, kidney which is corroborated with the findings of Charles (2014) [23]. *G. pentaphylla* leaf powder plays an important role to reduce ALT, AST, BUN and creatinine level. The increase in liver marker enzyme (AST and ALT) is responsible for the hepatotoxicity in arsenicosis which was improved by *G. pentaphylla* administration. Section of liver of arsenic treated (I_1) group animals showed diffused fatty changes with local neurobiotic changes at the hepatocytes (**Fig. 16)**. Section of liver of animals of groups I_2 and I_3 showed liver fibrosis in the portal area were mild and other parenchyma area did not reveal any significant changes (**Fig. 10, Fig. 11**).

The significant increase in urea and creatinine values in arsenicosis in rats suggest renal impairment which may be corrected by *G. pentaphylla* treatment. It is transpired from histopathological findings that section of kidney of the experimental control group (I_1) was damaged by arsenic (**Fig. 17**) which was actually excreted out through the kidney resulting partially damaged Bowmen capsule in the cortex as well as loops of Henleys. After treated with *G. pentaphylla* leaf powder of 250mg/kg for 30 day, it had been found that the degenerative changes in the kidney was reduced and a repairative activity in the form of focal interstitial nephritis was noticed (**Fig. 9**).

Increased level of creatinine was reported by Faires (2004) [29] in arsenic intoxicated cattle. Patel and Kalia (2010) [30] also obtained higher level of serum creatinine in arsenic induced rats. Nandi *et al.*, (2006) [31] and Rana *et al.,* (2008) [32] also suggested that arsenic is a potential nephrotoxic agent – Arsenic acts on renal capillaries, tubules and glomerule to cause several renal damage [33]. Arsenic is rapidly and extensively accumulated in liver where it inhibits NAD linked oxidation of pyruvate or α-ketoglutarate.

This occurs by complexation of trivalent arsenic with vicinal thiols necessary for oxidation of this substrate [34]. Toxic effect of arsenic on hepatic parenchymal cells reflucted by elevation of liver enzymes AST and ALT in blood. GP plays an important role to reduce ALT, AST, BUN and creatinine level.

CONCLUSION: *G. pentaphylla* leaf powder may have some ameliorative effects to reduce chronic arsenicosis in rats.

ACKNOWLEDGMENT: The first author thanks Vice Chancellor of the West Bengal University of Health Sciences for giving him permission for Ph.D from where the present data have been generated. Authors are grateful to Dean, Faculty of Veterinary and Animal Sciences and Vice Chancellor, West Bengal University of Animal & Fishery Science for providing laboratory facilities for the work. Authors also convey their thanks to Raju Dasgupta, College of Medicine and JNM Hospital, West Bengal University of Health Science for his valuable helps towards statistical analysis of data.

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How to cite this article:
De A, Nath S, Das AK, Bandyopadhyay SK, Banerjee MC and Mandal TK: Effects of *Glycosmis pentaphylla* leaf powder against chronic arsenicosis in rats. Int J Pharm Sci Res 2017; 8(5): 2287-97.doi: 10.13040/IJPSR.0975-8232.8(5).2287-97.