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ORIGINAL RESEARCH ARTICLE

# Anti-diabetic Effect of *Emblica-officinalis* (Amla) Against Arsenic Induced Metabolic Disorder in Mice

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**Abstract** Chronic exposure to arsenic through drinking water and occupational exposure has been found to be associated with the diabetic symptoms. Earlier, we reported that arsenic induced enhanced oxidative stress, inflammation, dislipidemia and hepatotoxicity in mice have been protected by treatment with *Emblica officinalis* (amla). The present study has therefore been focused to investigate the efficacy of amla in mitigation of arsenic induced hyperglycemia in mice. Arsenic exposure (3 mg/kg b.w./day for 30 days) in mice altered glucose homeostasis and significantly decreases hepatic glucose regulatory enzyme, glucokinase (43%), glucose-6 phosphate dehydrogenase (38%), malic enzyme (60%) and significantly increases the level of glucose-6 phosphates (65%), phosphoenolpyruvate carboxykinase (43%), lactate, (59%) $Na^+$ (6.8%) $Cl^-$ (10.4%), anion gap (13.9%) and pancreatic (IL-1β, TNF-α) inflammation markers (52%, 53%) as compared to controls. Arsenic exposure also significantly decreased serum insulin (44%) and c-peptide protein (38%) in mice as compared to controls. Co-administration of arsenic and amla (500 mg/kg b.w./day for 30 days) balanced blood sugar level, hepatic glucose regulatory enzyme (glucokinase, glucose-6 phosphate dehydrogenase, malic enzyme (68%, 37%, 45%) and significantly decreases glucose-6 phosphatase (25%), phosphoenolpyruvate carboxykinase (22%), blood ion concentration and also lactate, $Na^+$, $Cl^-$ and anion gap (20%, 4.6%, 6.7%, 5.2%), pancreatic (IL-1β, TNF-α) inflammation marker (21%, 24%) and significantly increased the serum insulin (57%) and c-peptide protein (31%) as compared to those treated with arsenic alone. Results of the present study suggests that the hypoglycemic and antioxidant property of amla could be responsible for its protective efficacy in arsenic induced hyperglycemia.

**Keywords** Arsenic · Amla · Hyperglycemic · Inflammation · Mice · Metabolic syndrome

## Introduction

Millions of people around the globe are exposed to unsafe levels of arsenic due to consumption of contaminated drinking water. Its sub-toxic levels may not be fatal, but the accumulation of lower levels of arsenic for a longer period of time leads to chronic exposure and cause adverse health effects, including metabolic disorders [1, 2]. The toxic effect of arsenic has been found to be increased in malnourished population as they are mainly depends on the available water contaminated with arsenic. Both the USEPA and the World Health Organization (WHO) have adopted drinking water standard of 10 μg/L (10 ppb) [3, 4]. The food levels arsenic currently not regulated and it easily transmitted to the food chain and may create dangerous effects to human and ecological systems, in the long term [5]. On the other hand irrigation of agricultural soils with arsenic-contaminated groundwater leads to accumulation of arsenic in both soil and plants [6]. Epidemiological

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studies have demonstrated that chronic exposure of arsenic through drinking water increased rates of various diseases, including various cancers, nervous system disorders, peripheral vascular disease (black foot disease, a peripheral artery disease) and endocrine dysfunction [4].

Studies have also suggested that high levels of arsenic exposure increase the risk of type-2 diabetes mellitus (T2DM) which is more prevalent than type-1 diabetes mellitus [7]. In India, the WHO reported that about 32 million people suffered from diabetes in 2000. According to the International Diabetes Federation, the total number of diabetic patients is nearly 40.9 million, which is supposed to increase to 69.9 million in 2025 [4]. Environmental and lifestyle factors are the main causes of this remarkable increase in metabolism syndrome and high prevalence T2DM [8]. T2DM is a widespread global metabolic disorder, distinguished by the unusual metabolism of carbohydrates and lipids, mainly resulting either from insulin resistance and impaired glucose uptake by peripheral tissues, consisting of skeletal muscle and adipose tissue [9]. Arsenic ingestion through the food chain may affect physiological and biochemical processes in the body and plays an etiological role in diabetes development. Low or moderate arsenic exposure plays a positive role, while a high level of arsenic is associated with the risk of developing T2DM [10]. Arsenic or its metabolites impair insulin dependent glucose uptake, leading to insulin resistance and cause T2DM which leads to glucose toxicity by increasing protein glycation and activating the polyol pathway associated with the protein of poly ADP ribose polymerase (PARP) and protein kinase-C expression [11]. At the same time involvement of oxidative stress linked with mitochondrial dysfunction in the arsenic induced T2DM has been well reported [12]. T2DM has also been found to be associated with the increased generation of ROS resulting in inflammation, cell death and system organ dysfunction [13].

The use of traditional medicines has been increased in recent years and most of the population of developing countries depends on the herbal remedies for their healthcare needs [14]. The significant advantages of therapeutic uses of medicinal plants are due to their safety besides being economical and effective [15]. *Emblica officinalis* (amla) is an important medicinal plant in Ayurveda and Unani systems of medicine [16]. Amla fruits are well known for their pharmacological activities as well as antidiabetic properties [17]. Numerous studies have revealed that herbal agents consisting antioxidant activities are capable of neutralizing free radicals are effective in preventing as well as reducing the severity of diabetic complications [18]. Earlier studies have demonstrated that arsenic induced enhanced oxidative stress and inflammation linked to apoptosis in immune organ and induced renal and hepatic toxicity in mice could be protected through simultaneous treatment with amla [19, 20]. Recently it has also been reported that arsenic-induced cardiovascular risk factors through simultaneous treatment with arsenic and amla is due to its anti-inflammatory, hypo-lipidimic activity and metal binding property of amla which could reduce the load of arsenic in spleen and thymus and help to decrease the generation of reactive oxygen and nitrogen species and imparts its protective roles [21, 22]. In view of the multiple pharmacological spectrum of amla, the present study has been focused to delineate the hypoglycemic role of amla against arsenic induced diabetes in mice.

## Materials and Methods

### Animals and Treatment

The study was approved by the Institutional Animal Ethics Committee of King George's Medical University, Lucknow (No. 121 IAH/Pharma-11), India and all the experiments were carried out in accordance with guidelines set by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests (Government of India), New Delhi, India. Male Balb/c mice (23 ± 2 g) were obtained from the animal breeding colony of CSIR-Indian Institute of Toxicology Research (Lucknow). Mice were housed in an air-conditioned room at 25 ± 2 °C, relative humidity 50% with 12 h light/dark cycle under standard hygiene conditions.

Mice had free access to a pellet diet and filtered water ad libitum. The dose of fruit extract of *Emblica officinalis* and arsenic is based on earlier studies [20–22] and for the study, the mice were randomly divided into four groups with 8 animals/group: and the dose of arsenic and amla were given orally with the help of canula after dissolving it in suitable solvent:

*Group I* Mice treated with vehicle (2% gum acacia) for the duration of the treatment and served as control.
*Group II* Mice treated with sodium arsenite (dissolved in distilled water at 3 mg/kg body weight, *per os* daily for 30 days).
*Group III* Mice treated with fruit extract of *Emblica officinalis* (500 mg/kg body weight, suspended in 2% gum acacia, *per os* daily for 30 days).
*Group IV* Mice co-treated with arsenic and fruit extract of *Emblica officinalis* daily for 30 days as in Groups II and III.

### Assay of Fasting Blood Glucose (FBG)

At the last day of the experimental period, the overnight fasting animals were anesthetized with ether. Fasting blood glucose was measured by cutting the tail tip and glucose levels were determined using a blood glucose that uses test strips to assess a glucose oxidoreductase mediated dye reaction, according to the manufacturer's instruction.

Immediately after, heart puncture 2 mL of blood was quickly collected in 10% EDTA tubes for the separation of plasma used for the biochemical assessment were performed [23].

### Assay of Oral Glucose Tolerance Test (OGGT)

After 4 experimental weeks, in order to oral glucose tolerance test (OGTT) assessment, all animals were fasted overnight and D-Glucose (2 g/kg body weight) dissolved in distilled water and orally gavaged to the fasted mice. Then, blood samples were immediately collected from a tail-clip bleed and blood glucose levels were measured using glucometer before and 30, 60, 90, 120 and 120 min after glucose administration [24].

### Blood Collection/Tissues Preparation

At the end of the experimental period, FBG and OGGT assay was performed all the animals were sacrificed by cervical dislocation. After heart puncher blood was quickly collected 1 mL fresh blood stored for the assessment of blood ion analysis and remaining blood was stored at 10% EDTA tubes for the separation of serum. Liver and Pancreatic tissue were isolated immediately and placed in ice cold NaCl (0.15 M) solution, perfused with the same solution to remove blood cell, blotted on the filter paper, quickly homogenized by using biochemical examination.

### Assay of Blood Ion and Metabolite Concentration Analysis

Freshly collected Blood sample was performed by blood ion and metabolite concentrations. An Ultra analyzer (Waltham, MA, USA) was used to assess the pH, lactate, bicarbonate (HCO3), hemoglobin (Hb), $Na^+$, and $Cl^-$ ion levels in the freshly collected whole blood. The anion gap values were calculated using the formula ($Na^+$–[$Cl^-$+$HCO_3^-$]).

### Assay of Hepatic Glucose Regulating Enzymes

The mice livers were quickly rinsed and lysed in homogenizing buffer containing 0.25 M sucrose, 0.02 M triethanolamine (pH 7.4), and 0.12 mM dithiothreitol. The cytosolic fractions were then prepared by centrifugation at 10,000 g for 1 h, and they were used for further enzyme assays. Glucose-6-phosphate dehydrogenase (G6PD), Glucose-6-phosphatase (G6P), and malic enzyme (ME) levels were measured using a spectrophotometer. Glucokinase isozymes (GK) were assayed as described by [25] using the coupled enzymatic reaction system using Nicotinamide adenine dinucleotide phosphate (NADP) at 25 °C. Phosphoenolpyruvate carboxykinase (PEPCK) enzyme activity was assayed at 25 °C in the reverse direction, carboxylation of phosphoenolpyruvate to form oxaloacetic acid in the presence of NADH [26].

### Assay of Serum Insulin and C-Peptide Protein

Fasting serum insulin and C-peptide levels were measured using mice insulin and C-peptide enzyme-linked immunosorbent assay (Sigma-Aldrich) kits. According to the manufacturer's protocol.

### Assay of Pancreatic Tissue Interleukin 1 Beta (IL-1β) and Tumor Necrosis Factor (TNF-α)

The levels of Interleukin-1 beta and tumor necrosis factor in Pancreatic tissue samples of mice exposed to arsenic and simultaneous treatment of arsenic and amla were estimated by using the Quantikine mouse IL-1β and TNF-α kit obtained from R&D systems. The 96-well pre-coated plate with polyclonal antibody specific for mouse IL-1β and TNF-α was used. The intensity of the colour was measured in proportion to the amount of pancreatic tissue IL-1β and TNF-α bound to the sample. The levels of IL-1β and TNF-α were calculated using a standard curve.

### Statistical Analysis

The statistical analysis was carried out by Graph Pad Prism 3.02 using one way analysis of variance followed by Newman–Keuls test for multiple pairwise comparisons among the groups. All values have been expressed as mean ± SEM. $P$ value $< 0.05$ has been considered significant.

## Results

### Effect on Glucose Homeostasis and Tolerance

Exposure to arsenic in mice caused a significant increase in fasting blood sugar (48% $p < 0.001$) as compared to controls suggesting the diabetogenic effect of the arsenic (Figs. 1, 2). OGTT level time dependent was significantly increased 30 min (71%, $p < 0.001$), 60 min (65.4%

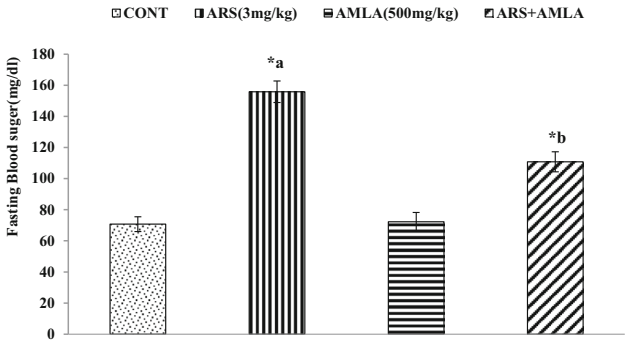



**Fig. 1** Effect on fasting blood sugar in mice exposed to arsenic, amla and their co-treatment for 30 days. Values are mean ± SEM of five animals in each group. *[a]Compared to control group; *[b]compared to arsenic treated group. *Significantly differs ($p < 0.05$)

$p < 0.001$), 90 min (61.5% $p < 0.001$), 120 min (56.7% $p < 0.01$), 150 min (41.6%, $p < 0.01$) as compared to control group. Co-treatment with arsenic and amla decreases fasting blood sugar level (36%, $p < 0.05$) and also time dependent OGTT blood sugar level was decreases 30 min (22%, $p < 0.01$), 60 min, (26.3%, $p < 0.01$), 90 min (28.5%, $p < 0.01$), 120 min (31.7%, $p < 0.001$), 150 min (41.6, $p < 0.001$) as compared to mice treated with arsenic alone. No significant effect on OGTT was observed in mice treated with amla alone as compared to controls (Figs. 1, 2).

## Effect on Blood Ions Levels in Mice

Exposure to arsenic in mice caused a significant decrease in pH and $HCO_3$ concentrations (7. 23, 25%, $p < 0.01$), and Similarly, significantly increases Lactate, $Na^+$, $Cl^-$, Anion gap (59%, $p < 0.001$, 6.8%, $p < 0.01$, 10.4%, $p < 0.05$, 13.9%, $p < 0.05$) in the blood of mice as compared to controls suggesting the blood toxic effect of the arsenic (Table 1). Co-treatment with arsenic and amla increases in pH and $HCO_3$ (7.44, 15%, $p < 0.01$), and significantly decreases Lactate, $Na^+$, $Cl^-$, and Anion gap (20.3%, $p < 0.05$, 4.6%, $p < 0.05$, 6.7%, $p < 0.05$, 5.2%, $p < 0.05$) as compared to mice treated with arsenic alone. No significant effect on blood parameters and ion concentration levels observed in mice treated with amla alone as compared to controls (Table 1).

## Effect on Hepatic Glucose Regulating Enzymes

Exposure to arsenic in mice caused a significant decrease in glucokinase, glucose-6 phosphate dehydrogenase, malic enzyme, (43.8, $p < 0.05$, 38%, $p < 0.05$, 60%, $p < 0.01$) in hepatic glucose regulating enzyme and significantly increases glucose-6 phosphates, phosphoenolpyruvate carboxykinase (65.4%, $p < 0.01$, 43%, $p < 0.05$) as compared to controls suggesting the risk factor of diabetic effect on the arsenic treated group (Table 2). Co-treatment with arsenic and amla increases glucokinase, glucose-6 phosphate dehydrogenase, malic enzyme (68%, $p < 0.05$, 37.1%, $p < 0.05$, 45%, $p < 0.05$) significantly decreases glucose-6 phosphatase, phosphoenolpyruvate carboxykinase (25.3%, $p < 0.05$, 22.2%, $p < 0.05$) as compared to mice treated with arsenic alone. No significant effect was observed in mice treated with amla alone as compared to controls (Table 2).

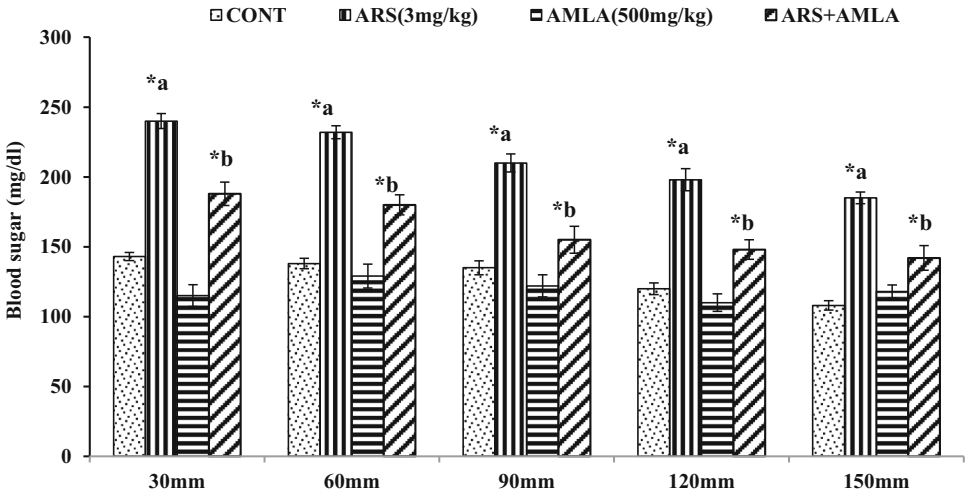



**Fig. 2** Effect on OGTT in mice exposed to arsenic, amla and their co-treatment for 30 days. Values are mean ± SEM of five animals in each group. *[a]Compared to control group; *[b]compared to arsenic treated group. *Significantly differs ($p < 0.05$)

**Table 1** Effect on blood ion level in mice exposed to arsenic, amla and their co-treatment for 30 days

| Parameters | Treatment groups | | | |
|---|---|---|---|---|
| | CONT | ARS (3 mg/kg) | AMLA (500 mg/kg) | ARS + AMLA |
| PH | 7.52 ± 0.72 | 7.23 ± 1.4*[a] | 7.42 ± 0.30 | 7.44 ± 0.51 |
| Lactate (mmol/L) | 4.92 ± 0.49 | 7.85 ± 0.50*[a] | 4.87 ± 0.45 | 6.25 ± 0.47*[b] |
| HCo3− (mmol/L) | 28.38 ± 0.73 | 21.28 ± 0.66*[a] | 27.28 ± 0.73 | 24.5 ± 0.78*[b] |
| Na+ (mmol/L) | 146 ± 1.47 | 156.5 ± 2.39*[a] | 145.3 ± 2.05 | 149.3 ± 1.49*[b] |
| Cl− (mmol/L) | 105.3 ± 2.49 | 116.5 ± 1.93*[a] | 102.5 ± 1.84 | 108 ± 2.97*[b] |
| Anion gap | 12.32 ± 0.95 | 18.72 ± 1.78*[a] | 14.52 ± 1.68 | 16.8 ± 1.85*[b] |

Values are mean + SEM of five animals in each group

*Significantly differs ($p < 0.05$)

*[a]Compared to control group; *[b]compared to arsenic treated group

**Table 2** Effect on hepatic glucose regulatory enzyme in mice exposed to arsenic, amla and their co-treatment for 30 days

| Parameters | Treatment groups | | | |
|---|---|---|---|---|
| | CONT | ARS (3 mg/kg) | AMLA (500 mg/kg) | ARS + AMLA |
| GK (U/g tissue) | 0.57 ± 0.05 | 0.32 ± 0.02*[a] | 0.54 ± 0.09 | 0.53 ± 0.02*[b] |
| G6PD (U/g tissue) | 6.9 ± 0.05 | 4.23 ± 0.55*[a] | 6.43 ± 0.44 | 5.8 ± 0.55*[b] |
| G6P (U/g tissue) | 14.67 ± 1.76 | 25.0 ± 1.52*[a] | 10.67 ± 1.20 | 18.67 ± 1.45*[b] |
| ME (U/g tissue) | 2.0 ± 0.05 | 0.8 ± 0.15*[a] | 1.93 ± 0.08 | 1.16 ± 0.29*[b] |
| PEPCK (U/g tissue) | 76.75 ± 7.98 | 110 ± 4.56*[a] | 78.75 ± 7.45 | 85.5 ± 10.22*[b] |

Values are mean + SEM of five animals in each group

*Significantly differs ($p < 0.05$)

*[a]Compared to control group; *[b]compared to arsenic treated group

### Effect on Serum Insulin and C-Peptide Protein

Effect of arsenic and co-treatment of arsenic and amla on mice has been presented in Figs. 3 and 4. Exposure to arsenic in mice caused a significant decrease in serum insulin and C-peptide protein in sample (44.8%, $p < 0.05$, 38.2%, $p < 0.05$) as compared to controls suggesting the dibetogenic effect of the arsenic. Co-treatment with arsenic and amla significantly increased the serum insulin and C-peptide protein (57%, $p < 0.05$, 31.7%, $p < 0.05$) as compared to mice treated with arsenic alone. No significant effect on serum insulin and C-peptide protein was observed in mice treated with amla alone as compared to controls (Figs. 3, 4).

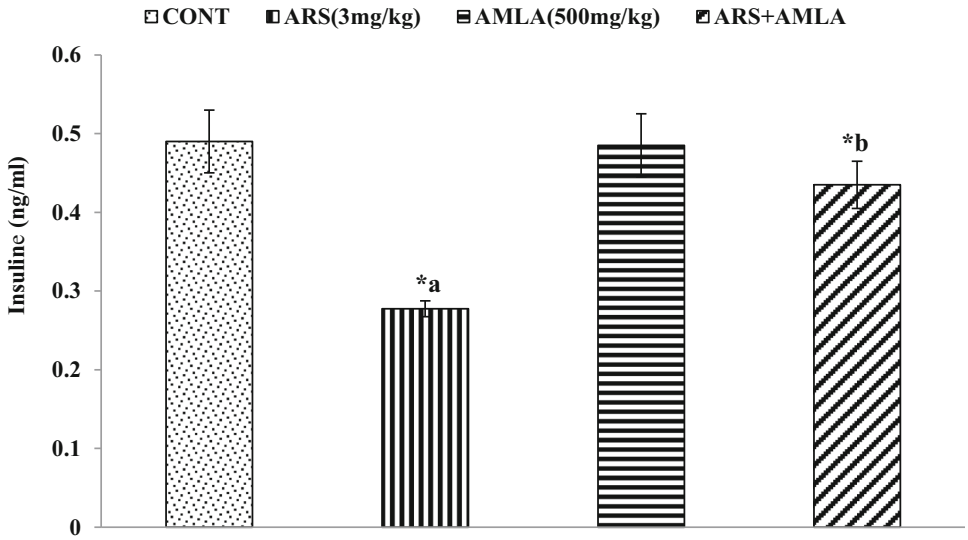



**Fig. 3** Effect on serum insulin in mice exposed to arsenic, amla and their co-treatment for 30 days. Values are mean ± SEM of five animals in each group. *[a]Compared to control group; *[b]compared to arsenic treated group. *Significantly differs ($p < 0.05$)

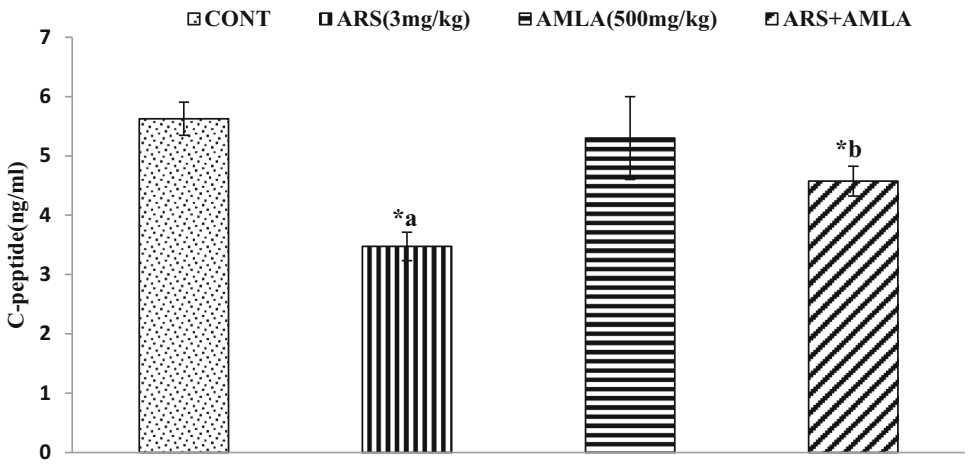



**Fig. 4** Effect on c-peptide protein in mice exposed to arsenic, amla and their co-treatment for 30 days. Values are mean ± SEM of five animals in each group. *[a]Compared to control group; *[b]compared to arsenic treated group. *Significantly differs ($p < 0.05$)

### Effect on the Pancreatic Tissue Interleukin-1 Beta (IL-1β)

Exposure to arsenic in mice caused a significant increase in pancreatic tissue Interleukin-1β sample (52%, $p < 0.01$) as compared to controls, suggesting the pancreaotoxic effect of the arsenic (Fig. 5). Co-treatment with arsenic and amla decreases the level of Interleukin-1β (21%, $p < 0.05$) as compared to mice treated with arsenic alone. No significant effect on Interleukin-1β was observed in mice treated with amla alone as compared to controls (Fig. 5).

### Effect on the Pancreatic Tissue Tumor Necrosis Factor (TNF-α)

Exposure to arsenic in mice caused a significant increase in tumor necrosis factor-α sample (53.8%, $p < 0.01$) as compared to controls suggesting the pancreao inflammatory effect of the arsenic. Co-treatment with arsenic and amla decreases level in tumor necrosis factor-α (24.9%, $p < 0.01$) as compared to mice treated with arsenic alone. No significant effect on TNF-α was observed in mice treated with amla alone as compared to controls (Fig. 6).

## Discussion

Metal induced oxidative stress found to affect insulin gene and alter the molecular mechanism in glucose regulations and decrease insulin release, impairing insulin receptor and disrupting the glucose uptake, decreasing peripheral utilization of glucose and impaired glucose metabolism [27]. T2DM is a metabolic disorders associated with the chronic exposure to arsenic through consumption of contaminated drinking water and occupational exposure of arsenic [28]. Gribble et al. [29] reported that the association between arsenic and its methylated metabolites may induce diabetes by impairing insulin production by pancreatic β-cells or inhibiting basal or insulin-stimulated glucose uptake by peripheral tissues [24]. In the diabetic conditions, hepatic

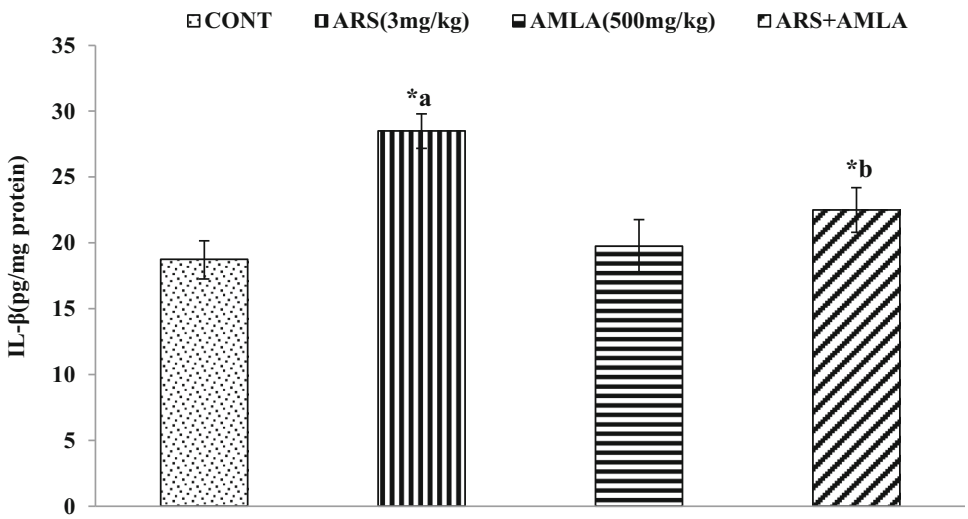



**Fig. 5** Effect on IL-β in mice exposed to arsenic, amla and their co-treatment for 30 days. Values are mean ± SEM of five animals in each group. *[a]Compared to control group; *[b]compared to arsenic treated group. *Significantly differs ($p < 0.05$)

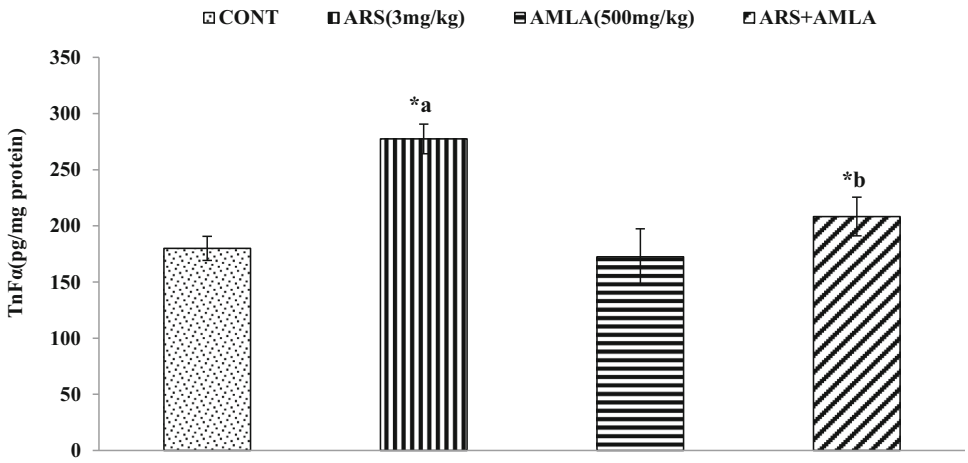



**Fig. 6** Effect on TNF-β in mice exposed to arsenic, amla and their co-treatment for 30 days. Values are mean ± SEM of five animals in each group. *[a]Compared to control group; *[b]compared to arsenic treated group. *Significantly differs ($p < 0.05$)

glucose overproduction is occurred which further leads to hyperglycemia. Hyperglycemia occurs in T2DM because of the toxic conditions destroy the pancreatic β-cells, leading to a deficiency in insulin secretion. This effect subsequently causes disturbances in all the biochemical mechanisms of the body, leading to hyperlipidemia as well as cardiac and renal failure [30]. Studies have reported that increases blood glucose level of arsenic exposed mice indicate hyperglycemic condition could be due to the impaired insulin secretion from β-cell of pancreases as impaired glucose metabolism in liver [31]. In addition, c-peptide, a protein that connects the α- and β-chains of insulin in the proinsulin molecule, is important for insulin synthesis [32]. Recently, Grau-Perez et al. [33] reported that consumption of seafood having high level of arsenic could be responsible of type-2 diabetes in Spanish people. Further, Muñoz et al. [34] reported that diabetes mellitus in human population is largely associated with arsenic exposure. Idress and Batool [35] also suggested that unprotected chronic arsenic in drinking water may be a risk factor of T2DM in Pakistan population. In the present study sub chronic arsenic exposure exhibited altered glucose homeostasis, hepatic glucose regulatory enzyme, increased blood ion concentration and pancreatic inflammation as compared to controls. Arsenic exposure also significantly decreased serum insulin, c-peptide protein and altered hepatic anatomical structure in mice as compared to controls are consistent with the earlier studies.

The use of natural agents and alternative therapies in the treatment and management of diabetes mellitus is becoming increasingly popular not only to reduce the side effects of synthetic medicines but also to lower the overall financial burden caused by the disease. Many indigenous medicinal plants and herbs contain a number of active principles, which have shown anti-hyperglycemic, anti-hyperlipidemic and anti-inflammatory effects in animal models and could therefore be useful for treating many diseases including diabetes [36]. Amla has also been reported to be beneficial in the treatment of acute pancreatitis in rats. The potent antioxidant, anti-inflammatory and free radical scavenging activities of amla fruit extracts might play an important role in controlling the hyperglycemia and dyslipidemia and may reduce the risk of diabetes and other diseases [19, 20]. It consist of both anti-hyperglycemic and lipid-lowering properties and might be used as an ideal plant food supplement in developing successful alternative therapies in the prevention and treatment of diabetes, dyslipidemia, obesity and cancers in general population [22]. It has been shown to effectively lower the plasma glucose levels and improve other diabetic-related parameters, such as liver gluconeogenesis and serum lipid-parameters [24].

In the present study, we investigated whether treatment with amla alone or in combination could have protective efficacy against arsenic induced hyperglycemia in mice. The results showed that the co-administration of arsenic and fruit extract of amla maintained blood sugar level, balance the hepatic glucose regulatory enzyme, blood ion concentration as compared to those treated with arsenic alone. Also, the decreased levels of serum insulin and c-peptide protein in arsenic treated mice caused by the destruction of pancreatic β-cells were restored in the group co-treated with amla suggesting the hypoglycemic effects of amla in arsenic treated mice that might be due to the restoration of these hepatic glucose regulating enzymes. Impairment of electrolyte balance including $Na^+$, $Cl^-$ and the anion gap are very common in diabetic patients due to increased urinary loss. These symptoms were also found to be improved in the group co-treated with amal as compared to those treated with arsenic alone that could possibly due to the modification of hyperglycemia and insulin deficiency consistent with the earlier studies [37].

The findings of the present study clearly revealed that arsenic exposures in altered hepatic glucose regulatory

enzyme, pancreatic inflammation, decreased serum insulin and c-peptide protein in mice. It also altered the hepatic anatomical structure associated with enhanced oxidative stress in mice. Simultaneous treatment of arsenic and fruit extract of amla scavenge the arsenic induced free radicals and showed its anti-diabetic properties as evident by maintaining blood sugar level, balance the hepatic glucose regulatory enzyme, blood ion concentration, serum insulin and c-peptide protein in mice. The hypoglycemic and antioxidant property of amla could be responsible for its protective efficacy in arsenic induced hyperglycemia, as recent evolving nutigenomics and nutrigenetics has predicted impact of nutrients not only on gene but also on whole genome [38]. Further studies are required to understand the molecular mechanisms of arsenic induced hyperglycemia and its protection by amla.

**Acknowledgements** The study was approved by the Institutional Animal Ethics Committee of King George's Medical University, Lucknow (No. 121 IAH/Pharma-11), India and all the experiments were carried out in accordance with guidelines set by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests (Government of India), New Delhi, India.

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**Compliance with Ethical Standards**

**Conflict of interest** All authors declare that they have no conflict of interest.

**Human and Animal Rights** Manuscript complies with the Ethical Rules (Animal based study) applicable for this journal.

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