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## ROLE OF *ANDROGRAPHIS PANICULATA* ON ALTERED STEROIDOGENESIS AND OXIDATIVE IMPAIRMENT IN OVARY OF MICE SUBJECTED TO ARSENIC INTOXICATION

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**ABSTRACT:** The present study was designed to determine the role of *Andrographis paniculata* (AP; 50 mg/kg) against the oxidative stress caused by the arsenic (0.5 and 1.0 mg/kg) for 30 days in adult mice. The results of *in-vivo* studies demonstrated that arsenic treatment resulted in a significant dose-dependent increase in the ovarian arsenic level and lipid peroxidation (LPO), followed by a marked reduction in gravimetric data, levels of total ascorbic acid, glutathione and in the activities of superoxide dismutase, catalase, and glutathione peroxidase. A significant reduction in the activities of  $3\beta$  and  $17\beta$  hydroxysteroid dehydrogenases along with elevated levels of cholesterol indicated ovarian endocrine dysfunction. These results suggest that an increase in free radical formation relative to loss of antioxidant defense system during arsenic exposure may render ovary more susceptible to oxidative damage leading to their functional inactivation. On the other hand, co-administration of arsenic with *Andrographis paniculata* (AP) restored altered biochemical variables, antioxidant balance, and gravimetry which suggests that the free radical-mediated damage during arsenic-induced oxidative stress could have been ameliorated by *A. paniculata* (AP) by its anti-oxidative potential.

**INTRODUCTION:** Inorganic arsenic compounds are well known for their high toxicity. Natural contamination of groundwater by arsenic has become a critical water quality problem in many parts of the world, particularly in Southeast Asia. Today, chronic low-dose arsenic exposure *via* drinking water presents a major concern because it affects human populations and causes severe biochemical and pathological problems such as hyperkeratosis, black foot disease, cardiovascular disease, diabetes mellitus and cancer of the liver, kidney, lung and bladder <sup>1,2</sup>.

Inorganic arsenic increases the rate of formation of reactive oxygen species including superoxide anion radical and hydroxyl radical through a chain reaction <sup>3</sup>. It has further been demonstrated that reactive oxygen species are directly involved in oxidative damage to many cellular components such as lipids, proteins, and DNA in cells exposed to arsenic, which can ultimately lead to cell death <sup>4,5</sup>. Most cases of human exposure to arsenic compounds result from natural environmental source like drinking water, in which it is difficult to remove the source of contamination then inclusion of protective factors in the diet may be useful to prevent arsenic toxicity <sup>6</sup>.

Antioxidants play an important role against the reactive oxygen species (ROS). Reports indicate that there is an inverse relationship between the dietary intake of an antioxidant and the incidence of human diseases. Hence, the search for natural

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antioxidant is essentially important. *Andrographis paniculata* (Family: Acanthaceae), a native plant in Southeast Asia, has been widely used in traditional medicine to treat various chronic and infectious diseases. It has been demonstrated a number of different pharmacological actions in *in-vitro* and animal studies<sup>7</sup>. Anticancer<sup>8</sup>, immunomodulatory, anti-inflammatory<sup>9</sup>, antipyretic, hepatoprotective<sup>10, 11</sup>, hypoglycemic<sup>12</sup>, antiplatelet and antioxidant<sup>10, 12</sup> activities have all been reported<sup>13</sup>. Since, AP extract contains diterpenoids, flavonoids, and steroids of which diterpene lactones (andrographolides) are the main components and have been reported to contain various therapeutic efficacies<sup>14, 15, 16</sup>. Hence, the present study aimed to evaluate the possible pharmacological role of AP in arsenic mediated ovarian dysfunction.

### MATERIALS AND METHODS:

**Animals:** Healthy, adult female albino mice (*Mus musculus*) of Swiss strain weighing between 30-35 gm were procured under the Animal Maintenance and Registration No. 167/1999/ CPCSEA from the Ministry of Social Justice and Empowerment, Government of India. All the animals were acclimatized seven days prior to the commencement of the treatment. They were housed in an air-conditioned animal house at a temperature of  $26 \pm 2$  °C and exposed to 10-12 h of daylight and relative humidity of 30-70%. Animals of different groups were caged separately and were maintained on standard chow (National Institute of Occupational Health (NIOH), containing wheat 70%, gram-20%, fish meat - 5% and yeast powder - 5%) and water was given *ad libitum*.

**Treatments:** Arsenic trioxide ( $As_2O_3$ ) was purchased from Hi-Media Laboratories Ltd., Mumbai, India, and *Andrographis paniculata* (AP) was obtained from Natural Remedies, Bangalore, India. A stock solution of arsenic trioxide was prepared in double-distilled water and given to mice with feeding tube attached to a hypodermic syringe. Both the doses for arsenic are derived from its  $LD_{50}$  value<sup>17</sup>.

Animals were divided into following five groups: Group I served as untreated (control), Group II was orally given 0.5 mg/kg by. wt  $As_2O_3$  (Low dose-LD) while Group III was orally treated with 1 mg/kg by. wt  $As_2O_3$  (High dose- HD) for 30 days.

Group IV was given 50 mg/kg by wt *Andrographis paniculata* only. Animals in Group V were orally administered 1 mg  $As_2O_3$ /kg + 50 mg/kg AP. At the end of each treatment, the animals were weighed and then sacrificed using light ether anesthesia. The ovary of mice was dissected out carefully, blotted free of blood and weighed up to the nearest milligram and used for the different assays.

Lipid peroxidation (LPO) was determined by the method of Ohkawa *et al.*<sup>18</sup> The activities of catalase (CAT; E.C.1.11.1.6) and superoxide dismutase (SOD; E.C.1.15.11) were analyzed by the modified method of Luck<sup>19</sup> and spectrophotometric method of Kakkar *et al.*,<sup>20</sup> respectively and glutathione (GSH) was estimated by the method of Grunert & Philips<sup>21</sup>. The activity of glutathione peroxidase (GPx; E.C.1.11.19) was assayed by the modified method of Pagila & Valentine<sup>22</sup>. Protein levels were estimated by the method of Lowry *et al.*,<sup>23</sup> and total ascorbic acid (TAA) was assessed by the method of Roe & Kuether<sup>24</sup>. Cholesterol level was analyzed by the method of Zlatkis *et al.*,<sup>25</sup>  $3\beta$ -hydroxy steroid dehydrogenase and  $17\beta$ -hydroxysteroid dehydrogenase were measured according to the method Talalay<sup>26</sup>. Arsenic retention was estimated by Arsenic Test kit obtained from Germany. For all biochemical estimations a minimum of 8 replicates was done for each parameter. Data were statistically analyzed using the student's t-test.

**RESULTS:** Arsenic exposure caused a significant ( $p < 0.001$ ) reduction in body and organ weights of arsenic-treated groups. The groups treated with arsenic alone showed arsenic deposition in the ovary when compared with the control group. Upon treatment with AP, a marked recuperation in gravimetric values and the elementary arsenic content in the ovary were observed in **Table 1**. Ovarian  $3\beta$  and  $17\beta$  hydroxysteroid dehydrogenase (HSDs) activities had a significant ( $p < 0.01$ ) decrease accompanied by a marked ( $p < 0.001$ ) elevation in cholesterol levels. A significant ( $p < 0.001$ ) drop in the ovarian protein content was also observed in arsenic-treated groups. In this study, the altered level of steroidogenic parameters and protein content were restored significantly with AP supplementation **Table 2**.

**TABLE 1: GRAVIMETRIC PARAMETERS & ARSENIC RETENTION IN ARSENIC AND ANDROGRAPHIS PANICULATA EXPOSED MICE**

	Group-1	Group-2	Group-3	Group-4	Group-5
Body weight (gm)	31.25±0.52	25.50±0.33 <sup>†</sup>	24.75±0.23 <sup>†</sup>	30.50±0.33 <sup>ns</sup>	28.75±0.52 <sup>ns</sup>
Organ weight (gm)	12.81±0.36	8.13±0.34 <sup>†</sup>	5.31±0.34 <sup>†</sup>	12.31±0.23 <sup>ns</sup>	11.18±0.40 <sup>ns</sup>
Arsenic levels (µg/100mg)	0.00	0.01	0.05	0.00	0.005

(Values are mean ± SE from 8 animals in each group). P-values: \*<0.05; \*\* <0.01; <sup>†</sup><0.001 <sup>ns</sup> Not significant when compared with control group. Group 1 – Control, Group 2 – Arsenic (Low dose), Group 3 – Arsenic (High dose), Group 4 – *Andrographic paniculata*, Group 5 – Arsenic + *Andrographic paniculata*.

**TABLE 2: EFFECT OF ANDROGRAPHIS PANICULATA ON STEROIDOGENIC & METABOLIC PARAMETERS IN THE OVARY OF ARSENIC EXPOSED FEMALE MICE**

	Group-1	Group-2	Group-3	Group-4	Group-5
Cholesterol (mg/100 mg)	8.29±0.25	15.48±0.31 <sup>†</sup>	19.68±0.46 <sup>†</sup>	8.78±0.37 <sup>ns</sup>	8.85 ±0.33 <sup>ns</sup>
3β HSD (mg androstenedione formed/ mg protein/min)	0.44±0.07	0.24±0.06*	0.19±0.06*	0.43±0.10 <sup>ns</sup>	0.39±0.10 <sup>ns</sup>
17β HSD (mg androstenedione formed/ mg protein/min)	0.40±0.05	0.21±0.06*	0.16±0.06*	0.41±0.07 <sup>ns</sup>	0.37±0.05 <sup>ns</sup>
Protein (mg/100 mg)	14.52±0.26	11.89±0.24 <sup>†</sup>	10.67±0.37 <sup>†</sup>	14.77±0.29 <sup>ns</sup>	13.73±0.40 <sup>ns</sup>

(Values are mean ± SE from 8 animals in each group). P-values: \*<0.05; \*\* <0.01; <sup>†</sup><0.001 <sup>ns</sup> Not significant when compared with control group. Group 1 – Control, Group 2 – Arsenic (Low dose), Group 3 – Arsenic (High dose), Group 4 – *Andrographic paniculata*, Group 5 – Arsenic + *Andrographic paniculata*.

The lipid peroxidation levels recorded a marked (p<0.001) increase in the ovary of arsenic-treated groups. Exposure of arsenic further led to a significant (p<0.001; p<0.01) depletion in GSH levels and in the activities of SOD, CAT, and GPx

in treated mice. Similarly arsenic treatment brought about a remarkable (p<0.001) reduction in the TAA levels. Co-treatment with AP extract significantly restored the altered levels of these indices to metalloid treated groups **Table 3**.

**TABLE 3: EFFECT OF ANDROGRAPHIS PANICULATA ON OXIDATIVE STRESS AND RELATED PARAMETERS IN THE OVARY OF ARSENIC EXPOSED FEMALE MICE**

	Group-1	Group-2	Group-3	Group-4	Group-5
LPO (MDA/mg/60 min)	52.65±0.55	74.52±0.50 <sup>†</sup>	104.22±1.06 <sup>†</sup>	51.72±0.55 <sup>ns</sup>	53.44±0.69 <sup>ns</sup>
GSH (µg/100 mg)	36.99±0.55	21.92±0.68 <sup>†</sup>	19.93±0.56 <sup>†</sup>	35.97±0.67 <sup>ns</sup>	36.01±0.58 <sup>ns</sup>
GPx (nanomoles of NADPH Oxidised/mg protein)	5.95±0.24	3.11±0.26 <sup>†</sup>	2.06±0.29 <sup>†</sup>	5.40±0.28 <sup>ns</sup>	5.19±0.23 <sup>ns</sup>
CAT (µg/H <sub>2</sub> O <sub>2</sub> ) consumed/ mg protein/min)	11.12±0.51	8.41±0.56 <sup>†</sup>	7.20±0.56 <sup>†</sup>	11.45±0.47 <sup>ns</sup>	10.60±0.50 <sup>ns</sup>
SOD (Units/mg protein)	2.13±0.22	1.72±0.28 <sup>†</sup>	1.21±0.18 <sup>†</sup>	2.09±0.22 <sup>†</sup>	1.95±0.27 <sup>†</sup>
TAA (mg/gm)	2.01±0.14	1.64±0.07 <sup>†</sup>	0.98±0.15 <sup>†</sup>	1.98±0.09 <sup>†</sup>	1.90±0.09 <sup>†</sup>

(Values are expressed as mean ± SE from 8 animals in each group). P-values: \*<0.05; \*\* <0.01; <sup>†</sup><0.001 <sup>ns</sup> Not significant when compared with control group. Group 1 – Control, Group 2 – Arsenic (Low dose), Group 3 – Arsenic (High dose), Group 4 – *Andrographic paniculata*, Group 5 – Arsenic + *Andrographic paniculata*.

**DISCUSSION:** Reduction in body weight reflects a variety of responses including rejection of food or water because of treatment induced anorexia. In arsenic treated groups, body and organ weights were significantly decreased with respect to control indicating the systemic toxicity. The weight loss of the female organ in arsenic-treated animals may be due to the possibility of low hormonal levels <sup>27, 28</sup>.

These reduced gravimetric values thus indicated the lethal nature of the toxicant. Corroborating with the present study Rao and Avani <sup>28</sup> also reported altered gravimetric and arsenic retention in arsenic-treated animals. Since the production of reactive oxygen species is high in reproductive tissue due to

active metabolism and steroidogenesis, the tissue is under continuous oxidative stress. The result of the present investigation demonstrated the adverse effect of arsenic treatment on female gonadal steroidogenesis and antioxidant defense mechanism <sup>29</sup>. In ovarian steroidogenesis 3β and 17β - HSDs are the key regulatory enzymes, the suppressed activities of these enzymes along with elevated cholesterol levels by arsenic suggest alteration in its hormone synthesis <sup>27, 30, 31</sup>.

This is in agreement with the previous findings where arsenic treatment was associated with inhibition of ovarian steroidogenesis <sup>27, 32, 33</sup>. To minimize the risk caused by ROS, supplementation

of *Andrographis paniculata* in arsenic-treated mice resulted in a significant increase in ovarian enzyme activities and reduction in cholesterol levels. Altered protein levels in ovary also induced changes leading to biochemical defects, structural disorders and altered physiological functions. A number of sulfhydryl containing proteins and enzyme systems have been found to be altered by exposure to arsenic<sup>33</sup>. Thus a significant reduction in protein level in our study indicates toxicity status of the tissue by arsenic which binds to -SH groups leading to protein synthesis inhibition<sup>34</sup>.

Lipid peroxidation is regarded as one of the basic mechanisms of tissue damage caused by free radicals. The enzymatic antioxidants SOD, CAT, and GPx counteract the free radical and reduce the oxidative stress. SOD accelerates the conversion of superoxide radicals to hydrogen peroxide while CAT or GPx converts hydrogen peroxide to water. An increase in LPO level was presumably associated with increased free radicals, confirming the fact that the free radicals reduced the antioxidant status in ovary of arsenic-treated mice<sup>35</sup>. The observed alterations might be attributed to the utilization of these antioxidants to alleviate free radical-induced oxidative stress<sup>36</sup>.

Earlier studies also suggest that ROS produced due to arsenic treatment leads to the generation of oxidative stress<sup>37</sup>. Glutathione is a tripeptidyl molecule and is present in either the reduced (GSH) or the oxidized state (GSSG) by forming a disulfide bond between two molecules. It has pleiotropic roles, which includes the maintenance of cells in a reduced state and the formation of conjugates with some harmful endogenous and xenobiotic compounds. In our study, glutathione levels were found to be decreased significantly. This reduction is suggested to be due to the consumption of glutathione while protecting against the arsenic-induced oxidative stress.

Cellular toxicity of arsenic was also found to be inversely related to intracellular GSH levels and thus may be enhanced by GSH depletion<sup>38</sup>. Ascorbic acid is known to be a powerful reducing agent, which helps in activating several enzymes, and acts as an antioxidant for detoxifying toxic substances. A decrease in level of TAA under arsenic-induced stress suggested that the ascorbic

acid is rapidly oxidized in the ovary. In support of our data, studies by Chinoy<sup>33</sup> reported altered ascorbate metabolism in the ovary by arsenic treatment. In the present study administration of extract of *Andrographis paniculata* in arsenic treated mice found to enhance the steroidogenic and antioxidant indices which were drastically reduced in the arsenic treated animals suggest that arsenic induced ovarian damage and functions were reversed by extract possibly through its pharmacological activities<sup>39,40,41</sup>.

The protective role may be due to the direct reaction of compounds of *Andrographis* with free radicals<sup>42,44</sup> and showed remarkable retrieval in body and organ weights, regulate the enzymic and non-enzymic antioxidant defenses and other metabolic indices along with a reduction in arsenic levels of ovary<sup>45</sup>. Studies by Kishore *et al.*,<sup>46,47</sup> also reported that AP inhibits the formation of oxygen-derived free radicals and normalized the level of antioxidant indices<sup>48</sup>. Thus, it is evident that adult female mice of Swiss strain on chronic oral exposure to arsenic developed oxidative stress to cause detrimental effects on the ovarian functions. But simultaneous administration of the *Andrographis paniculata* extract enhanced the antioxidant defense system and functions of the ovary in female mice.

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**CONFLICT OF INTEREST:** Nil

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