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ORIGINAL ARTICLE

Protective effect of gallic acid against arsenic-induced anxiety −/depression- like behaviors and memory impairment in male rats

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Abstract

The purpose of the present study is to determine the effects of gallic acid (GA) on sodium arsenite (iAS)-induced behavior deficits and memory alteration in male rats. Thirty six animals were divided in to 6 groups (six animals in each) (i) saline+saline; (ii) saline+GA (50 mg/kg); (iii) saline+ GA (100 mg/kg) (iv) iAS + saline; (v) iAS + GA(50 mg/kg); (vi) iAS + GA (100 mg/kg). Animals were treated with iAS (2.5 mg/kg/ml); GA (50 and 100 mg/kg/ml) and saline (0.9%; 1 ml/kg) for 4 weeks. Repeated administration of iAS increases immobility time in forced swim test and decreases time spent in open arm (elevated plus maze) and light box (light dark activity box test) suggests depression like and anxiety-like symptoms respectively. On the other hand, animals treated with iAS + GA decreases immobility time and increases time spent in open arm and light box than saline+iAS treated animals suggests anxiolytic and antidepressant-like behavior of GA. Repeated administration of iAS also involves in memory impairment as observed in the Morris water maze test that is reversed by co-administration of GA, indicates that GA also involves in the enhancement of memory. Brain malondialdehyde (MDA) levels, antioxidant enzymes and acetylcholinesterase (AChE) activities also observed in the present study. Results show that iAS produces oxidative stress by increasing lipid peroxidation and decreasing antioxidant enzyme activity. Conversely co-administration of GA produces antioxidant effects by normalization of oxidative stress induced by iAS. Alteration in iAS induced AChE activity is also reversed by GA. It is suggested that GA via its antioxidant potential, has protective effects on iAS induced behavioral deficits and memory alteration. The findings have a strong implication on iAS induced neurological diseases, such as depression, anxiety, Alzheimer's disease and dementia etc.

Keywords Arsenic, Gallic acid, anxiety · Depression · Memory · Oxidative stress · Antioxidant

Introduction

Arsenic (iAS) is an element that naturally occurring in food, soil, and water. Exposure of iAS has become a global human health apprehension of utmost significance. Acute and chronic exposure of iAS has been associated with various toxic indices. Drinking water (0.01–3.7 mg/l) is the major source of iAS exposure in living organisms. iAS can contribute to a spectrum of diseases like cancers (skin, lung, bladder, liver) and other chronic effects like diabetes, keratosis, hyperkeratosis, hepatopathy, neuropathy and gastrointestinal disorders either by acute or chronic exposure. Excessive generation of reactive oxygen species (ROS) is the main cause of various diseases that caused genetic inequity and malfunctioning of body's antioxidant defence mechanism (Hei et al.1998). Studies on experimental animals have shown that iAS cause neurotoxicity and deteriorate myelin sheath, vanishing of axons, vacuolar disintegration, and loss formation of the synapse (Piao et al. 2011) and leads various neurological diseases including memory impairment, anxiety and depression (Nutt and Stein 2006; Boyer 2000).

ROS, which causes oxidative stress (OS) causing an imbalance between the antioxidant defence system levels and the production of free radicals, are produced by environmental toxicants to prompt various types of neurological diseases (Coyle and Puttfarcken 1993; Jomova et al. 2011). Neuronal injuries have long been established to play a vital role in

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toxicant-induced OS leading to neuronal cells death and impairment of brain functions, because the brain relies on aerobic respiration, utilizes a huge amount of oxygen, and has high poly-unsaturated lipid contents, making it vulnerable to OS deterioration (Loh et al. 2006). iAS directly inhibits mitochondrial complex I resulting in increased ROS generation and thiol oxidation (Nutt et al. 2005). The blockade of complex II has been shown to result in reduced ATP production and increased OS and membrane depolarization, triggering cell death pathways (Brouillet et al. 1999). Mitochondria have been shown to play a crucial role in the regulation of cell death pathways. Moreover, many recent studies have provided evidence that OS is significantly related to the development of toxic metals-induced pathophysiological progress of neurodegenerative diseases, including iAS (Ahmed et al. 2011). A significant relationship between neuronal cell death and impaired brain function related to iAS-induced ROS overproduction and production of inflammatory cytokines (Yu et al. 2017) which involved in the progression of neurological diseases such as anxiety, depression and memory (Więdłocha et al. 2018; Bharathi Ravid and Rao 2006). Moreover, iAS-induced OS is also linked with the activation of MAPKs/PI3KAkt/NF kappa β/mTOR/endoplasmic reticulum stress-regulated signaling pathways that lead to diverse cellular responses such as cell growth, differentiation, apoptosis and stress responses to environmental stimuli (Estan et al. 2012; Yen et al. 2012).

There have been fabulous struggles to thrive valuable components from medicinal plants with the purpose to accomplish an ideal level of neuroprotection. Consideration has been waged to an extensive variation of natural antioxidants that can hunt free radicals and shield cells from oxidative deterioration, such as resveratrol, quercetin, curcumin and catechins (Han et al. 2004; Lee et al. 2004). Gallic acid (GA) or 3,4,5-trihydroxybenzoic acid and its derivatives are polyphenol natural products mainly found in processed beverages such as red wine and green tea (Graham 1992). GA induces antioxidant, anti-inflammatory, anti-microbial, and anti-cancer activities (Bachrach and Wang 2002; Borges et al. 2013; Kubo et al. 2001) that are associated with different signaling pathways including MAPKs/NF kappa β/TGF-β (Huang et al. 2016, 2017) GA-containing plant extracts have been reported to contain anti-diabetic, anti-angiogenic and anti-melanogenic effects in addition to reducing the incidence of myocardial infarction, and oxidative liver and kidney damages (Constat 1997; Jadon et al. 2007; Kim 2007). GA also protects neural cells against in vitro β-amyloid peptide (Aβ)-induced death (Bastianetto et al. 2006). It can be used further as an antioxidant in foods, cosmetics, and in pharmaceuticals (Zhao et al. 2011). GA is nontoxic to mammals at pharmacological doses. The lethal dose at which 50% of the animals died (LD50) for GA is 5 g/kg body weight in rats (Shahrzad et al. 2001).

Based on the antioxidant effects of GA, many in vitro studies on cell lines have been reported (Serrano et al. 2010). We hypothesized that, being a polyphenol, GA may produce protective effects against iAS induced alteration in behavioral activity and memory function. In view the role of GA against intoxication of iAS, the present study aims to explore the protective effects of GA on iAS induced oxidative stress (OS), behavioral deficits and memory impairment in rats.

Material and method

Animals

Due to hormonal cycle variation in female and male; extensive studies reported on male rats. In the present study, Sprague Dawley male rats (weighing 170–190 g, 4–5 months by age) were confined alone 3 days prior to the start of the experiment. The entire study is approved by the Institutional Ethics and Animal Care Committee.

Chemicals and reagents

Sodium arsenite (iAS), GA, Thiobarbituric acid (TBA), H2O2 stock (35%) solution, Nitroblue tetrazolium (NBT), Trichloroacetic acid (TCA) and Dithio-bisnitrobenzoic acid (DTNB) and all other analytical grade reagents were bought from Sigma chemicals Co. (St. Louis, USA).

Experimental

Thirty-six rats were at random alienated into 6 groups (6 animals in every set). (i) saline+saline (ii) saline+GA (50 mg/kg/ml) (iii) saline+GA (100 mg/kg/ml) (iv) iAS + saline (v) iAS + GA (50 mg/kg/ml) (vi)iAS + GA (100 mg/kg/ml). iAS (2.5 mg/kg/ml; Ola-Davies and Ajani 2016), GA (50 and 100 mg/kg/ml; Sarkaki et al. 2014) and saline (0.9%; 1 ml/kg) administered intraperitoneally (i.p), one by one as per group division with no interval as reported in other studies (Haleem et al. 2007; Samad et al. 2007; Samad and Haleem 2014). The drugs were administered daily for 4 weeks. Assessment of behavioral activities (Light dark activity box, Elevated plus maze, Forced swim test and Morris water maze) were conducted on next day. Animals were killed after the behavioral analysis following 4 weeks administration of iAS and GA to the gather the whole brain as done formerly by Samad and Saleem (2018). The samples were preserved at a set of temperature of −20 °C for the biochemical estimations. Malondialdehyde [MDA; lipid peroxidation (LP)] acetylcholinesterase (AChE) and antioxidant enzyme activity i.e. superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in the brain.

Behavioral tests

Elevated plus maze (EPM) test

The plus maze tools used in the current analysis was comprised of four arms in which two were closed and two were opened as described before (Naqvi et al. 2012). The arms were of the same length (50 cm) and width (10 cm). Arms were connected by middle area of 5 cm^2. The maze was high from the floor at an elevation of 60 cm. To find out the commotion rat was positioned in the middle of the plus maze and time used up (spent) in the open arms was recorded for 300 s.

Light-dark activity box (LDA) test

The experiment was performed in a home-made box (Samad et al. 2005). The partition of equal size (26x26x26cm), with an entrance (12x12cm) between the compartments, differed in their sensory properties. Walls of on compartment were transparent and other Black. Rat positioned in this box probable to get ahead of more time in the dark box. To find out the commotion rat was launched via the black box. Time spent in the transparent box was recorded for a mean time of 300 s.

Forced swim test (FST)

The FST apparatus contained a glass chamber with 56 cm height and 30 cm width, which limited water at the height of 22 cm and temperature of 25 °C. In this glass chamber animals were independently forced to swim for 300 s. The height of water was designated so that animal was barred from moving the bottom of the glass chamber and to avertits escape from the glass chamber. The FST is usually used as standard pharmacological model for appraising depression like symptoms in rats/mice (Porsolt 1981). When the mice/rat is placed in an inevitable chamber which is filled with water then the progress of the state of immobility imitates the termination of determined escape directed behavior. In this test animal's swimming behavior was monitored which can be defined as movement throughout the swim chamber (glass tank). The immobility time was observed. The animal is considered immobile when it makes no further tries to escape andonly tries to keep its head above the water.

Morris water maze (MWM) test

Morris Water Maze (MWM) test was done to observe the effects on spatial memory as designated by Haider et al. (2011). We have evaluated learning acquisition, long-term memory (LTM) and short-term memory (STM) in terms of expectancy to locate the escape platform. The test is based on two segments: the training segment and the test segment. Memory functions of the ratwere verified by observing down the holding latency. The cut off time was 120 s for each session. Primarily, the training session (once; Samad and Saleem 2018) was attained throughout which each rat has positioned into the water in such a way that their face was to the wall of the tank. Each animal was given 120 s to find and stand onto the concealed platform by using distal extra maze indications. Indications must be observable and useful to mice. They must be far enough to require the rat to use spatial analysis, rather than connotation, to resolve the task. If the rat positioned the platform it was permitted to stay on it for 10 s. Time on the platform must be enough for them to feel the location and to see the meticulous position. If it unsuccessful to locate the platform during the owed time, then it was guided moderately onto the platform. The test involved three trials: training, STM and LTM. After training of animals, STM was evaluated 60 min after a training session, and LTM was assessed after 24 h of training.

Biochemical analysis

Determination of LP

LP was evaluated by determining levels of MDA in the whole brain of mice. MDA was evaluated by calculating thiobarbituric reactive species using the method of Chow and Tappel (1972) in which the thiobarbituric acid reactive substances react with thiobarbituric acid to produce a red colored complex having peak absorbance at 532 nm.

Determination of activity of SOD

The SOD was assessed by the method of Naskar et al. (2011). An aliquot of brain homogenate (10%) was treated with 0.75 ml of ethanol and 0.15 ml of ice chilled chloroform then centrifuged. Then 0.5 ml of EDTA (0.6 mM) and 1.0 ml of carbonate-bicarbonate (0.1 M; pH 10.2) buffer was added in 0.5 ml of supernatant. The reaction was started by adding 0.5 ml of epinephrine (1.8 mM) and the absorbance was measured for 3 min at 480 nm. Blank contained all reagents except supernatant. Finally, the percent inhibition of SOD was calculated.

Determination of activity of CAT

CAT was estimated using a previously reported method (Pari and Latha 2004). Brain homogenate (10%) in 0.01 M phosphate buffer (pH 7.0) was prepared and filtered. Then 0.1 ml of filtrate was mixed with 1.4 ml of a reaction mixture that contained 0.4 ml of 2 M hydrogen peroxide and 1 ml of same phosphate buffer. The reaction was terminated after 1 min by adding 2.0 ml of dichromate-acetic acid reagent. Blank was contained distilled water in place of filtrate. The absorbance of

both test and blank were measured at 620 nm to calculate percent inhibition of CAT.

Determination of activity of GPx

GPx activity was measured by the procedure of Flohe and Gunzler (1984). One ml of the reaction mixture was prepared which contained 0.3 ml of phosphate buffer (0.1 M, pH 7.4), 0.2 ml of reduced glutathione (2 mM), 0.1 ml of sodium azide (10 mM), 0.1 ml of H2O2 (1 mM), and 0.3 ml of brain supernatant. After incubation at 37 °C for 15 min, the reaction was terminated by addition of 0.5 ml 5% TCA. Tubes were centrifuged at 1500×*g* for 5 min, and the supernatant was collected. Phosphate buffer 0.2 ml (0.1 M, pH 7.4) and DTNB 0.7 ml (0.4 mg/ml) were added to 0.1 ml of reaction supernatant. After mixing, absorbance was recorded at 420 nm. Activity of GPx was expressed as μmol/min/g of the brain.

Determination of activity of AChE

The activity of AChE in homogenate was determined according to the method of Ellman et al. (1961) using ATC as a substrate. The reaction mixture contained 0.4 ml brain homogenate (0.02 g/ml), 2.6 ml phosphate buffer (0.1 M, pH 8.0), 100 μl DTNB. The reaction mixture was mixed by bubbling air and placed in the spectrophotometer. Once the reaction content was stable, the absorbance was noted at 412 nm for the basal reading followed by addition of 5.2 μl of ATC to this cuvette. Any change in absorbance was recorded from zero time followed by 10 min at 25 °C. The activity of AChE was expressed as μmol/min/g of brain tissue.

Statistical analysis

All the data statistically analyzed by Tukey's test followed by two-way ANOVA. $P < 0.05$ was taken as significant.

Results

Effect of GA on iAS induced anxiety observed in elevated plus maze activity

Figure 1 shows the effects of GA on anxiety profile in iAS treated rats observed in EPM. Data for time spent in open arm analyzed by two-way ANOVA revealed that the significant effect of iAS [$F_{1,30} = 11.11$, $p < 0.01$], GA [$F_{2,30} = 274.15$, $p < 0.01$], and interaction between iAS× GA [$F_{2,30} = 124.80$, $p < 0.01$]. Tukey's test showed that sub-chronic administration of iAS substantially decreased time spent in the open arm than control animals. Time spent in open arm substantially increased in GA (50 and 100 mg/kg) + saline and GA(50 and 100 mg/kg/ml) + iAS treated than their counterparts. Time spent in open arm substantially greater in GA + iAS than GA + saline treated animals. The result suggested that GA (50 and 100 mg/kg) have the potential to attenuate iAS induced anxiety in rats.

Effect of GA on iAS induced anxiety observed in light dark box activity

Figure 2 shows the effects of GA on anxiety profile in iAS treated rats observed in LDA. Data for time spent in open arm analyzed by two-way ANOVA revealed that the effect of iAS ($F_{1,30} = 0.64$ $p > 0.05$) was not significant. Whereas effect of GA [$F_{2,30} = 180.09$, $p < 0.01$], and interaction between iAS× GA [$F_{2,30} = 24.03$, $p < 0.01$] were significant. Tukey's test showed that sub-chronic administration of iAS substantially decreased the time spent in light box than control animals. Co administration of GA increased time spent in light box of saline and iAS treated animals than saline+saline and iAS + saline treated rats respectively. It is indicated that co-administration of GA prevented iAS induced anxiety-like behaviors.

Effect of GA on iAs induced depression-like symptoms observed in the forced swim test

Figure 3 shows the effects of GA administration on immobility time observed in FST in iAS treated rats. Data for time spent in open arm analyzed by two-way ANOVA revealed that the significant effect of iAS [$F_{1,30} = 45.94$, $p < 0.01$], GA [$F_{2,30} = 341.99$, $p < 0.01$], and interaction between iAS× GA [$F_{2,30} = 82.81$, $p < 0.01$]. Tukey's test showed that sub-chronic administration of iAS substantially increased immobility time than saline treated animals. GA (50 and 100 mg/kg) + saline and GA(50 and 100 mg/kg) + iAS treated rats exhibit decreased immobility time than their counterparts. The result suggested that co administration of GA has antidepressant effects.

Effects of co-administration of GA on iAS induced memory impairment

MWM was conducted to asses learning and memory function in animals treated with GA and iAS. Latency escape in MWM activity is conducted immediately after training (acquisition, Fig. 4a), 1 h (short term memory, Fig. 4b) and 24 h (long term memory, Fig. 4c). Results on acquisition analyzedby two-way ANOVA revealed that significant effect of iAS [$F_{1,30} = 68.03$, $p < 0.01$], GA [$F_{2,30} = 81.37$, $p < 0.01$], and iAS× GA [$F_{2,30} = 31.00$, $p < 0.01$]. Two-way ANOVA for short term memory showed that significant effect of iAS [$F_{1,30} = 85.08$, $p < 0.01$], GA [$F_{2,30} = 115.63$, $p < 0.01$], and iAS× GA [$F_{2,30} = 29.03$, $p < 0.01$]. Two-way ANOVA for long term memory showed that significant effect of iAS [$F_{1,30} = 40.72$, $p < 0.01$], GA

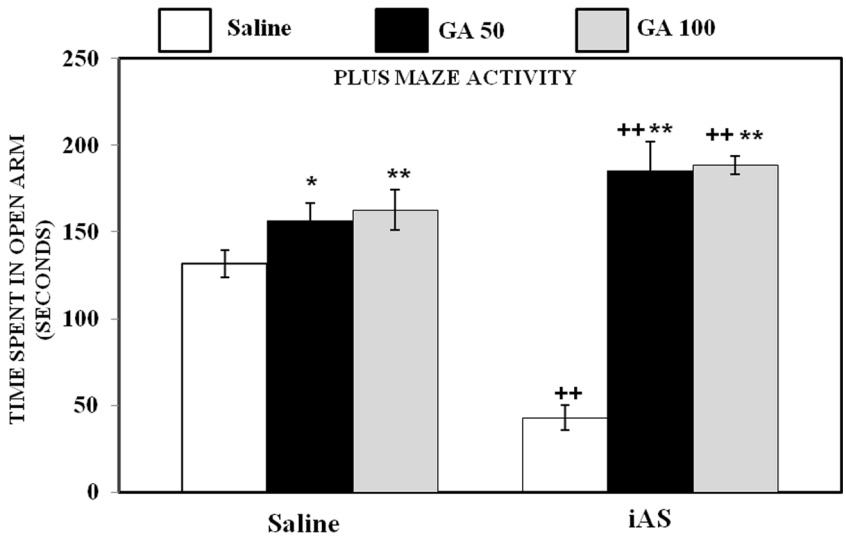

Fig. 1 Effect of administration of iAS on time spent in open arm in Elevated plus maze test for the saline and GA treated rats. Values are mean ± SD ($n = 6$). Data was analyzed by Tukey's test following two-way ANOVA. Statistical difference is represented as $^{**}p < 0.01$ and $^{*}p < 0.05$ versus respective control and $^{++}p < 0.01$ versus saline + saline and saline+GA (50 and 100 mg/kg) treated animals

[$F_{2,30} = 61.43$, $p < 0.01$], and iAS× GA [$F_{2,30} = 16.21$, $p < 0.01$]. Tukey's test demonstrated that administration of iAS substantially increased latency escape, while GA (50 and 100 mg/kg) + iAS and while GA (100 mg/kg) + saline treated showed decreased latency escapethan their respective control during acquisition. Analysis of short term memory revealed that time to reach hidden platform was significantly greater in iAS + saline than saline+saline treated animals. This time substantially reduced byGA (50 and 100 mg/kg) + iAS and GA (50 and 100 mg/kg) + saline when compared to saline+iAS and saline+saline respectively. GA (50 mg/kg) + iAS showed greater latency escape than GA (50 mg/kg) + saline injected rats. Evaluation of long term memory revealed that latency escape was significantly greater in iAS + saline than saline+saline treated animals. The latency escapes substantially reduced by GA (50 and 100 mg/kg) + iAS than saline+iAS. GA (100 mg/kg) + saline showed smaller latency escape than saline+saline treated rats. Results showed that the co-administration of GA has protective effects on iAS induced disturbed short term and long term memory.

Effect of GA on iAS induced increased brain LP

Figure 5 shows the effects of GA on brain levels of MDA (LP) in iAS treated rats. Data analyzed by two-way ANOVA revealed that the significant effect of iAS [$F_{1,30} = 68.47$, $p < 0.01$], GA [$F_{2,30} = 138.78$, $p < 0.01$], and interaction between iAS× GA [$F_{2,30} = 27.74$, $p < 0.01$]. Tukey's test showed that sub-chronic administration of iAS substantially increased LP. GA (50 and 100 mg/kg) + saline and GA (50 and 100 mg/kg) + iAS treated rats exhibit decreased MDA levels than their counterparts. It is indicated that GA reduced brain LP or oxidative stress.

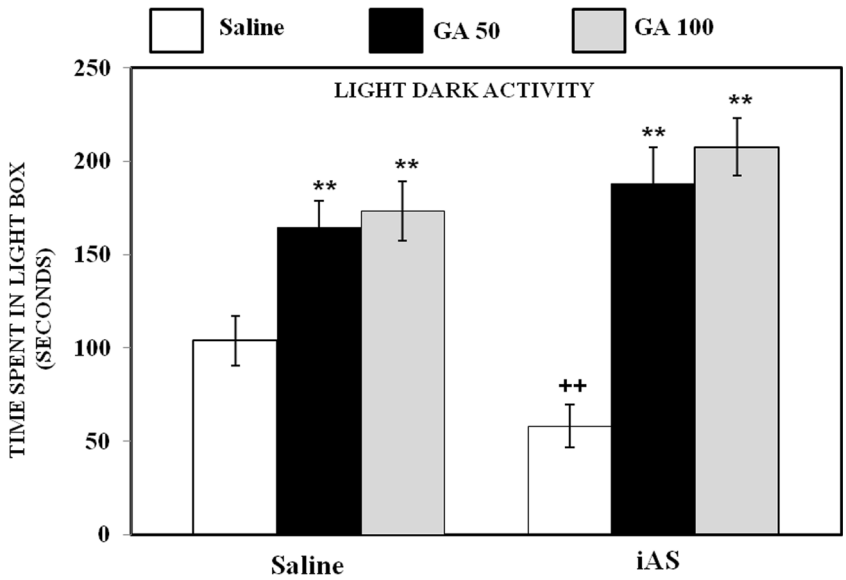

Fig. 2 Effect of administration of iAS on time spent in light box in light dark box test in animals treated with saline and GA. Values are mean ± SD ($n = 6$). Data was analyzed by Tukey's test following two-way ANOVA. Statistical difference is represented as $^{**}p < 0.01$ versus respective control and $^{++}p < 0.01$ versus saline+saline treated rats

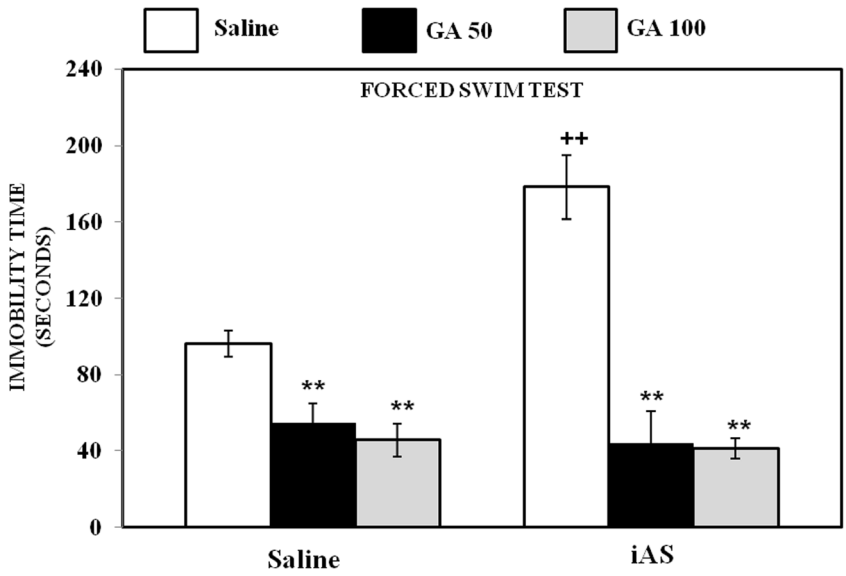

Fig. 3 Effect of administration of iAS on immobility time in Forced swim test in animals treated with saline and GA. Values are mean ± SD ($n = 6$). Data was analyzed by Tukey's test following two-way ANOVA. Statistical difference is represented as**$p < 0.01$ versus respective control and ++$p < 0.01$ versus saline+saline treated rats

Effect of co-administration of GA on iAS induced alteration in brain antioxidant enzymes activity

Figure 6 shows the effects of GA on brain antioxidant enzyme activity in iAS treated rats. Data on SOD activity (6a) analyzed by two-way ANOVA revealed that the significant effect of iAS [$F_{1,30} = 30.11$, $p < 0.01$], GA [$F_{2,30} = 127.66$, $p < 0.01$], and interaction between iAS × GA [$F_{2,30} = 15.84$, $p < 0.01$]. Tukey's test showed that sub-chronic administration of iAS substantially decreased % inhibition of SOD. GA (50 and 100 mg/kg) + iAS treated rats exhibit increased % inhibition of SOD than their counterparts.

Data on CAT activity (6b) analyzed by two-way ANOVA revealed that the significant effect of iAS [$F_{1,30} = 12.21$, $p < 0.01$], GA [$F_{2,30} = 85.95$, $p < 0.01$], while interaction between iAS× GA [$F_{2,30} = 2.62$, $p > 0.05$] was not significant. Tukey's test showed that GA (50 and 100 mg/kg) + saline and GA (50 and 100 mg/kg) + iAS treated animals exhibit increased CAT levels than saline+saline and saline+iAS treated rats.

Data on GPx activity (6c) analyzed by two-way ANOVA revealed that the significant effect of iAS [$F_{1,30} = 19.83$, $p < 0.01$], GA [$F_{2,30} = 38.21$, $p < 0.01$], while interaction between iAS× GA [$F_{2,30} = 0.68$, $p > 0.05$] was not significant. Tukey's test showed that sub-chronic administration of iAS substantially decreased activity of GPx. GA (50 and 100 mg/kg) + saline and GA (50 and 100 mg/kg) + iAS treated rats exhibit increased GPx levels than their counterparts. Results showed that GA via is potential antioxidant activity enhanced the activity of antioxidant enzyme in the brain.

Effect of GA on brain acetylcholinesterase activity

Figure 7 shows the effects of GA on brain AChE activity in iAS treated rats. Data on AChE activity analyzed by two-way ANOVA revealed that the significant effect of iAS [$F_{1,30} = 15.03$, $p < 0.01$], GA [$F_{2,30} = 68.94$, $p < 0.01$], and interaction between iAS × GA [$F_{2,30} = 14.05$, $p < 0.01$]. Tukey's test showed that sub-chronic administration of iAS substantially increased the activity of AChE. GA (50 and 100 mg/kg) + saline and GA (50 and 100 mg/kg) + iAS treated animals exhibit the decreased activity of AChE than their respective controls. It is suggested that GA has a role in memory function by decreasing AChE activity.

Discussion

AS is an element found in the earth's crust and biosphere and has been known as a human poison for centuries (Banu et al. 2009). A large quantity of AS results in the prospect of daily exposures to humans, which may be via ingestion through drinking water (major route) or through inhalation and skin absorption (minor route) (Shi et al. 2004). The present study, for the first time, evaluated the behavioral and biochemical effects of GA in iAS-induced OS. Clinical studies demonstrated that arsenicosis patients show psychiatric illnesses such as depression, mixed anxiety, and depressive disorder (Sen and Biswas 2012). In animal studies, perinatal exposure to relatively low levels of AS (0.05 mg/L) also significantly increase learned helplessness and immobility in a forced swim task that predisposes affected offspring to depressive-like behavior in the affected adult C57BL/6 J mouse model (Martinez et al. 2008). In the present work, we confirmed that sub-chronic administration of iAS induces anxiety-like and depression-like behaviors in control rats. After 4 weeks of iAS administration, the animal showed obvious anxiety-like behaviors in both behavioral tests for anxiety (EPM, LDA) (Figs. 1 and 2). Similarly, sub-chronic treatment of iAS also showed obvious

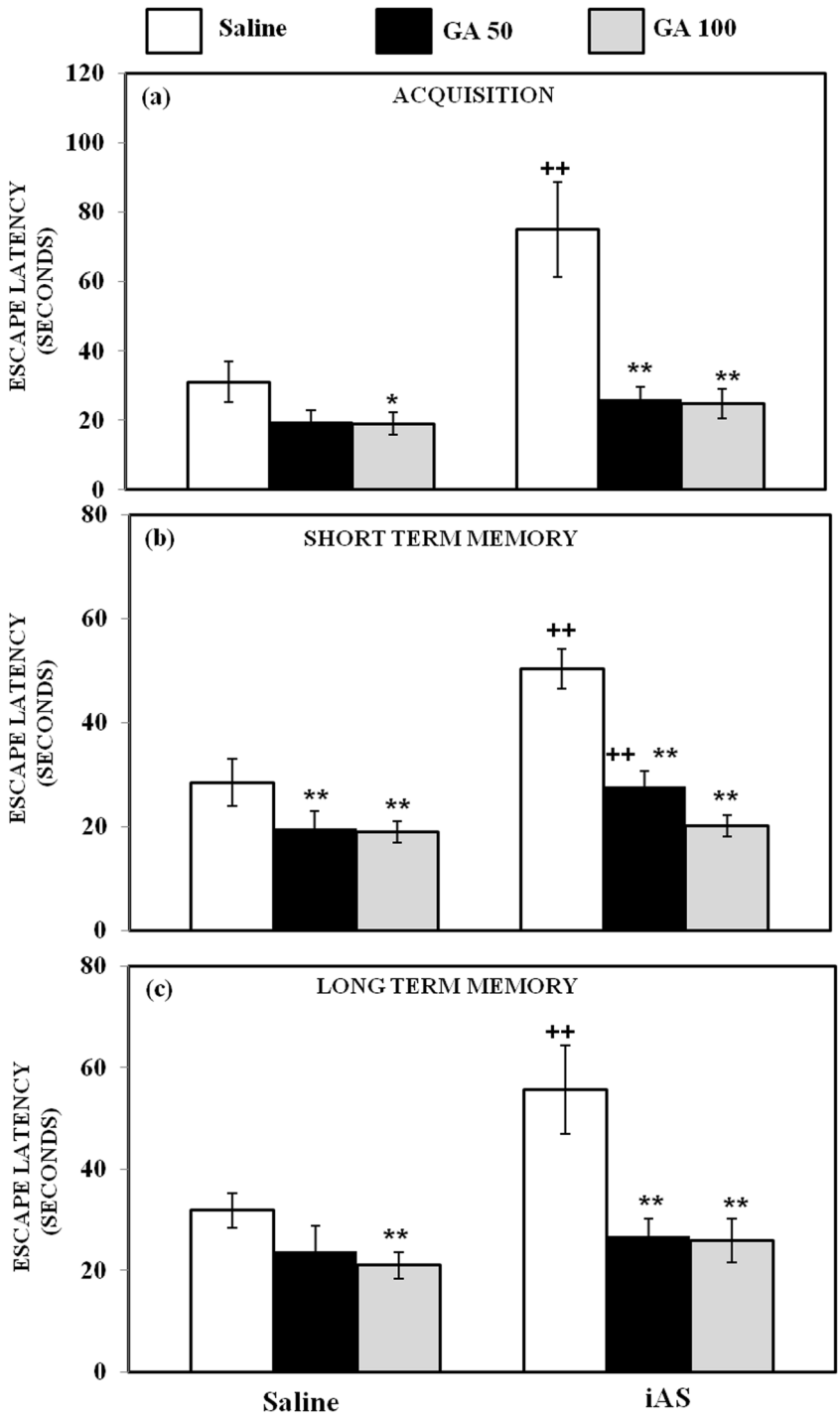

Fig. 4 Effect of administration of iAS on acquisition **a** short term memory **b** and long term memory **c** in terms of escape latency (s) assessed by Morris water maze in animals treated with saline and GA. Values are mean ± SD (n = 6). Data was analyzed by Tukey's test following two-way ANOVA. Statistical difference is represented as$^{**}p < 0.01$and $^{*}p < 0.05$ versus respective control and $^{++}p < 0.01$ versus saline+saline and saline+GA (50 mg/kg) treated groups

depression like behavior in the FST (Fig. 3). On the contrary, the reversal of both anxiety- and depression-like behaviors occurred by co-treatment with GA (50 and 100 mg/kg).

An imbalance between OS biomarkers and antioxidants has also been known in a stress situation. Extensive studies reported that stress (anxiety and depression) diminished levels of antioxidant enzymes in human (Liu et al. 2015; Daglia et al. 2017) and animal (Samad et al. 2018) as well. Furthermore, it has also been reported that antidepressant (Liu et al. 2015), anxiolytic (de Almeida et al. 2014), various plant extracts (Samad et al. 2018) and their active components (Haider et al. 2015; Samad et al. 2018) can regulate the mechanism of antioxidant enzymes such as SOD, CAT and GPx, suppress inflammatory markers and inhibit OS. Previously it has reported that GA produces its antidepressant (Can et al. 2017), anti-anxiety

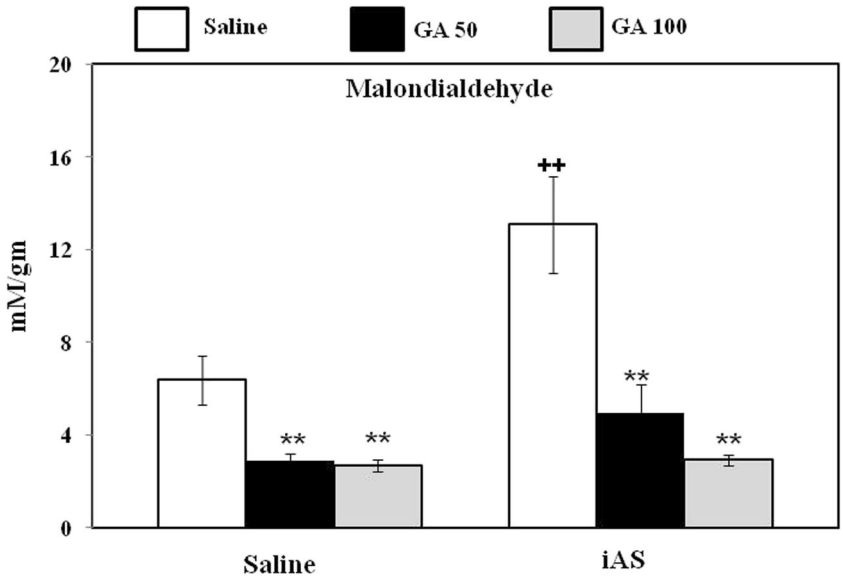

Fig. 5 Effect of administration of iAS on brain MDA level in animals treated with saline and GA. Values are mean ± SD (n = 6). Data was analyzed by Tukey's test following two-way ANOVA. Statistical difference is represented as**$p < 0.01$ versus respective control and ++$p < 0.01$versus saline+saline treated rats

(Mansouri et al. 2014) properties via potential antioxidant mechanism (Popovic-Milenkovic et al. 2014). The present study also shows that iAS induced depression and anxiety-like behaviors (Figs. 1, 2 and 3) overturned by co-administration of GA (50 and 100 mg/kg) through its antioxidant potential.

OS has a significant importance in iAS toxicity. Cellular antioxidant mechanism become impairs due to the large production of ROS and RNS that involves in the generation of inflammatory markers including TNF-α, IL-1β and IL-6 (Ingawale et al. 2014) and deteriorate the cellular components (Manna et al. 2008). OS is indicative by LP. MDA is the final product of LP, and its quantity can quantitatively imitate the level of LP in vivo (Całyniuk et al. 2016). The sub-chronic treatment of iAS elevates the levels of MDA (Fig. 5) which is an indicative of OS. AS-induced ROS production may be the thru consequence of metabolites of AS that may play a role as free radicals and involved in the depletion of antioxidants (Flora 2011). Antioxidant enzymes are also badly distorted by AS-induced toxicity, which diminished their action by obligatory to Thiol group (Isuzugawa et al. 2001). Antioxidant enzymes are weighed to be the first line of cellular defense against oxidative harm. An antioxidant metalloenzyme SOD lessens superoxide radicals to Water and Oxygen (McCord et al. 1976). A hemoprotein CAT that lessens hydrogen peroxide to oxygen and water (Gutteridge 1995). An increase in the production of superoxide radicals was observed following treatment of AS, due to the lower levels of SOD in the brain (Yamanaka et al. 1991). The activity of CAT was also reduced in the brain of the animal following intoxication of iAS. GPx is also important for the lessening of organic hydroperoxides (Flora 1999). So, in bulk generation of ROS can enhance the level of inflammatory markers and cease the activity of these antioxidant enzymes. In our study the % inhibion of SOD and activity of GPx was decreased following administration of iAS, while the activity of CAT is comparable to control (Fig. 6), confirms that iAS involves in the induction of OS by increasing LP and decreasing antioxidant enzymes mechanism.

Extensive studies have evidenced that, GA showed its antioxidant activity (Bachrach and Wang 2002; Moghadas et al. 2016) by hunting the ROS, decreasing the inflammatory activity (Saygin et al. 2016), inhibiting the activation of MAPKs/NFkappa β/TGF-β (Ahad et al. 2015) or correcting the antioxidant enzyme activity (Ker et al. 2013). `It is reported earlier that SOD is the first line of defence against OS (Samad et al. 2018). The free radical hunting activity of SOD is active only when it is tracked by the actions of CAT and GPx, as the dismutase activity of SOD produces hydrogen peroxide from the superoxide ion, which is more lethal than oxygen derived free radicals and requires to be hunted further by CAT and GPx (Blake et al. 1987). We observed that GA recovers the iAS-induced behavioral commotion (Figs. 1, 2 and 3) by regularizing the activity of SOD and withdrawing the negative properties of iAS toxicity on CAT, resulting in regular activity of GPx (Fig. 6). The results showed that co-treatment by GA (50 and 100 mg/kg) diminished the OS (Fig. 5) with enhancement in the activity of antioxidant enzymes (Fig. 6). These properties may be ascribed to the minimized OS subsequent in lessening of adverse effects of

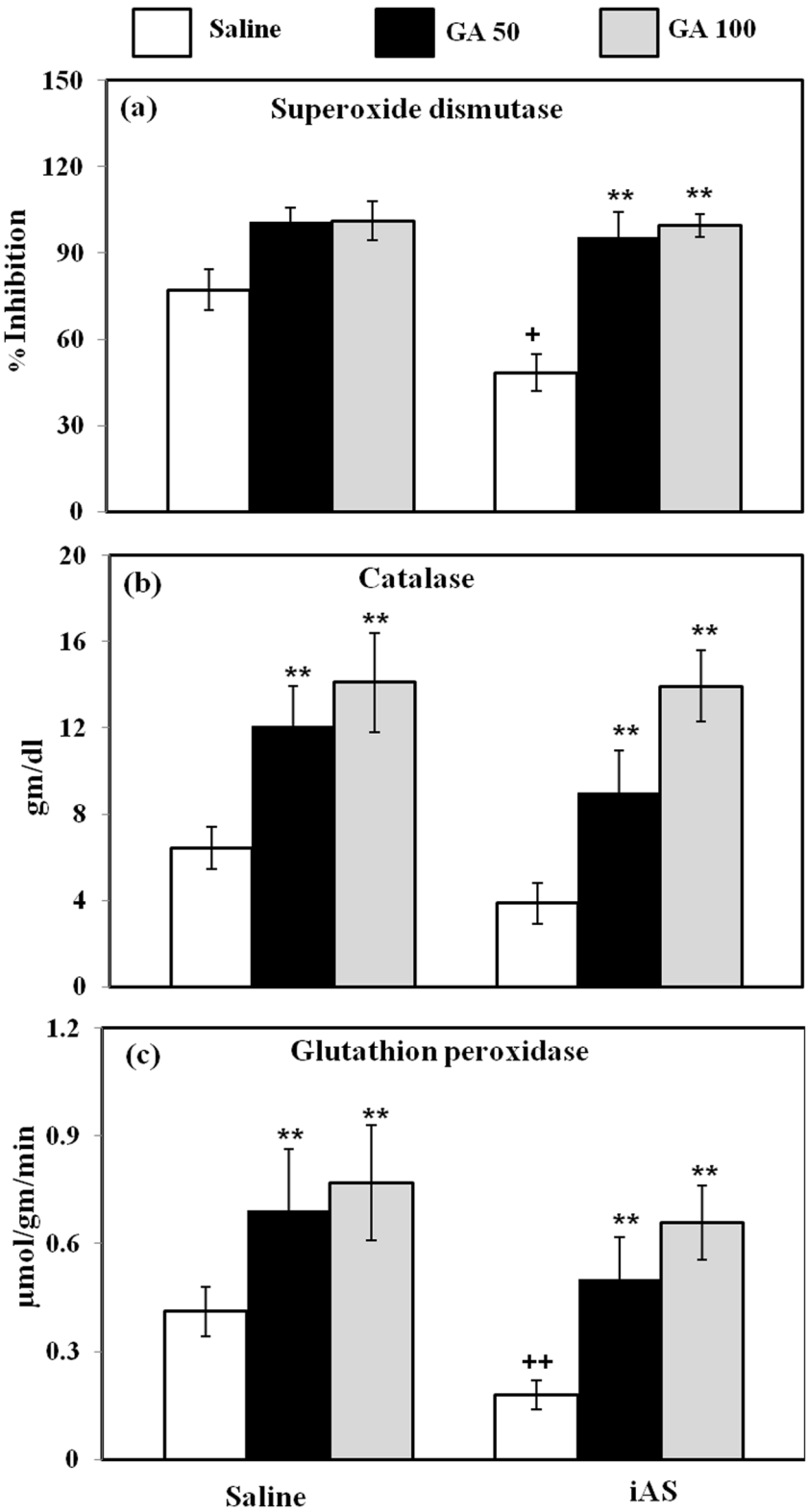

Fig. 6 Effect of administration of iAS on brain SOD (**a**), CAT (**b**) and GPx (**c**) activity in animals treated with saline and GA. Values are mean ± SD ($n = 6$). Data was analyzed by Tukey's test following two-way ANOVA. Statistical difference is represented as $^{**}p < 0.01$ versus respective control and $^{++}p < 0.01$and $^{+}p < 0.05$ versus saline+saline treated animals

iAS induced toxicity on behaviors. Literature cited has shown that reduction of OS (Ker et al. 2013) may also suppress inflammatory responses (Saygin et al. 2016) with inhibition of activated signaling pathways (Ahad et al. 2015) by GA. On the basis of earlier reported protective effects of GA, results of the present study are also indicated that, the antidepressant and anxiolytic activity of GA is due to its antioxidant potential.

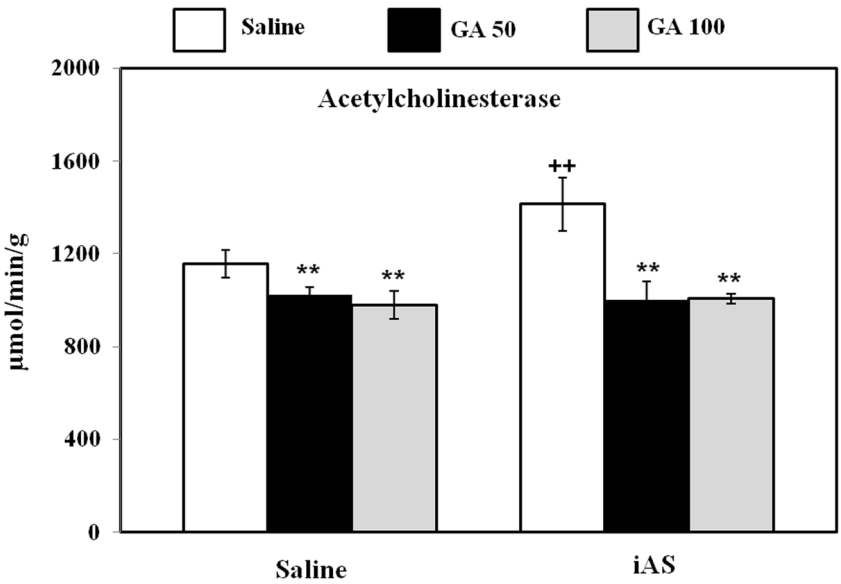

Fig. 7 Effect of administration of iAS on brain AChE activity in animals treated with saline and GA. Values are mean ± SD (n = 6). Data was analyzed by Tukey's test following two-way ANOVA. Statistical difference is represented as**$p < 0.01$ versus respective control and ++$P < 0.01$ versus saline+saline treated animals

Co-administration of GA reduced escape latency during memory assessment (STM and LTM) in saline and iAS treated rats, indicating memory improving effects of GA (Fig. 4). Escape latency was increased in STM as well as LTM examine in iAS + saline treated rats, that is representing iAS as a toxic element that impairs the memory (Fig. 4). Acetylcholine is one of the neurotransmitters involves in memory function. Acetylcholine is not only present in central nervous system it also involves in other functions at the periphery level. AChE (a biomarker) which is used to determine the cholinergic functions (Lian et al. 2017; Emad et al. 2017; Papandreou et al. 2011). Previously it has been reported that sub-chronic (Wang et al. 2018) and chronic (Sun et al. 2015) administration of iAS disturbs the cognitive function (Wang et al. 2018; Sun et al. 2015) and increases AChE activity (Chandravanshi et al. 2014). Our presented data is also consistent with these results of increased AChE activity (Fig. 7) and impaired learning and memory (Fig. 4) following sub-chronic administration of iAS, most likely by falling of acetylcholine at the synapse (Kaufer et al. 1998). GA on the other hand increased the STM (Fig. 4b) and LTM (Fig. 4c) as well as acquisition (Fig. 4a), which may be ascribed to the decreased AChE activity (Fig. 7) in iAS treated animals. Various reports have shown that taurine (Guan et al. 2017), curcumin (Yadav et al. 2011) enhanced memory in AS-treated rats with decreased activity of AChE and inflammatory surge. In view of previous report, we assume that GA improves the neuronal plasticity (Hajipour et al. 2016) by reduction in inflammatory responses (Yadav et al. 2018) and inhibition of MAPK (Ma et al. 2018), NF-kβ (Khare et al. 2017) signaling pathways, which in turn affects the brain neurotransmitter levels. Hence an increase in the brain acetylcholine levels, the substrate for the enzyme, could be the cause of decreased AChE activity that was observed in the present study (Fig. 7), however, a novel finding is that GA may increase cognition beside iAS induced toxicity via its antioxidant potential.

In conclusion, the results of this present study support the previous studies of the antioxidant ability of GA. The present study,consequently,emphasizes the use of dietary sources rich in GA contents and/or supplementation of GA as an effective remedy for intoxication of iAS and associated disorders.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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