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Succimer modulates the effects of arsenic exposure on oxidative stress, behavioural and histological alterations in the brain of a rat

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ABSTRACT

Arsenic is an environmental pollutant with potent neurotoxicity debilitating the individuals with other ailments. The succimer is a chelating agent used in therapeutic effects of heavy metal toxicity. This study reports the modulatory effect of succimer on oxidative stress, behavioural and histological impairments in the rat treated with arsenic. Adults rats were divided into four groups: control, arsenic (100ppm/kg BW), arsenic (100ppm/kg BW)+Succimer (50mg/kg BW) and Succimer (50mg/kg BW). The treatments were delivered for 15 days. After the treatment period, behavioural studies were conducted, and the brain was used for biochemical and histological evaluation. Arsenic-treated rats showed a significantly decreased motor coordination (Rotarod test), increased paw withdrawal latency period (Hotplate test), lipid peroxidation content (LPO) as well as a significantly declined superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activities. The histological changes such as neural cells with irregular shape and axon, cyton, and dendrite degenerated in the cerebral cortex region of the brain. In Arsenic + Succimer group, succimer significantly reversed the adverse effects of arsenic on the oxidative stress, behavioural and histological alterations compared to the arsenic group. Succimer alone treatment has not shown any adverse effect. Thus succimer showed protective effects against arsenic generated oxidative stress, behavioural deficits and inhibiting neuronal alterations. Thus, succimer prove to be a useful therapeutic component against arsenic-induced neurotoxicity.

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INTRODUCTION

The contamination of arsenic a well-known human toxicant, in groundwater which is regularly used for human irrigation and industrial activities has implications of worldwide humankind health. Nidhi and flora (2011), recently reported arsenic poisoning to co-exist in certain areas of the world including China, India and Bangladesh. The major sources of arsenic contamination in drinking water is the use of arsenic-having insecticides, herbicides, pesticides, rodenticides and also through polluted food (Lalit *et al.,* 2014). According to Flora *et al.,* (2005), arsenic enter the human body by the respiratory tract, alimentary tract and skin, then combines with haemoglobin and is rapidly scattered to many organs, including the kidney, lung, liver and brain. Arsenic exposure renders the brain tissue vulnerable to attack by free radicals resulting in abnormal apoptosis of neural cell (Shoufang *et al.,* 2014). The continuing intake of arsenic trioxide escalates the risk of disease in people with cardiovascular disorders (Flora *et al.,* 2011). Halina *et al.,* (2010), demonstrated the injection of arsenic causes neural injury. The neurological deficits such as

Parkinson's disease and dementia are associated with arsenic (Gordon and Sid, 2010).

The changes in antioxidant enzyme activities enhance apoptosis in arsenic-exposed animals (Jiang *et al.,* 2013). Arsenic produces free radicals resulting in cell injury and death through oxidative sensitive signalling pathways (Yadav *et al.,* 2010). The mitochondrial damage and impaired mitochondrial functions in arsenic-exposed animals. Arsenic crosses the brain through the blood-brain barrier (BBB) and leading to neurobehavioral alterations (Ning *et al.,* 2010) and Rajesh *et al.,* (2009), also noticed abnormal behaviour and impairment of memory and learning functions in arsenic intoxicated rats. Neurotransmitters such as epinephrine, norepinephrine, serotonin and dopamine were altered in the hippocampus and cerebral cortex regions of the brain on chronic arsenic exposure (Yadav *et al.,* 2010). Further, arsenic exposure results in destabilisation and disturbance of the cytoskeletal framework leading to neuronal degeneration (Gopalkrishnan and Rao, 2006). Additionally, epidemiological reports have indicated tissue architecture change in kidney and liver by arsenic (Abu *et al.,* 2015).

Certain effects have been made to assess the neuroprotective ability of certain active compounds in arsenic-induced neurotoxicity with an emphasis on antioxidant property. Succimer is one of the protectants and have chelating properties. Succimer has been proved to be an efficient antidote for various heavy metals and metalloids, including antimony, lead, mercury and arsenic and to possess some antidotal efficiency for others, such as platinum, tin and cobalt (Bradberry *et al.,* 2009). Recent reports have proposed that treatment with succimer has no side effects on rats. Yuka *et al.,* (2017), reported that succimer showed effective chelation of Lead and protection against histological changes significantly. The chelating effects and antioxidant activity of succimer are because of two SH groups in its structure (Flora *et al.,* 2004). Studies have shown that mice and rats injected with succimer effectively increased mercury elimination (Ying and Guifeng, 2017). There are no reports on the neuroprotective role of succimer against arsenic neurotoxicity through oxidative stress in the brain. Hence, the present study was aimed to assess the protective efficacy of succimer against arsenic-induced neurotoxicity through oxidative parameters, behavioural and histological impairments in the brain of rats.

MATERIALS AND METHODS

Chemicals: Succimer and arsenic were purchased from Sigma-Aldrich chemicals and other chemicals were purchased from local chemical suppliers (Himedia).

Animals and treatment: Experiments were conducted using albino Wistar rats (*Rattus norvegicus*) weighing 200-250 g that were fed a standard chow diet with water available *ad libitum*. Six rats were housed in each plastic cage under a 12-h light/12-h dark cycle at a constant temperature of 25±2 ^{0}C with 42±5% relative humidity. The study protocols conformed with the guidelines of the Osmania University ethical committee (CPCSEA No: 383/01/a/CPCSE). Twenty-four rats were randomly divided into four groups of 6 rats and treated as described below for 15 successive days.

Group I: Control group received distilled water.
Group II: Arsenic group received drinking water with arsenic (100ppm/kg BW).
Group III: Arsenic+ Succimer group received drinking water with arsenic (100ppm/kg BW) and succimer (50mg/kg BW) through oral gavage daily.
Group IV: Succimer group received daily administration of succimer (50mg/kg BW) through oral gavage.

After 15 days we conducted behavioural studies (Rotarod and Hotplate test), and the rats were sacrificed, and brains were dissected out to perform biochemical (LPO, SOD, CAT, and GPx) and histology studies (Golgi-cox stain).

Behavioural tests

Rotarod test: The rotarod test was conducted according to the method of Hutter *et al.,* (2012). The rotarod test has been widely used to measure the fore and hind limb coordination and motor skills: the time of the instrument (Dolphin TM instruments) adjusted to 0 s and the rotational speed to 20 RPM. The time was noted and expressed as time in second.

Hotplate test: The hot plate test was performed as per the method Gunn *et al.,* (2011). Rat's response latency on Analgesiometer-Eddy's Hot Plat was recorded and expressed as time in second.

Measurement of oxidative stress markers

Assay of Lipid peroxidation (LPO)

Malondialdehyde levels were estimated as per the method of Garcia *et al.,* (2005) and results were shown as nanomole MDA/gm weight of tissue.

Assay of Superoxide dismutase (SOD)

Superoxide dismutase activity was carried out according to the method of Marklund and Marklund (1974). The enzyme activity was expressed as Units/mg protein.

Assay of Catalase activity (CAT)

Catalase activity was carried out according to the method of Aebi (1984), and results were expressed as moles of degraded/min/mg/ protein.

Assay of Glutathione peroxidase (GPx)

Glutathione peroxidase activity was determined according to the modified version of Flohe and Gunzler (1984). The enzyme activity was expressed as units/mg protein.

Histology: The Golgi-cox stock solution-fixed brain tissues were sliced at 4-10 µm thickness. The slices were subjected to golgicox staining according to the procedure of Gibb and Bryan (1998). Histopathological changes were observed using Lawrence & mayo microscope (Magnification 40X).

Statistical analysis: The results were presented as mean± S.E. Data was also analysed for statistical comparison using ANOVA test. Significant differences between the groups were conducted using t-test — a significance of ($p<0.01$ and $p<0.05$) level was considered significant.

RESULTS

Behavioural studies

Rotarod test: The control group rats showed normal motor coordination, while the arsenic intoxicated group showed significantly (**p<0.05) decreased motor coordination and normal activities, whereas arsenic along with succimer administered group showed significantly (***p<0.05) improved motor coordination and behavioural activities. The group administered with succimer alone showed normal behavioural alteration as that of the control group (Fig-1).

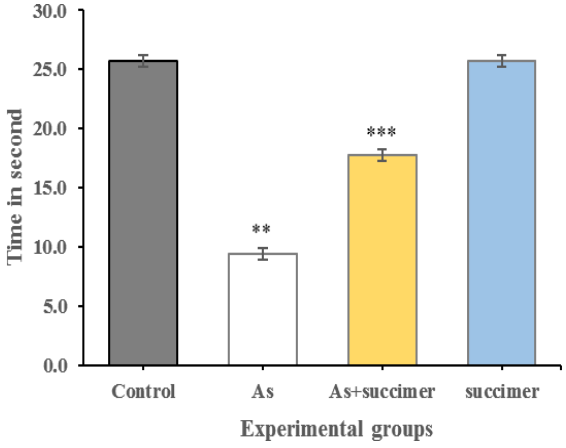

Figure 1: Effect of succimer treatment on motor coordination (Rotarod test) in rats exposed to arsenic for 15 days. (**p<0.05) as compared to the Control group and (***p<0.05) as compared to arsenic-treated group and results are shown in time in seconds

Hotplate test: The paw withdrawal in hot plate test latency period significantly (**p<0.05) increased in arsenic exposure rats over control rats, and Arsenic + succimer and succimer treated rats showed significantly (***p<0.05) improved the paw withdrawal latency period compared to arsenic-treated rats (Fig. 2).

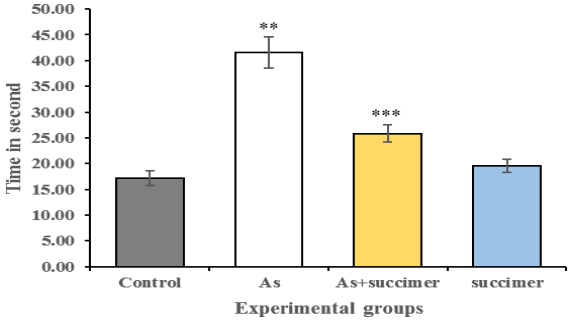

Figure 2: Effect of succimer treatment on the latency period (Hotplate test) in rats exposed to arsenic for 15 days. (**p<0.05) as compared to the Control group and (***p<0.05) as compared to arsenic-treated group and results are shown in time in seconds.

Oxidative stress markers

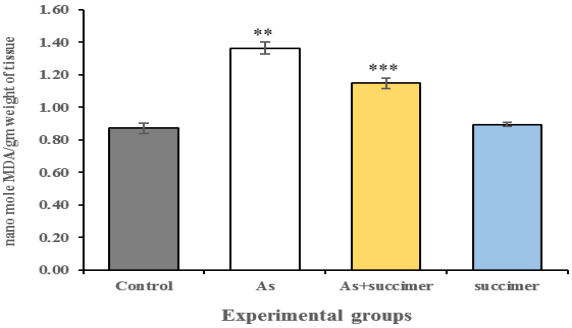

Figure 3: Effect of Succimer treatment on LPO content in rats exposed to arsenic for 15 days. (**p<0.05) as compared to the control group and (***p<0.05) as compared to arsenic-treated group and results are expressed in nanomole MDA/gm weight of tissue.

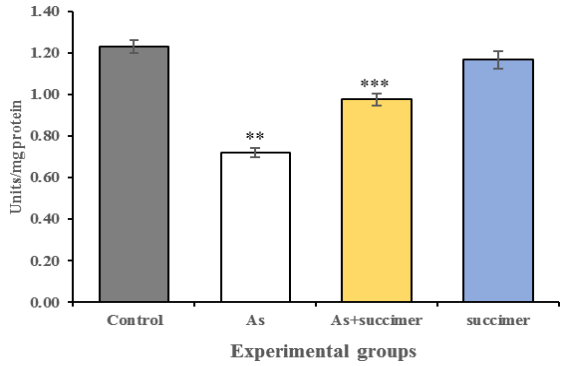

Figure 4: Effect of Succimer treatment on SOD level in rats exposed to arsenic for 15 days (**p<0.05) as compared to the control group and (***p<0.05) as compared to arsenic-treated group and results are expressed in Units/mg protein.

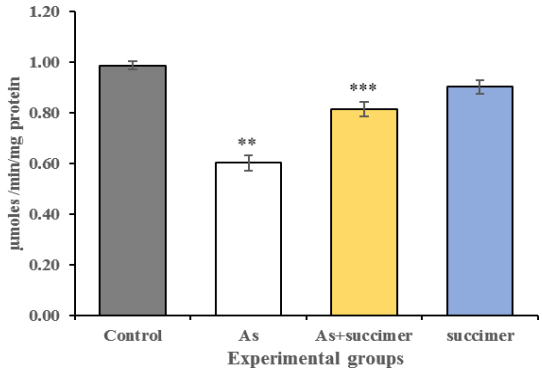

Figure 5: Effect of succimer treatment on Catalase level in rats exposed to arsenic for 15 days (**p<0.05) as compared to the control group and (***p<0.05) as compared to arsenic-treated group and results are expressed in µmoles /min/mg protein.

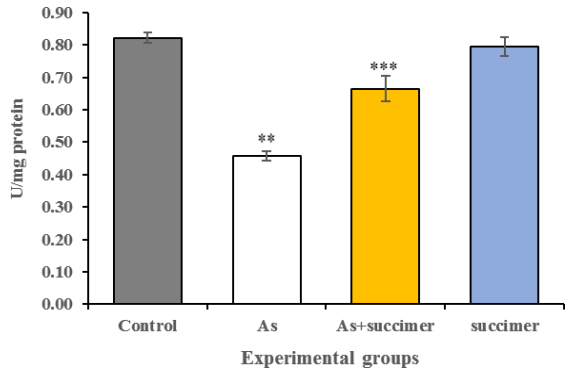

Figure 6: Effect of succimer treatment on GPx level in rats exposed to arsenic for 15 days (**p<0.05) as compared to the control group and (***p<0.05) as compared to arsenic-treated group and results are expressed in U/mg.

Oxidative status in the brain: The LPO level and SOD, CAT, and GPx activities are shown in figures 3, 4, 5 and 6 respectively**.** Arsenic exposure significantly (**p<0.05) increased the brain lipid peroxidation level and also declined the superoxide dismutase, catalase and glutathione peroxidase activities when compared with control. The treatments of Arsenic along with Succimer has shown protective effect via decreasing significantly (***p<0.05) the elevated LPO content to the level of normal and also significantly increasing the reduced antioxidant enzyme activities such as superoxide dismutase, catalase and glutathione peroxidase when compared with arsenic exposure to that of the normal level. The succimer alone treatment has no significant different values from that of control.

Histology: The histological sections with Golgi cox stain of cerebral cortex region of rat brain treated with arsenic and succimer (Magnification 40X) are shown in Figure 7. In Golgi cox stain, neural cells with irregular shape and axon, cyton, and dendrite degenerated in Arsenic intoxicated rat cerebral cortex region of the brain. The Arsenic+succimer, succimer alone treated groups were detected with neurons arranged closely, axon, cyton and dendrite were clear in the brain compared to the arsenic-treated group.

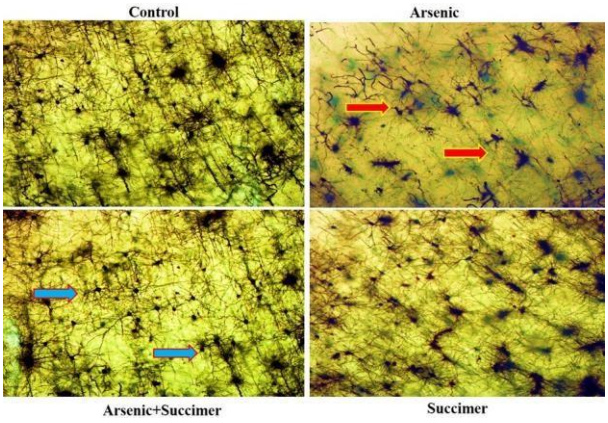

Figure 7: Brain Histopathological studies in the cerebral cortex by golgicox stain in control, Arsenic, Arsenic+ succimer, succimer alone treated groups (Magnification 40x). Blue colored marks showing the neurons arranged closely, axon, cyton and dendrite was clear.

DISCUSSION

Arsenic accumulation in the brain causes neurotoxic effects (Dhar *et al.,* 2005). The arsenic intoxicated rats have shown significant alterations in oxidative stress, histopathological and neurobehavioral alterations.

Further, the succimer treatment has reversed the alteration above of arsenic-exposed rats. The rotarod test and paw withdrawal test (hot plate test) were used for the assessment of motor coordination and nociceptive pain. Declined motor coordination in rotarod task in repeated trials demonstrates the motor altered coordination function in animals. Previous studies have also indicated that chronic or acute exposure to arsenic causes nervous system dysfunctions including cognitive impairment and c (Rajesh *et al.,* 2009). Arsenic exposure reduces motor-neuronal coordination through inhibition of the effects of neurotransmitters (Ning *et al.,* 2010).

Further, arsenic-induced behavioural amendments could be due to disturbance of glutamate catecholamine and acetylcholine transmitters systems along with neurodegeneration (Delgado *et al.,* 2000). In this study, we have used a hot plate test for the evaluation of nociceptive pain processes. Antigona *et al.,* (2011), reported midazolam-induced antinociception for inflammatory pain. Only a few studies report the arsenic toxicity effects on nociceptive pain (Mccormack, 1994). The

increased latency of the hot-plate test in arsenic-treated rats shows the inhibition of pain sensitivity which was reversed in the succimer treatment. Our result confirms that chelation therapy following Arsenic treatment resulted in a reversal of altered motor coordination and paw withdrawal activities.

Oxidative stress results with an imbalance of pro and anti-oxidant systems, which is implicated in the pathogenesis of a variety of disorders such as cardiovascular, neurodegenerative diseases, cancer, and inflammatory diseases (Xi *et al.,* 2010). Oxidative stress play a vital role in the neurodegenerative process. Both acute and chronic arsenic exposure altered the oxidative stress markers and morphological changes of cells in soft tissues. The reduced ability for cellular regeneration in contrast to other organs such as kidney, liver and heart, the neural tissue is specifically vulnerable to the damaging affects of ROS. Many antioxidants have been shown to prevent the formation of oxidative compounds linked with many diseases such as cardiovascular and neurodegenerative diseases (Ramakrishnan *et al.,* 2017). Schieber and Chandel, (2014), demonstrated oxidative stress is also concerned with ineffective deletion of reactive oxygen species from the cells. The studies have shown the oxidative stress involved in arsenic-induced hepatotoxicity and cardiotoxicity (Ghosh *et al.,* 2011). The content of lipid peroxidation, as well as levels of superoxide dismutase, catalase and glutathione significantly altered in arsenic intoxicated animals (Rai *et al.,* 2010). According to Prakash *et al.,* (2015), arsenic toxicity is due to the formation of reactive oxygen species and results in oxidative effects on proteins and lipids. The reduced glutathione plays a key role in protecting cells against oxidative stress and acts as important pivotal in the detoxification mechanisms of arsenic (Richa and Flora, 2006). Moraes *et al.,* (2013), reported declined CAT activity in arsenic-exposed animals as catalase decomposes hydrogen peroxide, therefore protect cells from reactive oxidative species and balance the oxidative stress status. Treatment with arsenic, showed a decline in body weight, brain weight gain, water and food intake. Parental undernutrition may induce oxidative stress, which can result in damaged neurodevelopment, alterations in learning and memory, increased anxiety, and alterations antioxidative enzymes such as, SOD, CAT, GPx levels and lipid peroxidation content (Lalit *et al.,* 2014; Xi *et al.,* 2010). Our results corroborate the earlier studies indicating a disturbance of the antioxidant defense system in arsenic toxicity as observed in other pathological situations. Oxidative stress marks such as lipid peroxidation content significantly enhance as well as SOD, CAT and GPx enzymes levels significantly declined in arsenic-exposed rats. Arsenic along with succimer treated rats showed significantly improved activities of LPO, SOD, CAT and GP_X enzymes suggesting its antioxidant action. The succimer alone administration maintained enzymatic levels which are similar to control rats.

Histopathological observation is one of the major objective of this study. According to Gora *et al.,* (2014), arsenic intoxicated rats showed hepatocytic and vacuolar degeneration followed by hepatic necrosis. Earlier studies have demonstrated arsenic-induced histological alterations such as tubular relapse, intratubular degeneration, congestion observed in kidney tissue (Abu *et al.,* 2015). The brain sections revealed structural degeneration of neuron in the arsenic-exposed animal. In the cerebral cortex region of the brain, neurons indicated cell swelling and vacuolar disintegration in cytoplasm and karyolysis as well as karyorrhexis in the nucleus of arsenic intoxicated animals (Ning *et al.,* 2010). Fengyuan *et al.,* (2005), reported histological alterations such as neuritic loss, lysis of neurons and nuclear vacuolation in the brain of rats treated with arsenic. This study reports the arsenic mediated tissue degeneration in the brain by using Golgi-cox stain. We have observed altered neurons, and axon structure, density and morphology as well as neuron degeneration in arsenic-exposed rats brain tissue and arsenic along with succimer intoxicated rats showed normal neural cells and their structure.

CONCLUSION

In conclusion, this study demonstrates that succimer has potent protective effects against arsenic-induced neurotoxicity through oxidative stress with histopathological and behavioural alterations rat. We propose a potential protective effect of succimer. Here we proved that succimer administration attenuated arsenic-induced neuronal dysfunction. Succimer attenuated arsenic-induced oxidative stress markers alterations such as LPO, SOD, CAT and GPx in the brain of the rat. Succimer treatment could effectively abrogate arsenic-induced declined motor coordination and increased paw withdrawal latency period in the rat. Hence, this study reported that succimer is potent neuroprotectant against arsenic-induced neurotoxicity.

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