IJBAHR

ASSESSMENT OF BEHAVIOURAL EFFECTS OF OXALATE ADMINISTRATION IN A NEUROPATHY MODEL IN RAT

Muhammad Farhan[*1], Atiqa Urooj Siddiqui[1], Anila Bibi[3], Ayesha Ahmed Somroo[1], Shoaib Ahmed[2], Syeda Rabab Zehra[1], Noor Un Nisa Soomro[4], Jaweria Kanwer

[1]Neurochemistry and Biochemical Neuropharmacology Research Unit, Department of Biochemistry, University of Karachi, Karachi, Pakistan[1].

[2]Department of Biochemistry, Federal Urdu University of Science and Technology, Karachi, Pakistan[2]

[3]Department of Biochemistry, Jinnah Sindh Medical University, Karachi. Pakistan

[4]Altamash Institute of Dental Medicine, Karachi. Pakistan

Abstract: Neurodegenerative illnesses are a general classification of neurological problems with an assortment of clinical and obsessive signs that influence explicit subsets of neurons in explicit practical anatomic frameworks. Oxidative pressure muddles the pathophysiology of neurodegenerative sicknesses like Alzheimer's and Parkinson's illness. Oxidative pressure is brought about by redox awkward nature, which incorporates either exorbitant creation of receptive oxygen species (ROS) or cell reinforcement framework brokenness. Oxalate is a neurotoxin with a high harmfulness level. Oxalate poisonousness can be exacerbated by dietary inadequacies. The penetrability of the blood brain barrier (BBB) can be expanded by OXT. OXT harming fundamentally affects sensory system work. The aim for this study was to investigate the behavioral changes in rodents subsequent to getting Oxalate consistently. The home enclosure movement test, open field test, raised in addition to labyrinth test, and light-dull change test utilized to evaluate the way of behaving of male Wister pale skinned person rodents who given Oxalate (10 mg/ml/kg, orally) or saline infusions day to day. Oxalate-treated rodents showed burdensome way of behaving, for example, expanded time spent fixed in the open field and expanded nervousness like way of behaving. With expanded Oxalate organization, be that as it may, time spent in the lit box diminished. These discoveries show that Oxalate was given to rodents for a lengthy timeframe, causing pressure and, accordingly, despondency..

Key words: Oxalate Administration, Neuropathy. Behavioural Effects

INTRODUCTION

Neurotoxicity occurs when the normal nervous system movement is altered by exposure to natural or artificial poisons (neurotoxicants). In the end, this can agitate or even kill neurones, which are important cells in the cerebrum and other parts of the nervous system that handle and transmit signals. Although there may be a considerable lag between exposure and the onset of neurotoxic effects, neurotoxicity typically resolves on its own after exposure stops and is rarely progressive in the absence of ongoing exposure (Spencer and Lein, 2014).The neurological symptoms of hypervitaminosis A, to which the above-mentioned are very close, include headache, pseudotumor cerebri, and embryotoxic effects that have been observed in patients receiving vitamin A analogues or retinoid. Vitamin D and retinoic acid (RA) receptors, which belong to a steroid receptor superfamily and are known to control gene expression and development, are found in the majority of tissues (Snodgrass, 1992). The study of neurotoxicity holds promise for bettering treatment and prevention approaches for conditions like Parkinson's and Alzheimer's. Its clinical uses in addiction medicine have not yet been sufficiently defined, though (Soleimani, Ekhtiari, & Cadet, 2016). The progressive loss of neuronal structure or function is the cause of a neurodegenerative disease. These conditions are regarded as incurable since there is no known method to stop the progressive degeneration of neurones; however, studies have revealed that inflammation and oxidative stress are the two main causes of neurodegeneration (Pereira *et al*., 2021). Neurodegenerative diseases are thought to affect 50 million people globally, and by 2050, that number is expected to rise to 115 million (Rodríguez *et al*., 2015).

One of the most prominent theories concerning the aetiology of these neurological conditions is oxidative stress. Numerous factors can cause oxidative stress, which disrupts

the intracellular oxidant and antioxidant homeostasis in brain cells and ultimately impairs normal brain functions (Yadav and Shukla, 2021). Nuclear factor, a transcription factor, primarily regulates the oxidative stress response. Numerous lines of evidence have strongly suggested that oxidative stress is a key factor in the aetiology of a number of neurological disorders. This chapter clarifies the specific functions of ROS and oxidative stress in the aetiology of a number of neurological disorders (Yadav & Shukla, 2021). Certain tissues, particularly the brain, are far more susceptible to oxidative stress due to their increased oxygen consumption and the resulting production of large amounts of ROS. However, cells have a complex network of defence mechanisms to neutralise excess ROS and reduce oxidative stress (Cui *et al*., 2004). Also referred to as oxalic acid, oxalates are a naturally occurring chemical found in plants. We consume these plant-based oxalates through our food, and our bodies eliminate them as waste. Leafy greens, legumes, and other foods high in oxalates are rich in numerous nutrients that are good for your health. However, because oxalates bind to calcium as it leaves the body, they may raise the risk of kidney stones in certain individuals. The most acidic organic acid found in bodily fluids, oxalic acid is used commercially to remove rust from automobile radiators. The main reason substances like antifreeze (ethylene glycol) are toxic is because they can be converted to oxalate. Approximately 80% of kidney stones are caused solely by calcium oxalate salt. The focus of the research was to ascertain the impact of Oxalate that caused the neurodegenerative-like symptoms in Albino Wister rats. In fact, Oxalate also made the animal to experience some stress and anxiety and thus, its behaviour was changed. Experts, however, mostly agree that regardless of different causes, the final outcome is the activation of apoptosis or programmed cell death, which is the intentional death of the cell for the purpose of saving other nearby neurons from the toxic substances.

MATERIALS AND METHODS

Animals

Male albino wister rats of 180-220 gm. weight were procured from Dow University, Karachi. Experiments and analyses were carried out in strict adherence to the protocol and assembled design, along with the complete guide for the care and use of laboratory animals.

Drugs

All the chemicals and drugs used for the experiment were of Merck Company origin. Various parameters were used for the recording of each rat's behavioral activity. The drug effects were noticed as changes in behavior.

Experimental Protocol

Twenty-four male albino Wister rats weighing between 250-300 gm. were randomly divided into two groups; (1) control and (2) test. Animals of the control group were orally given 0.9% saline once daily for 28 days and animals of the test group were administered with Oxalate (10mg/ml/kg) orally for 28 days consecutively. Food intake and body weight were recorded daily. All behavioral parameters were assessed on the following day of the 1st, 7th and 14th day of administration**.**

BEHAVIORAL ASSESMENT

Food Intake

Rats of the same weight were all housed in separate cages. They were given a freshly made, weighed standard laboratory diet that was 40% carbs, 30% fat, and 30% protein. Each cage was filled with food, and the amount of food left in the cages was weighed the following day of the first treatment day and then on a regular basis.

Growth Rate (Body Weight)

To determine the impact of diet or medication on growth, body weights were measured. Before the experiment started, all of the rats were weighed, and after the daily drug administration, the weight changes were tracked on a regular basis.

Activity Box

The laboratory rodents' locomotors activity is tracked using the home cage activity. The home cages give the rodents a comfortable and familiar environment. Its most effective and straightforward method of supporting behaviour that indicates a change in the animal's physiology. The study's equipment is a 26×26×26 cm square Perspex activity cage with a sawdust-covered floor and a lid on top. A rat is put inside the cage, and the number of times it crosses the cage is counted at the same time. Ten minutes is the deadline. The animals were habituated in their cages for fifteen minutes prior to activity monitoring.

Open Field Test

Open field activity test was a measure of exploratory locomotors activity in a new environment. The current experiment is about the activity of rats in an open novel setting, from which escape is prevented by surrounding walls. The open field device comprises opaque walls 42 cm high covering a square area of 76 ×76 cm. Lines split the floor of equipment into 25 equally sized squares. The rat's activity is determined by its latency to move when put in the central square of box and by the number of squares crossed with all four paws recorded over five minutes.

Elevated Plus Maze Test (EPM)

One of the most popular tests for assessing anxiety-like behaviour in rodent models of central nervous system disorders and for evaluating anxiolytic medications is the elevated plus maze test. The plus-shaped device has two open arms, two 10x50 cm closed arms, and a passageway in the middle. The device is 55 cm tall. The rat is put in the middle passageway and given free reign to roam around the plus maze The behaviour is noted and reported in terms of the quantity of open arms entries and the amount of time spent there.

Light-Dark Transition Test (LDT)

The drug induced anxiety or effect of anxiolytic in laboratory animals can be monitored in a light-dark transition test. The apparatus consist of two compartments; one of the compartments is dark while the other is light. The size of each

compartment is 26x26x26 cm and there is an opening between the compartments so the rats have free access. For activity monitoring rat is placed in the apparatus, number of entries in the light box and time spent in light box is observed with 5 minutes cutoff time.

STATISTICAL ANALYSIS

Data was displayed as Mean± SD. Data on drug administration in test and control rats were examined using a two-way ANOVA (Repeated Measured Design).SPSS (version 17) was the analysis program utilized. For post-hoc comparison, the Newman-Keuls test was employed. $p<0.05$ is regarded as a significant value.

RESULTS

Oxalate impact on rat food intake for 28 days

Each week after the administration of Oxalate, the amount of food consumed was measured for each animal. The total food consumption could be tracked on a day-to-day basis following the initial administration of the drug. The statistical analysis performed on the data utilized two-way repeated measures ANOVA, which revealed that the administration of Oxalate ($F=118.24$, $df=1,21$, $p<0.01$), repeated measures ($F=178.18$, $df=1,21$, $p<0.01$), and the interaction between the two factors ($F=101.21$, $df=1,21$, $p<0.01$) had an impact on food intake. As determined by post hoc testing with the Newman-Keuls test, from the first to the second week of administration, food intake decreased ($p<0.01$) significantly in both one-time and repeated treatment groups administered Oxalate. Additionally, rats receiving saline prior to the drug had peaked at intake around day 14 and then dropped considerably thereafter during continued treatment with Oxalate ($p<0.01$).

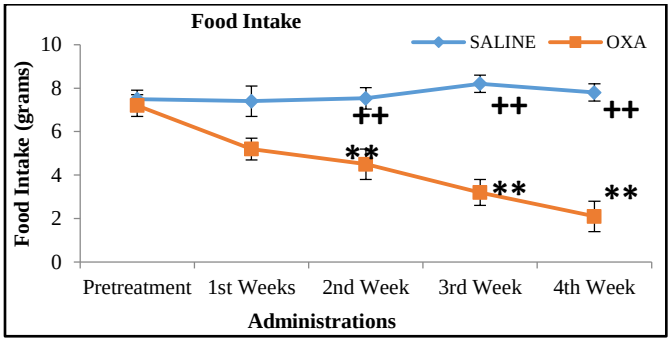

Figure 1: Means and standard deviations (n=6) were determined the day after the first-day administrations of oxalate or saline and each subsequent administration during the eight-week period. Newman-Keuls multiple comparisons tests were used to determine if any significant differences occurred. The asterisk indicates significance compared to saline, and the plus sign shows values were compared to the saline or oxalate administered to the same animal on the same day, based on two-way ANOVA repeated measures designs.

Oxalate impact on rat growth for 28 days

Following multiple doses of Oxalate to rats, the effects on the animals were measured by viewing periodic changes in the amount of weight gained over the course of 28 days (as illustrated in Figure 2). On day one after the first dose, the animals were weighed and then weighed again at least every seven days. All data were analyzed using repeated measures ANOVA design with a two-way analysis of variance (ANOVA). Significant results were seen using the two-way design for both Oxalate effect ($F=13412$, $df=1, 21$, $p<0.01$) and Days effect ($F=9231$, $df=1, 21$, $p<0.01$), as well as the interaction of both drugs and Days ($F=7943$, $df=1, 21$, $p<0.01$). Post hoc Newman-Keuls testing confirmed that Oxalate reduced both the acute and repeated growth rates in comparison to an animal that received a saline control dose. Significant changes occurred at days fourteen, twenty-one, and twenty-eight ($p<0.01$). All growth rates at day thirty from Oxalate treatment had been reduced in comparison with that of an animal treated with the same dose on the first day. After the second, third, and fourth weeks of receiving Oxalate treatment, significant decreases occurred in the growth rates ($p<0.01$).

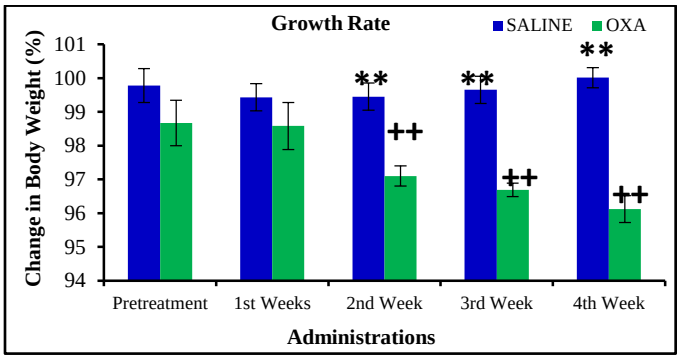

Figure 2: Values shown are means ± standard deviation (n=6) calculated post 1st day administration & subsequently weekly. Significant differences exist among treatments according to Newman-Keuls test: *p<0.05; **p<0.01 with respect to results from control (saline) & treated (Oxalate) animals; +p<0.05; ++p<0.01 with respect to results from control (saline) & similarly treated (saline or Oxalate) animals on the 1st day, as analyzed via two-way ANOVA (repeated measures).

Effect of oxalate on rat in activity box for 28 days

The effects of the long-term administration of oxalate on home cage activity in rats, which were performed over duration of 28 days and followed the initial administration of the oxalate or saline solutions. Randomly selected rats, which after receiving the first oxalate treatment were monitored the next day, had their home cages monitored every week. All data analyses were conducted using repeated measures two-way ANOVA. The analyses indicated that in terms of the effects of days, there was a significant effect ($F = 108.76$, $df = 1, 21$, $p < 0.01$) and the effects of oxalate also had a significant effect ($F = 139.41$, $df = 1, 21$, $p < 0.01$) and that the interaction of these factors was statistically significant ($F = 129.10$, $df = 1, 21$, $p < 0.01$). Post hoc Newman-Keuls analysis determined that oxalate administration caused a significant decrease in familiar environmental (home cage activity) while compared to saline-treated rats with both single dose administration and repeated administration. Statistically significant ($p < 0.01$) decreases were observed on days two, three and four. In a comparison of the saline-treated and the oxalate-treated rats during the first day of administration, the oxalate-treated rats also had lower numbers of cage cross-overs. Statistically significant ($p < 0.01$) decreases were observed on days 14, 21 and 28.

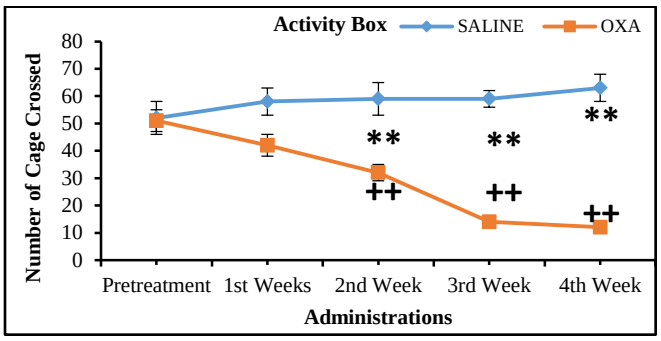

Figure 3: Data are presented as means (+/-) standard deviation (n=6) recorded on the day follow-up to first week administration of all treatment groups (also see below table). Statistically significant values were evaluated and separated into two groupings in this experiment (using the Newman-Keuls test): (i) comparison of treatment groups versus saline administered animals (significance level); (ii) treatment groups using two-way analysis of variance (repeated measures designs) for comparisons of treatment groups on similar days (i.e., day 1 administration to day 7 administration) again by Newman-Keuls test.

Effect of oxalate on light/Dark Transition test (No. of Entries) of rat foe 28 days

Behavioral changes caused by repeated Oxalate administration on activity in the light-dark transition box (Figure 4). This was measured by counting the number of entries into the light box in rats over 28 days. Observations were made the day after the first drug dose and then weekly. Data were analyzed using two-way ANOVA with repeated measures. The results indicated significant effects for days ($F=92.40$, $df=1, 21$, $p<0.01$), Oxalate ($F=101.29$, $df=1, 21$, $p<0.01$), and the interaction between Oxalate and days ($F=132.60$, $df=1, 21$, $p<0.01$). Post hoc analysis with the Newman-Keuls test revealed that Oxalate administration reduced activity, measured by the number of entries into the light box, both acutely and with repeated doses in rats compared to those given saline. A significant decrease ($p<0.01$) was observed after the 1st, 2nd, 3rd, and 4th weeks of administration. When comparing the Oxalate group to similarly treated rats on the first day, the entries into the light box decreased in the Oxalate group. Significant decreases were noted on the 7th ($p<0.05$), 14th, 21st, and 28th days after administration.

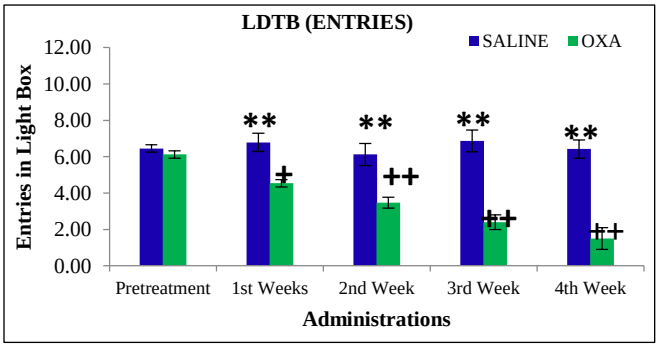

Figure 4: The values are means + SD (n=6) as reported on the following day of the 1st, then weekly treatment. a, b, c, d = P-value; **p<0.01; *p<0.05; +p+0.05 from saline-treated animals by two-way ANOVA.

Effete of oxalate on light/dark transition test (Time spent) of rats for 28 days

Carefully observing the graphical representations, it has been revealed that Figure 5 indicates the effect of Oxalate repeated administration on activity in light dark transition box (time spent in light box) on rat for 28 days as it has been monitored on the next day of 1st drug administration, and then on weekly basis. The result, as revealed from the statistical analysis with 2 way ANOVA (repeated measuring design), the effect of Oxalate ($F=102.77$, $df=1,21$, $p<0.01$), effect of repeated measuring ($F=101.61$, $df=1,21$, $p<0.01$), effect of interaction of Oxalate and days ($F=39.10$, $df=1,21$, $p<0.01$), is significant. Furthermore, on performing the Newman-keuls post hoc multiple comparison test, it has been observed that Oxalate administration reduced activity in light dark box (time spent in light box) as compared to saline administered rats on single administration as well as on repeated administration. It has been identified that significant ($p<0.01$) reduction has been observed after the 2nd, 3rd, and 4th weeks of administration. In respect of 1st week of administration, a significant ($p<0.05$) reduction has been observed. In relation to similar condition of saline administered as well as Oxalate administered rat, the number of times reduced has been revealed in Oxalate administered rat. It has been identified that significant ($p<0.01$) reduction has been observed on 14th, 21st, & 28th days of administration.

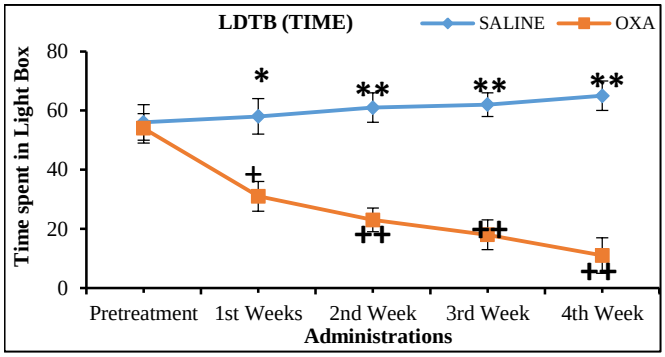

Figure 5: The means ± Jn the table SD (n=6) were computed the day after the administration and then weekly after that. It was determined the group means were significantly different from one another by the Newman-Keuls test: *p<0.05, **p<0.01 from saline administered; +p<0.05, ++p<0.01 one-way ANOVA from saline or oxalate administered on the first day after administration performed a two-way repeated measures ANOVA.

Effect of oxalate on open field activity (Latency Time) of rats for 28 days

The impact of repeated doses of oxalate on the amount of ambient stimulation (latency period) in an unfamiliar setting, measured over a 28-day period (Figure 6). Animals were tested on the days following the exposure to oxalate and on a week period thereafter. Two-way ANOVA, repeated measures was used to test differences in the effect of the vehicle (saline, n=11) and oxalate drugs over time ($F=55.48$, $df=1/21$, $p<0.01$) and the difference between oxalate and saline groups ($F=104.12$, $df=1/21$, $p<0.01$) was found to be statistically significantly different with a significant (interaction)($F=2.52$, $df=1/21$) difference between the oxalate and saline groups over time. A post hoc analysis using

Newman-Keuls procedure indicated that the administration of oxalate resulted in increased stimulation, as reflected by the time taken to enter the open field, to the same extent for both the initial and repeat doses as compared to the saline group. The increase was statistically significant at days 14, 21 and 28. The mean latency period from the oxalate groups was significantly longer than the same mean latency periods of the saline groups at weeks 3 and 4.

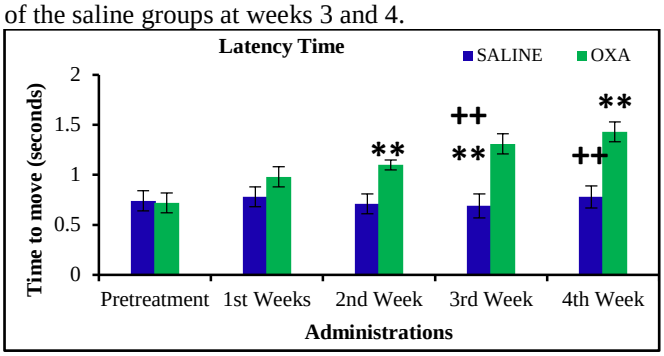

Figure 6: Values are shown as mean ± SD (n=6), tracked the day after the first dose and then weekly. Differences were checked using the Newman-Keuls test: *p<0.05, **p<0.01 compared to the saline group; +p<0.05, ++p<0.01 compared to the saline or Oxalate groups on day one, using a two-way ANOVA (repeated measures).

Effect of oxalate on elevated plus Maze (Time spent in open arm) of Rats for 28 Days

Effect of Oxalate repeated administration on activity in elevated plus maze (time spent in open arm) on rats for 28 days as they monitored after on next day of 1st drug administration and then monitored weekly. As the data analyzed by 2 way ANOVA (repeated measured designing) the effect of Oxalate ($F=121.29$, $df=1,21$, $p<0.01$) and the effect of repeated monitoring ($F=92.10$, $df=1,21$, $p<0.01$) and the effect of interaction between all factors ($F=103.78$, $df=1,21$, $p<0.01$) was found significant. Post hoc analysis by Newman-keuls test showed that administration of Oxalate decreased activity in an elevated plus maze (time spent in open arm) as compared to saline administrated rats on single as well as on repeated administration. Significant ($p<0.01$) decreased was found after 2nd, 3rd and 4thweeks of administration. As compared to similarly administered animals of saline or Oxalate administered rats from 1st day of administration, number of time spent decreased on in Oxalate administered rats. Significant ($p<0.01$) decreased was found after 14th, 21st and 28thday of administration.

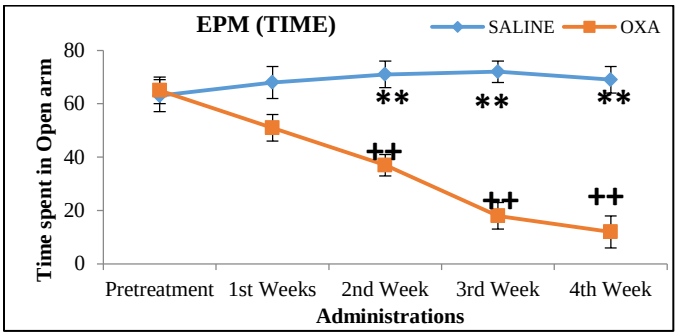

Figure 7: Values are means + SD (n=6) as monitored on next day of 1st and then weekly administrations. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline administrated animals; +p<0.05, ++p<0.01 from similarly saline or Oxalate administrated animals of 1st[u]00 day administration following two-way ANOVA (repeated measures design)

DISCUSSION

Research suggests that high levels of oxalate may affect neurotransmitter systems in the brain, leading to behavioral deficits such as: Cognitive impairments: High levels of oxalate have been linked to cognitive impairments such as memory loss, difficulty with problem-solving and decision-making, and slower reaction times (Pfau *et al*., 2021). Anxiety and depression: Studies have shown that increased levels of oxalate in the brain can lead to anxiety and depression-like behaviors in animal models. Impaired social behavior: Oxalate has been shown to disrupt social behavior in animal studies, causing animals to exhibit less social interaction and increased aggression. Motor deficits: High levels of oxalate can also cause motor deficits, such as decreased coordination and balance (Rehman *et al*., 2013). The present study was designed to investigate the effects of repeated administration of Oxalate on behavioral paradigms such as growth rate, food intake, home cage activity, open field activity, light dark transition and elevated plus maze test in rats. To carry out this experiment we took 24 male albino wistar rats weighing 100-150g and was divided into two groups namely control and test and was administered 0.98% NaCl (normal saline) and Oxalate (10 mg ml-1 kg-1) respectively. The route of administration was oral. The behavioral activities, body weight and food intake were performed on the 1stday, 7th day and 14th day of drug administration. The aim of the present study was to establish whether repeated administration of Oxalate induce behavioral deficits as well as memory and cognitive impairment in animal model of rats. In the present study it was found that repeated administration of Oxalate caused decline in growth rate of rats as compared to control group which was administered with normal saline and a significant decrease was observed after 7th and 14th day. A decrease in the food intake of animal is also seen in the Oxalate administered rats as compared to its control counterpart and similar to growth rate a significant decline was observed after 14th day of drug administration. Based on this observation it could be concluded that repeated administration of Oxalate over the time period of few weeks produce hypophagic effect. Male and female Long-Evans rats placed on a diet of Purina laboratory chow supplemented with 2.5 and 5.0% oxalic acid for a period of 70 days revealed decreased body weights and restricted growth rates. Ingestion of 5.0% oxalic acid depressed absolute organ weights of several visceral and endocrine tissues but enhanced the organ/body weight ratios of both male and female rats. Vaginal smears indicated disrupted estrous cycles (Goldman *et al*.,1977). Home cage activity test is performed to determine the behavior of rats in familiar environment by the number of cage crossed with cut off time of 10 min. In the present study the animals administered with Rotenone (10 mg/ml/kg) showed decreased number of cage crossed as compared to it control counterpart and significant decline was observed after 14th

day of drug administration. Open field activity is used to determine the locomotors activity and exploratory activity of rats. Open field test have two aspects namely latency to move and number of squares crossed. Latency to move is the time taken by the animal to make first movement while number of squares gives insight in the exploratory mechanism of rat. The test group repeatedly administered with Oxalate showed decreased latency time with reference to its locomotive impairment while control group administered with normal saline showed otherwise. Also this decrease in latency time is quite significant after the 14th day. On the other hand the number of squares crossed by the Oxalate administered rats was decreased significantly after 14th day, showing locomotive impairment and rigidity in the animal. Light dark transition test was used to determine the anxiety like behavior in rats (Arrant *et al.*, 2013). This test is based on the intrinsic instinct of light aversion in rats. In the present study the Oxalate administered rats showed decrease in the number of entries as well as time spent in lit box. In both the aspects the decline was significant after the 14th day. Elevated plus maze test is performed to evaluate the fear inducing behavior of rats. In the above performed present study all the animals administered with Oxalate showed decrease in the number of entries in open arm as well as in the time spent in the open arm, the significant decline was after 14th day of drug administration. All the above mentioned results revealed that acute as well as repeated administration of Oxalate (10 mg/ml/kg) induce behavioral deficits in animal model of rat as compared to control group administered with normal saline (0.9% NaCl). This behavioral decline could also be characterized by the locomotors impairment and motor dysfunction as seen in previous studied Oxalate induced Neurodegenerative model of rats. The current review has been productive in the assurance of the impacts of Oxalate in Albino Wister rodents which incited side effects of Parkinson's sickness as well as pressure and nervousness in the creature causing conduct changes. Thusly, these discoveries can be valuable in creating information on the ensuing neurodegenerative and mental impacts of redundant use or openness of Oxalate -containing compounds.

CONCLUSIONS

Overall, the study provides important insights into the potential role of oxalate in the development of behavioral deficits, specifically in the context of depression. However, it is important to note that the study was conducted on animal models, and the results may not necessarily translate directly to humans. Further research is needed to confirm the findings and to investigate the potential clinical implications of these findings.

Conflict of interest

Authors declare no conflict of interest.

REFERENCES

Arrant A.E., N.L. Schramm-Sapyta and C.M. Kuhn (2013) Use of the light/dark test for anxiety in adult and adolescent male rats. *Behav Brain Res*. 256,119-127.

Cui, K., X. Luo, K. Xu and M.R. Ven Murthy (2004) Role of oxidative stress in neurodegeneration: recent developments in assay methods for oxidative stress and nutraceuticalantioxidants.*Prog. Neuropsychopharmacol. Biol. Psychiatry*, 28, 771-799.

Goldman M, G.J. Doering and R.G. Nelson. (1977) Effect of dietary ingestion of oxalic acid on growth and reproduction in male and female Long-Evans rats. *Res Commun Chem Pathol Pharmacol.* 18, 369-372.

Pereira T. M. C., Z. C. Larissa, A. M. M. Ton, S.S Meyrelles., M. Campos-Toimil, B. P. Campagnaro and E. C. Vasquez (2021) *Antioxidants*, 10, 1845-1875.

Pfau A, T. Ermer, S.G. Coca, M.C. Tio, B. Genser, M. Reichel, F.O. Finkelstein, W. März, C. Wanner, S.S. Waikar, K.U. Eckardt, P.S. Aronson, C. Drechsler and F Knauf. (2021) High Oxalate Concentrations Correlate with Increased Risk for Sudden Cardiac Death in Dialysis Patients. *J Am Soc Nephrol*, 32,2375-2385.

Rahman M.M., R.B. Abdullah and W.E. Wan Khadijah. A review of oxalate poisoning in domestic animals: tolerance and performance aspects. J Anim Physiol Anim Nutr (Berl). 2013 Aug;97(4):605-14.

Rodríguez, J.M, K. Murphy, C. Stanton, R.P. Ross, O.I. Kober, N. Juge, K. Rudi, A. Narbad, M.C. Jenmalm, J. R. Marchesi, E. Avershina and M.C. Collado (2015) The composition of the gut microbiota throughout life, with an emphasis on early life. *Microb. Ecol. Health. Dis.*26,26050-26066.

Snodgrass, S. R (1992) Vitamin neurotoxicity. *Mol Neurobiol*, 6, 41-73.

Soleimani, S. M., H. Ekhtiari and J. L. Cadet, (2016) Drug-induced neurotoxicity in addiction medicine: From prevention to harm reduction. *Prog. Brain. Res.* 223:19-41.

Spencer, P.S. and P..J. Lein(2014) Neurotoxicity. In: Wexler, P., Ed., Encyclopedia of Toxicology, 3rd Edition, Academic Press, Oxford, 489-500.

Yadav, N. and P. K. Shukla (2021) Role of Oxidative Stress in Neurodegeneration. In Antioxidants and Functional Foods for Neurodegenerative Disorders (1st edition).

Corresponding Author:
Dr. Muhammad Farhan
Department of Biochemistry,
University of Karachi

Submitted on 22-09-2025
Revised on 13-11-2025
Accepted on 12-12-2025