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TO STUDY THE ANTIDEPRESSANT EFFECT OF DOXAZOSIN BY AN EXPERIMENTAL MODEL IN SWISS ALBINO MICE

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ABSTRACT

Introduction: Doxazosin is an alpha-1 antagonist used for the treatment of benign prostatic hypertrophy (BPH) symptoms and hypertension. An α (1)-adrenergic receptor antagonist called Doxazosin is used to treat benign prostatic hyperplasia and excessive blood pressure. There is evidence linking peripheral α-adrenergic receptors to inflammation.

Aim and Objective: To study the antidepressant effect of Doxazosin by an experimental model in swiss albino mice**.**

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Material and Methods: The study was conducted in the Department of Pharmacology & Therapeutics at King George's Medical University, Lucknow. The present study was designed to evaluate antidepressant in an experimental model in Swiss albino mice. A total number of 18 female Swiss albino mice were included in the study. They were kept in the institutional animal house under standard conditions. They received normal pellet diet and water ad libitum. They were allowed to get acclimatized to the new environment for a period of 2 weeks. Mice were randomly divided into 3 groups, each group containing 6 mice.

Results: In the present study antidepressant activity was observed by the period of immobility in Forced swim test. Each activity was conducted on 18 mice, 6 mice in each group (Group A: Vehicle, Group B: Doxazosin, Group C: Imipramine). Therefore on Day 1, period of immobility of mice in the above 3 groups was found to be comparable. On Day 11, period of immobility of mice in the above 3 groups was found to be comparable again. It was observed that there was a slight decrease in period of immobility indicating that Doxazosin (4 mg/kg) may have some weak antidepressant activity at Day 21. Decreasing period of immobility significantly more than control indicating that Doxazosin (4 mg/kg) may have moderate antidepressant activity at Day 31.

Conclusion: Doxazosin (4 mg/kg) appeared to be a promising therapy option for patients presenting with depression.

Keywords: Doxazosin, Swiss albino mice, Imipramine, Forced swim test, depression

INTRODUCTION

The World Health Organisation (WHO) reported in its 2019 report that disorders like metabolic, respiratory, and cardiovascular conditions impact about 1.6 million, 4 million, and 18 million individuals, respectively. Additionally, it stated that stress, poor lifestyle choices, and little to no physical activity are the main factors raising the risk of chronic illnesses. These illnesses have the potential to increase mortality as well as cause long-term effects like obesity and elevated blood pressure, which account for 12.8% of all deaths (roughly 7.5 million) [1, 2]. They may also act as a trigger for conditions like depression, hypertension, vascular diseases, and cerebral vessel remodelling.

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There are number of symptoms associated with depression include low mood, loss of interest in routine tasks, anhedonia, feelings of worthlessness, problems sleeping, and suicidal thoughts. The major mechanisms are heightened oxidative and nitrosative damage [3], as well as anomalies related to monoamine neurotransmitters [2]. According to the monoamine theory, depression results from a decrease in monoamines including dopamine, serotonin, and norepinephrine in the frontal cortex, limbic system, and hippocampal regions [4]. Monoamine oxidase (MAO) is the main enzyme involved in the metabolism of these monoamines. Significantly depressed patients showed elevated oxidative and nitrosative stress and decreased antioxidant levels [5].

Some of these symptoms become resistant and even unresponsive to painkillers, tricyclic antidepressants, antiarrhythmic drugs and anticonvulsants[6]. Recent studies have demonstrated the role of α1-adrenoceptor antagonists in the modulation of pain perception, depression and anxiety.

Corticotrophin-releasing hormone hypersecretion and glucocorticoid response are impaired in depression [7]. Around 50% of depressive people (80% if seriously depressed) have hyperactivity in the hypothalamic–pituitary–adrenal axis. Antidepressants are thought to work on the central monoaminergic systems, primarily serotonergic and nor-adrenergic synaptic neurotransmission, in major depression. The most typically given medicines are selective serotonin-reuptake inhibitors such as Paroxetine and fluoxetine, as well as specialized serotonin-noradrenaline reuptake inhibitors such as Reboxetine and Desipramine [8]. Even though they are successful in treating most depressive episodes, a considerable proportion of depressed individuals do not show symptoms of improvement until 2–3 weeks after starting treatment. In addition, around a third of these individuals respond to treatment either partially or not at all [9]. Moreover, these medications might cause sedation, anticholinergic effects, seizures, impotence, postural hypotension, anxiety, dizziness, respiratory issues, weight gain, cheese response, cardiac dysrhythmias, insomnia, agitation, and fatigue [10].

Doxazosin is a traditional α1-adrenergic receptor (α1AR) antagonist that can inhibit hypertension. This drug has several potential additional advantages, including a long half-life of 22 h, minimal

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impacts on renal function, and an outstanding antihypertensive effect due to the reduction of smooth muscle tension in peripheral vascular beds that thereby reduces the total peripheral resistance without significantly affecting the heart rate or cardiac output [11-13].

In benign prostatic hyperplasia, Doxazosin relieves bladder outflow obstruction by reducing the prostate tone mediated by α1AR blockade. Doxazosin can also inhibit prostate cancer by inhibiting protein kinase B (PKB)/Akt activation and thereby inducing cell apoptosis via an α1ARindependent mechanism [14]. The antifibrotic effect of Doxazosin on hamsters has been reported, and Prazosin, another α1AR antagonist, has been reported to have a hemodynamic effect on the reduction in Pulmonary hypertension, suggesting that α1AR antagonists play important roles in the treatment of liver fibrosis [15].

In comparative studies Doxazosin has proven to be very effective as the comparator drug in the treatment of hypertension. Doxazosin has also been used such in combination with β-blockers, calcium channel antagonists, diuretics and angiotensin-converting enzyme (ACE) inhibitors in patients with hypertension that is not controlled with monotherapy.

Doxazosin has a beneficial effect on some of the risk factors associated with coronary heart disease, impaired glucose metabolism, insulin resistance, elevated serum lipid levels and left ventricular hypertrophy. Significant decreases in total cholesterol, triglycerides and low density lipoprotein cholesterol are also seen with Doxazosin therapy; while small increases in high density lipoprotein cholesterol and the high density lipoprotein cholesterol or total cholesterol ratio are consistently reported [16]. Some studies have reported an improvement in glucose tolerance although this effect has been more consistently seen in nondiabetic patients than in patients with non-insulin-dependent diabetes mellitus. Also it has been mentioned in literature that Doxazosin may produce a similar decrease in left ventricular hypertrophy as was seen in other antihypertensive agents [17,18].

In terms of long-term research, Doxazosin has withdrawal rates and an incidence of side effects comparable to other α1-adrenoceptor antagonists in the same class.

Recent clinical trials have confirmed Doxazosin's status as a reliable antihypertensive medication and extended its therapeutic range to encompass the management of PTSD, chronic prostatitis/chronic pelvic pain syndrome, and benign prostatic hyperplasia [19]. Therefore, the

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present study was undertaken to study the antidepressant effect of Doxazosin using an experimental model in Swiss albino mice.

MATERIAL AND METHODS

The study was conducted in the Department of Pharmacology & Therapeutics, King George's Medical University, Lucknow, after getting approval from the Institutional Animal Ethics Committee.

Experimental animals:

A total of 18 adult healthy female Swiss albino mice, weighing 20-30 gm (n=6 mice/group) were used in the study. Mice were obtained from animal house of Indian Institute of Toxicology Research (IITR), Lucknow. IITR is one of the certified center by Committee for Control and Supervision of Experiments on Animals (CCSEA) for breeding and housing of animals. The animals were allowed to access food and water ad libitum and were kept in the institutional animal house under temperature controlled environment [25±2◦C] with 12 hours light/12 hours dark cycle. A minimum of 14 days acclimatization period was allowed before the commencement of the study and their health was monitored regularly by a veterinary physician. The normal pellet diet was procured from Bharat Science Solution Company, Loknagar, Unnao, Uttar Pradesh.

The study was started after the approval of Institutional Animal Ethic Committee (IAEC) of King George's Medical University (K.G.M.U), Lucknow (**Project No 129/IAEC/2020).**

All experiments in the study were conducted as per the guidelines laid down by the Committee for Control and Supervision of Experiments on Animals (CCSEA).

DOSAGE FORMS, DOSAGE AND SOURCES OF THE DRUGS

Drugs and chemicals:

All test drugs and chemicals were purchased from Sigma chemical company, USA. Other chemicals were purchased from TCI, Japan.

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Drugs

1) **Doxazosin** – Test drug[20]

Administered in a dose of 4 mg/kg body weight.

Route: Intraperitoneal injection

2) **Imipramine** – Standard for depression model [21,22]

Administered in a dose of 20 mg/kg body weight.

Route: Intraperitoneal injection

Technique of intraperitoneal injection

The desired dose of drug was calculated and loaded in the syringe. The mouse was restrained manually by holding the complete body using all fingers and by gripping the loose skin at the nape of neck and tail restrained between ring and little finger, so as to avoid any trauma during the procedure. The abdomen was exposed and an imaginary line was drawn across the abdomen just above the knees. The injection site was disinfected and a 26 gauge needle with bevel facing up was inserted into the right lower quadrant of the abdomen at a point on this imaginary line close to the midline at an angle of 30-40°. This was done so as to avoid injury to any of the abdominal organs. This was also assured by gentle aspiration and if any fluid or blood was aspirated, the contaminated solution was discarded and the procedure was repeated.

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Figure 1 : Technique of intraperitoneal injection

EXPERIMENTAL PROTOCOL

The present study has been designed to evaluate antidepressant property of Doxazosin in an experimental model in Swiss albino mice.

ANIMAL GROUPS

A total number of 18 female Swiss albino mice were included in the study. They were kept in the institutional animal house under standard conditions. They received normal pellet diet and water ad libitum. They were allowed to get acclimatized to the new environment for a period of 2 weeks. Mice were randomly divided into 3 groups A, B,C groups, each group containing 6 mice.

Group A, B, C were used to evaluate the antidepressant effect of Doxazosin and the effect was compared with Imipramine. [Group A (vehicle), Group B (Doxazosin), Group C (Imipramine)].

For assessing antidepressant effect:

Forced swim test:

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Forced swim test is the most widely employed behavioural model for assessing antidepressant activity. The apparatus consists of a transparent cylinder filled with water at room temperature. In this test, each mice was placed in a cylinder with enough water (filled to 15 cm depth) so that it could not touch the bottom with its hind paws [24]. Immediately after dropping the mice in water, an immediate burst of activity was shown by the mice, it tried to escape, and then eventually adopted an "immobile" posture, where it makes only those movements necessary to keep its head above water [25,26]. The session for mice was for 6 minutes, consisting of pretest (initial 2 mins) and test (last 4 mins). The duration of immobility for baseline was recorded one day prior. On the day of testing, 30 mins after i.p. administration of drugs, mice were gently dropped individually dropped into the cylinder for 6 min [27]. Duration of immobility was recorded during the last 4 min swimming test. Mice were judged to be immobile when it floated in an upright position without movement or making minor movements of its limbs just necessary to keep it's head above water [28,29]. The 3 groups received the respective treatment for consecutive 30 days and the duration of immobility was noted again on the 11^{th}, 21^{st} and 31^{st} day. The water was changed after testing each animal and mice were dried before returning to their respective home cages.

Assessment:

The changes in immobility duration were studied after administering drugs in a separate group of animals.

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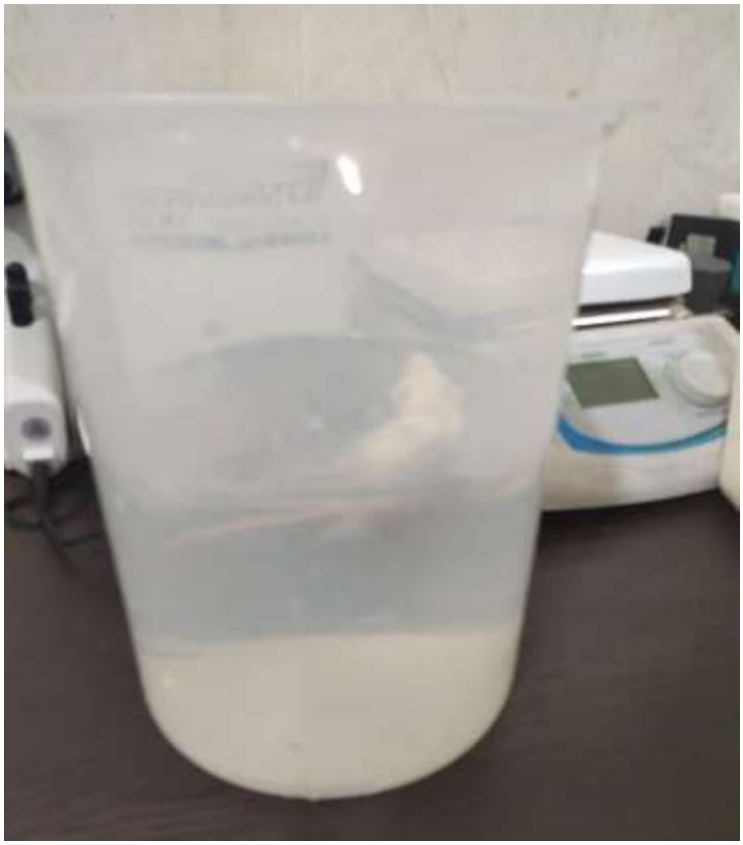

Figure 2 : Forced swim test

Statistical Analysis: The results of tests are expressed as Mean ± SD and analysed using single factor ANOVA. Further statistical analysis for individual groups was carried out by Tukey HSD post hoc test. The criterion for statistical significance is taken as $p < 0.05$ in all statistical evaluations.

RESULTS

The present study was conducted to evaluate the role of antidepressant properties of Doxazosin using an experimental model in Swiss albino mice and assessed against vehicle and standard drug used for antidepressant activity. Group wise distribution was done as given in Table 1

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Table 1: Groupwise distribution of experimental mice

SN	Activity	Group	Group name	Number of mice
1.	Antidepressant effect	Group A	Vehicle	6
		Group B	Doxazosin	6
		Group C	Imipramine (Standard)	6

Assessment of antidepressant activity-

Antidepressant activity was observed by the period of immobility in Forced swim test. Each activity was conducted on 18 mice, 6 mice in each group (Group A: Vehicle, Group B: Doxazosin, Group C: Imipramine).

Table 2: Intergroup comparison of period of immobility (seconds)

at Day1, 11, 21, 31

S. No.	Group	Day 1	Day 11	Day 21	Day 31
1	Control (Vehicle i.p.)	188.30±7.72	194.13±10.18	201.67±10.27	214.92±9.32
2	Doxazosin (4 mg/kg i.p.)	192.60±10.93	191.63±12.62	185.52±8.14 [b,d]	177.87±7.71 [a,d]
3	Imipramine (20 mg/kg i.p.)	184.23±13.14	180.20±9.96	167.82±10.64 [a]	157.27±7.95 [a]
4	ANOVA	F = 0.89 p = 0.42	F = 2.74 p = 0.09	F = 18.1 p < 0.001*	F= 73.29 p < 0.001*

* Statistically significant [a] p<0.001 as compared to control, [b] p<0.05 as compared to control, [c] p<0.001 as compared to Imipramine (20 mg/kg), [d] p<0.05 as compared to Imipramine (20 mg/kg)

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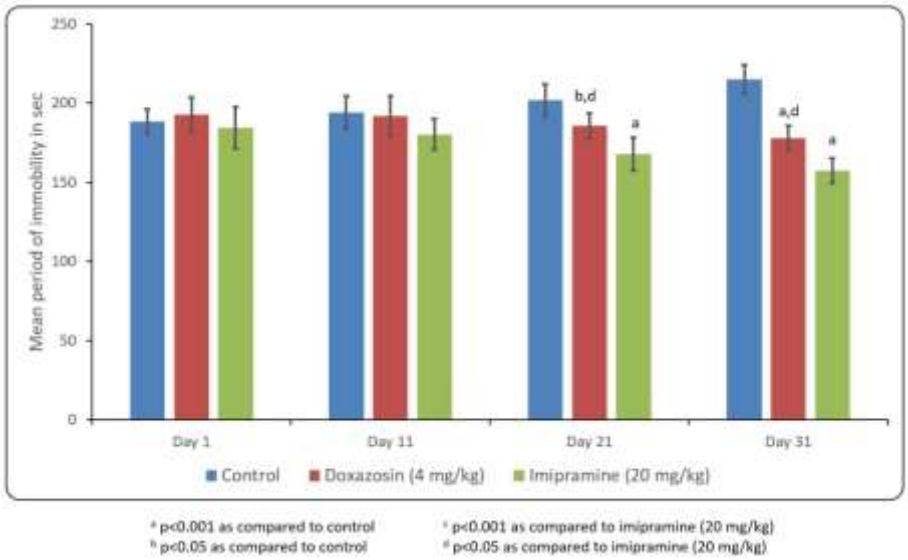

Figure 3: Mean period of immobility of different groups

Intergroup comparison:

On Day 1 (baseline), Doxazosin (4 mg/kg) (192.60±10.93) group had the most increase in period of immobility followed by control (vehicle) (188.30±7.72) group and minimum period of immobility was recorded for Imipramine (20 mg/kg) (184.23±13.14) group. On comparing the intergroup and between group differences of period of immobility, none of the differences amongst the groups were significant. Therefore on Day 1, period of immobility of mice in the above 3 groups was found to be comparable.

On Day 11 (After 10 days of administering the drugs), control (vehicle) (194.13±10.18) group had the most increase in period of immobility followed by Doxazosin (4 mg/kg) (191.63±12.62) group and minimum period of immobility was recorded for Imipramine (20 mg/kg) (180.20±9.96) group. On comparing the intergroup and between group differences of period of immobility, none of the differences amongst the groups were significant. Therefore on Day 11, period of immobility of mice in the above 3 groups was found to be comparable again.

On Day 21 (20 days after administration of the drugs), period of immobility was least for the Imipramine (20 mg/kg) (167.82±10.64) group followed by Doxazosin (4 mg/kg) (185.52±8.14) group and most for control (vehicle) (201.67±10.27) group. Intergroup difference

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was found to be significant ($p<0.001$). The difference in period of immobility in Forced swim test was highly significant ($p<0.001$) between control (vehicle) (201.67±10.27) group and Imipramine (20 mg/kg) (167.82±10.64) group, with Imipramine (20 mg/kg) (167.82±10.64) group showing the most reduction period of immobility. The difference in period of immobility was less significant

($p<0.05$) between Doxazosin (4 mg/kg) (185.52±8.14) group and Imipramine (20 mg/kg) (167.82±10.64) group and between control (vehicle) (201.67±10.27) group and Doxazosin (4 mg/kg) (185.52±8.14) group with Doxazosin (4 mg/kg) (185.52±8.14) group showing slight decrease in period of immobility indicating that Doxazosin (4 mg/kg) may have some weak antidepressant activity at Day 21.

On Day 31 (30 days after administration of the drugs), period of immobility was least for the Imipramine (20 mg/kg) (157.27±7.95) group followed by Doxazosin (4 mg/kg) (177.87±7.71) group and most for control (vehicle) (214.92±9.32) group. Intergroup difference was found to be significant ($p<0.001$). The difference in period of immobility in Forced swim test was highly significant ($p<0.001$) between control (vehicle) (214.92±9.32) group and Imipramine (20 mg/kg) (157.27±7.95) group, with Imipramine (20 mg/kg) (157.27±7.95) group showing the most reduction period of immobility. The difference in period of immobility in Forced swim test was highly significant ($p<0.001$) between control (vehicle) (214.92±9.32) group and Doxazosin (4 mg/kg) (177.87±7.71) group, and was less significant ($p<0.05$) between Doxazosin (4 mg/kg) (177.87±7.71) group and Imipramine (20 mg/kg) (157.27±7.95) group and with Doxazosin (4 mg/kg) (177.87±7.71) decreasing period of immobility significantly more than control indicating that Doxazosin (4 mg/kg) may have moderate antidepressant activity at Day 31.

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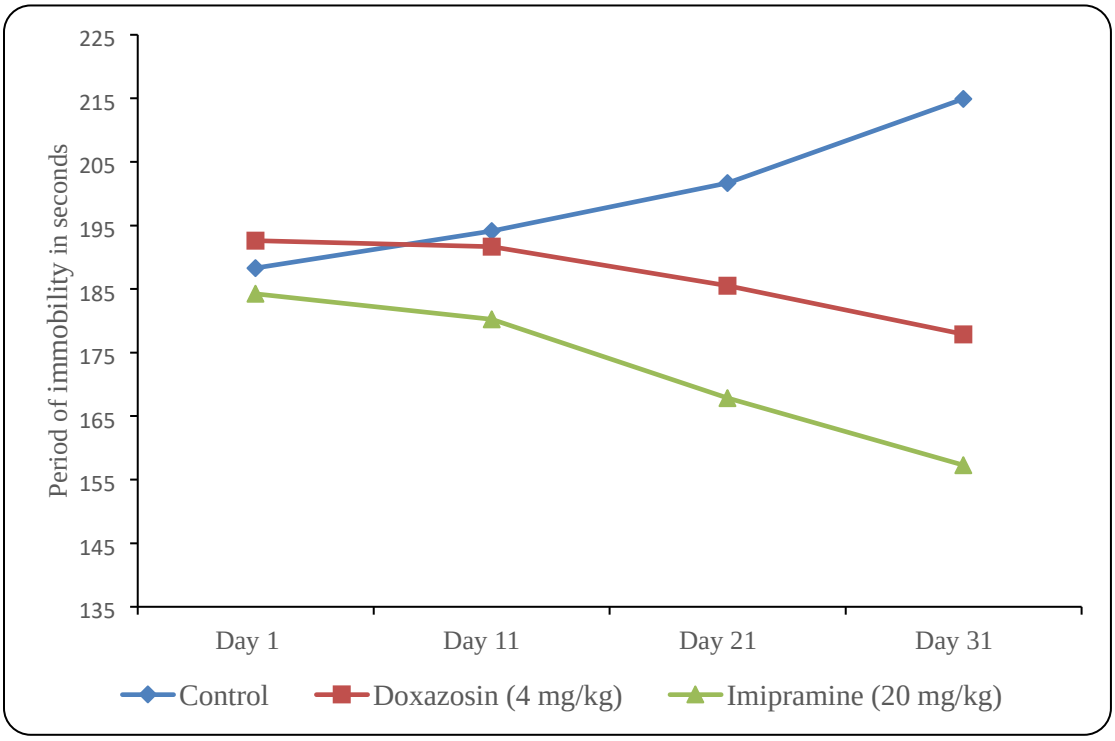

Figure 4: Trend of period of immobility of different groups

DISCUSSION

Non communicable diseases are increasingly becoming a major concern worldwide with a wide range of population being afflicted with them. It significantly makes the quality of life to become worse and may also lead to increased mortality. Risk factors responsible for the same include chronic stress, lack of physical activity and unhealthy lifestyle. This in turn may lead to a cascade of other features like obesity, hypertension and diabetes

Doxazosin is a long-acting α_1-blocker structurally related to Prazosin. Its antihypertensive effect is produced by a reducing smooth muscle tone of peripheral vascular beds which further decreases total peripheral resistance. In benign prostatic hyperplasia, Doxazosin's effect of relieving bladder outlet obstruction through a reduction in prostatic tone mediated via α_1-adrenoceptor blockade.

In comparative studies Doxazosin has proven to be very effective as the comparator drug in the treatment of hypertension. It has been used in a variety of patients including the elderly, smokers

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and patients with concomitant disease states e.g renal disorders, non-insulin-dependent diabetes mellitus (NIDDM), Hypercholesterolemia and respiratory diseases. Doxazosin has also been used in combination with β-blockers, calcium channel antagonists, diuretics and angiotensin-converting enzyme (ACE) inhibitors in patients with hypertension that is not controlled with monotherapy.

The standard drugs used for indications like depression are costly in nature and may lead to serious side effects like suicidal tendencies with antidepressants, etc. A lot of them only are helpful in providing a temporary relief and in the long term may lead to a plethora of serious side effects. Therefore, in the interest of the above points, it is the need of the hour to look for better and safer alternatives that are non habit forming, safer as well as cost effective.

There are various studies that link processes like derangement in RAAS, increase in levels of neuroinflammatory cytokines, sympathetic outflow, oxidative stress and calcium signalling as underlying pathology in conditions like pain, anxiety and depression. Therefore in this present study, we assessed the role of Doxazosin on depression.

The dose and dosage form chosen for the administration of Doxazosin was as per previous studies, Doxazosin (4 mg/kg) [24] was first solubilized in DMSO and then administered intraperitoneally through injection after diluting in normal saline.

Current study comprised a total number of 18 adult healthy female Swiss albino mice , randomly divided into 3 groups with 6 mice in each group. All the animals were allowed to get acclimatized to the new environment for 2 weeks. Groups A to C were used to assess the effect of Doxazosin on antidepressant activity.

Depression is a disorder that affects mood and thought and consists of loss of interest and reduced enthusiasm in activities that a person used to enjoy before. It can lead to interference among one’s daily activities and can effect daily work and hence can lead to lower productivity. The behaviour model for depression that was employed in the current study was forced swim test. It is a widely used test and shares similarities with factors influencing depression in humans. It has been observed that various other classes of antidepressants show a net decrease in immobility

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time depending on the dose of the drug administered, hence can be regarded as a useful model for screening of antidepressant drugs.

In this test, mice are placed in sufficient water so that the paws do not reach the bottom of the cylinder. The normal reaction elicited is immediate bursts of activity as the mouse tries to escape from drowning. It makes movement actively until a particular time comes when the animal ends up with an immobile posture leading to the inference that the animal has got depressed. Mice were administered the drugs intraperitoneally for 30 days and the test was conducted on Day 1, 11, 21 and 31 and observed for 6 min.

In our study, the test drug Doxazosin showed a decrease in period of immobility that was statistically significant ($p<0.001$) on Day 21 and Day 31 and proves that Doxazosin has antidepressant properties. The antidepressant effect of Doxazosin was lower than that of Imipramine (Table 2, Figure 4). Intergroup differences were significant on Day 21 and 31 following administration of drugs. The effect of Doxazosin was less pronounced as compared to Imipramine and the order of decrease in period of immobility was Group C > Group B > Group A.

There are various factors that are implicated in the pathophysiology of depression. The loss of neurotransmitters such as serotonin as well as noradrenaline have been mentioned an important factor in it’s generation. Other factors that may have a role in depression include oxidative stress, changes in neurogeneration and inflammation.

In one instance, Doxazosin (4 mg/kg) showed promise as a treatment modality for patients who present with depression. However, it was not able to decrease any parameter more than the corresponding standard drug of the research area.

That is why further testing will be necessary to confirm this finding.

CONCLUSION

Although Doxazosin's antidepressant effect was shown to be less than that of Imipramine the standard medication, it was nevertheless found to lessen the length of immobility, suggesting that Doxazosin may have some antidepressant function.

Declarations:

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Conflicts of interest: There is not any conflict of interest associated with this study

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors' contributions: Author equally contributed the work**.**

REFERENCES

1. Noncommunicable diseases and their risk factors [Internet]. World Health Organization. 2019 [cited 25 March 2019]. Available from: https://www.who. int/ncds/en/

2. Walker KA, Power MC, Gottesman RF. Defining the relationship between hypertension, cognitive decline, and dementia: a review. Current hypertension reports. 2017 Mar 1;19(3):24.

3. Leonard, B.; Maes, M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concimatants play a role in the pathophysiology of unipolar depression. *Neurosci. Biobehav. Rev.* 2012; *36*, 764–785.

4. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, LeBel AA, Levy RM, Mackey SC. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. InMayo Clinic Proceedings 2010 Mar 1; 85(3) S3-S14.

5. Williams AC, Craig KD. Updating the definition of pain. Pain. 2016 Nov 1;157(11):2420-3.

6. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020 Sep 1;161(9):1976-82.

7. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, Benoliel R, Cohen M, Cruccu G, Davis KD, Evers S. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain. 2019 Jan;160(1):53.

8. Bennett MI, Kaasa S, Barke A, Korwisi B, Rief W, Treede RD. The IASP classification of chronic pain for ICD-11: chronic cancer-related pain. Pain. 2019 Jan 1;160(1):38-44.

9. Wróbel, A.; Serefko, A.; Wlaź, P.; Poleszak, E. The effect of imipramine, ketamine, and zinc in the mouse model of depression. *Metab. Brain Dis.* 2015; *30*, 1379–1386

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 07 2024

10. Chen, J.; Xu, Y.; Han, Q.; Yao, Y.; Xing, H.; Teng, X. Immunosuppression, oxidative stress, and glycometabolism disorder caused by cadmium in common carp (*Cyprinus carpio* L.): Application of transcriptome analysis in risk assessment of environmental contaminant cadmium. *J. Hazard. Mater***.**2019; *366*, 386–394.

11. Liu, Y.; Yu, M.; Cui, J.; Du, Y.; Teng, X.; Zhang, Z. Heat shock proteins took part in oxidative stress-mediated inflammatory injury via NF-κB pathway in excess manganesetreated chicken livers. *Ecotoxicol. Environ. Saf.* 2021; *226*, 112833.

12. Miao, Z.; Miao, Z.; Teng, X.; Xu, S. Chlorpyrifos triggers epithelioma papulosumcyprini cell pyroptosis via miR-124-3p/CAPN1 axis. *J. Hazard. Mater.* 2022; *424*, 127318.

13. Dai, W.; Feng, K.; Sun, X.; Xu, L.; Wu, S.; Rahmand, K.; Jia, D.; Han, T. Natural products for the treatment of stress-induced depression: Pharmacology, mechanism and traditional use. *J. Ethnopharmacol.* 2022; *285*, 114692.

14. Cui, J.; Zhou, Q.; Yu, M.; Liu, Y.; Teng, X.; Gu, X. 4-tert-butylphenol triggers common carp hepatocytes ferroptosis via oxidative stress, iron overload, SLC7A11/GSH/GPX4 axis, and ATF4/HSPA5/GPX4 axis. *Ecotoxicol. Environ. Saf.* 2022 ; *242*, 113944

15. Suchareau, M.; Bordes, A.; Lemée, L. Improved quantification method of crocins in saffron extract using HPLC-DAD after qualification by HPLC-DAD-MS. *Food Chem.* 2021; *362*, 130199.

16. Zhang, Y.; Fei, F.; Zhen, L.; Zhu, X.; Wang, J.; Li, S.; Geng, J.; Sun, R.; Yu, X.; Chen, T.; et al. Sensitive analysis and simultaneous assessment of pharmacokinetic properties of Crocin and crocetin after oral administration in rats. *J. Chromatogr. B Analyt. Technol.*
B
i
Xu, M., Wu, R., Liang, Y., Fu, K., Zhou, Y., Li, X., et al. Protective effect and mechanism of QishiweiZhenzhu pills on cerebral ischemia-reperfusion injury via blood-brain barrier and metabonomics. *Biomed. Pharmacother.*2020; 131, 110723.
doi:10.1016/j.biopha.2020; 110723
d
. *Life Sci.* 2017; *1044–1045*, 1–7.

17.

18. Zhu, Y., Wu, X., Zhou, R., Sie, O., Niu, Z., Wang, F., et al. Hypothalamic-pituitary-endorgan axes: Hormone function in female patients with major depressive disorder. *Neurosci. Bull.* 2021; 37, 1176–1187.

Wei, Z. X., Xie, G. J., Mao, X., Zou, X. P., Liao, Y. J., Liu, Q. S., et al. Exosomes from patients with major depression cause depressive-like behaviors in mice with involvement

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 07 2024

19. of miR-139-5p-regulated neurogenesis. *Neuropsychopharmacology* . 2020; 1050–1058.

20. Tung D, Ciallella J, Cheung PH, Saha S. Novel anti-inflammatory effects of Doxazosin in rodent models of inflammation. Pharmacology. 2013; 91(1-2):29-34.

21. Kumar A, Garg R, Gaur V, Kumar P. Nitric oxide mechanism in protective effect of imipramine and venlafaxine against acute immobilization stress-induced behavioral and biochemical alteration in mice. Neuroscience letters. 2009 ;467(2):72-5.

22. Loiseau F, Le Bihan C, Hamon M, Thiébot MH. Effects of melatonin and agomelatine in anxiety-related procedures in rats: interaction with diazepam. European Neuropsychopharmacology. 2006 Aug 1;16(6):417-28.

23. Wolfe AM, Kennedy LH, Na JJ, Nemzek-Hamlin JA. Efficacy of tramadol as a sole analgesic for postoperative pain in male and female mice. Journal of the American Association for Laboratory Animal Science. 2015 Jul 1;54(4):411-9.

24. Can A, Dao DT, Arad M, Terrillion CE, Piantadosi SC, Gould TD. The mouse forced swim test. JoVE (Journal of Visualized Experiments). 2012 Jan 29(59):e3638.

25. Costa AP, Vieira C, Bohner LO, Silva CF, da Silva Santos EC, De Lima TC, Lino-deOliveira C. A proposal for refining the forced swim test in Swiss mice. Progress in NeuroPsychopharmacology and Biological Psychiatry. 2013 Aug 1;45:150-5.

26. Bogdanova OV, Kanekar S, D'Anci KE, Renshaw PF. Factors influencing behavior in the forced swim test. Physiology & behavior. 2013 Jun 13;118:227-39.

27. Młyniec K, Davies CL, Budziszewska B, Opoka W, Reczyński W, Sowa-Kućma M, Doboszewska U, Pilc A, Nowak G. Time course of zinc deprivation-induced alterations of mice behavior in the forced swim test. Pharmacological Reports. 2012 May;64(3):567-75.

28. Wang Z, Gu J, Wang X, Xie K, Luan Q, Wan N, Zhang Q, Jiang H, Liu D. Antidepressantlike activity of resveratrol treatment in the forced swim test and tail suspension test in mice: the HPA axis, BDNF expression and phosphorylation of ERK. Pharmacology Biochemistry and Behavior. 2013 Nov 1;112:104-10.

29. Bersudsky Y, Shaldubina A, Belmaker RH. Lithium's effect in forced-swim test is blood level dependent but not dependent on weight loss. Behavioural pharmacology. 2007 Feb 1;18(1):77-80.