



on serotonergic receptors.<sup>[5,6]</sup> Selenium, a trace element with an important role in protecting the brain against oxidative damage, suggests its potential for depression. Observational studies have consistently shown a positive association between selenium status, diabetes, insulin resistance and depression.<sup>[6,7]</sup> This study aimed to evaluate the effect of gliclazide and its combination with selenium in an experimental rat co-model of depression and diabetes mellitus.

## MATERIALS AND METHODS

### Study approval and drug procurement

The protocol (CPCSEA/ARCP/2022-23/01) for this study was authenticated and conducted in the Research Laboratory of the Pharmacology Department. Gliclazide was provided as a gift by Indoco Remedies Ltd., Navi Mumbai. Reserpine (Yarrow Chem Products), fructose (Chemdyes), alloxan (Sigma Aldrich) and selenium (Bluebonnet Nutrition Corporation) were purchased for the study.

### Animals and experimental design

Wistar rats of either sex weighing 150–200 g were procured from Zydus Health Care, Ahmedabad, and divided into four groups of eight animals each ( $n = 8$ ). The rats were housed under standard conditions according to the guidelines of the Committee for Control and Supervision of Experiments on Animals (CCSEA).

Group I animals ( $n = 6$ ) were administered 0.9% saline orally as a vehicle control for 32 days. The treatment regimen lasted for 31 days and was divided into two phases, as illustrated in Figure 1. The first phase involved the induction of diabetes, followed by the second phase as induction of depression. T2DM was induced in rats using the fructose-fed alloxan model, while depression was induced through reserpine administration. The test drugs evaluated in the study were gliclazide and selenium.

Diabetes mellitus was induced in all animals except vehicle group. For induction of diabetes, animals received 20% w/v fructose solution in drinking water for 14 days. On day 15, after an overnight fast, alloxan (150 mg/kg, *i.p.*) was administered. After 48 h, fasting blood glucose levels (BGL)

were measured using a digital one-touch glucometer, and animals with BGL  $\geq 200$  mg/dL were selected for further study.<sup>[8,9]</sup> Eighteen diabetic rats were randomly divided into three groups ( $n = 6$ ) and received reserpine (0.2 mg/kg/day *i.p.*)<sup>[10]</sup> for 14 days to induce depression. Group II (Model group) received only reserpine. Group III and Group IV additionally received gliclazide (10 mg/kg/day *p.o.*)<sup>[11]</sup> and a combination of gliclazide (10 mg/kg/day *p.o.*)<sup>[11]</sup> with selenium (0.2 mg/kg/day *p.o.*)<sup>[12]</sup> for the same duration.

### Behavioural tests

On day 31, following the last drug administration, behavioural tests were conducted in the following sequence: Open field test (OFT) and tail suspension test (TST). On day 32, the sucrose preference test (SPT) was performed.

#### OFT

The OFT was used to assess both locomotor and exploratory behaviours. Each rat was individually placed in the centre of a 60 × 60 × 40 cm box divided into nine equal quadrants. For a duration of 5 min, the number of quadrants crossed with all four paws (indicating locomotor activity) and the frequency of rearing on its hind limbs (indicating exploratory activity) were recorded.<sup>[13-15]</sup>

#### TST

The antidepressant-like effects of gliclazide and gliclazide with selenium were assessed using the TST. Rats were suspended 60 cm above the floor by adhesive tape about 1 cm from the tip of their tails. Immobility time was recorded over 5 min, with rats considered immobile when they remained motionless and hung passively.<sup>[13,14]</sup>

#### SPT

SPT, commonly used to evaluate depressive-like behaviour (anhedonia), was conducted over 24 h. On day 31, after a 23-h fasting period, each rat was presented with two bottles for the final hour, one containing 1% sucrose solution and the other containing simple drinking water. The volume of each solution consumed was recorded, and the percentage preference for sucrose was calculated using the following formula:<sup>[10,13,16]</sup>

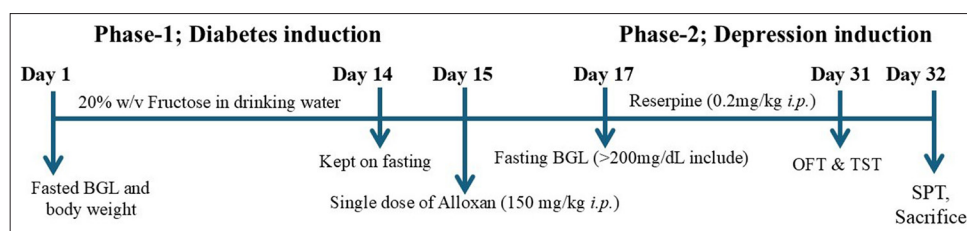


Figure 1: Study timeline.

$$\% \text{ Sucrose preference} = \frac{\text{Sucrose solution consumption (mL)}}{\text{Sucrose solution consumption (mL)} + \text{Water consumption}} \times 100\%$$

### Measurement of brain oxidative stress markers

Oxidative stress markers, including brain superoxide dismutase (SOD),<sup>[17]</sup> malondialdehyde (MDA)<sup>[18]</sup> and reduced glutathione (GSH),<sup>[19]</sup> were measured chemically.

### Statistical analysis

Data were expressed as mean  $\pm$  standard error of the mean and were analysed using one-way analysis of variance, followed by Dunnett's test. Statistical analysis was performed with GraphPad Prism 9.0 software, with a significance level set at  $P < 0.05$ .

## RESULTS

### Body weight changes

From day 0 to 17, Wistar rats treated with a 20% fructose solution and a single dose of alloxan showed significant increases in body weight across the model control, gliclazide-treated and gliclazide with selenium-treated groups. On day 17, body weights increased from initial values to  $200 \pm 2.58$ ,  $203.33 \pm 3.33$  and  $205 \pm 4.28$  g, respectively. This increase was statistically significant ( $P < 0.0001$ ) compared to the vehicle control group. From day 17 to 32, the model control group's body weight decreased significantly, while the other groups showed slight increases. By day 32, body weights in the model control group significantly differed from the vehicle control group ( $P < 0.0001$ ), with the gliclazide-treated and gliclazide with selenium-treated groups showing significant increases compared to the model control group ( $P < 0.001$ ) [Figure 2].

### Blood glucose level (BGL)

The administration of 20% fructose and alloxan significantly increased fasting BGL in the model control, gliclazide and gliclazide with selenium-treated groups by day 17. These groups showed BGL (mg/dL) of  $216.33 \pm 2.43$ ,  $217.83 \pm 3.59$  and  $218.16 \pm 2.82$ , respectively, which were significantly higher than the vehicle control group ( $P < 0.0001$ ). By day 32, the model control group had a further significant increase in BGL, while the gliclazide and gliclazide with selenium-treated groups showed significant reductions ( $P < 0.0001$ ) compared to the model control group [Figure 3].

### Behavioural tests

#### Open field test (OFT)

On the 31<sup>st</sup> day, the model control group showed significantly ( $P < 0.001$ ) reduced locomotion ( $133.33 \pm 1.81$ ) and rearing

( $13.16 \pm 1.13$ ) compared to the vehicle control group (rearing:  $20 \pm 2.29$ , locomotion:  $144.16 \pm 2.08$ ). The gliclazide-treated (rearing:  $25.5 \pm 1.54$ , locomotion:  $147.33 \pm 2.60$ ) and gliclazide with selenium-treated groups (rearing:  $29.66 \pm 1.45$ , locomotion:  $150 \pm 1.87$ ) showed significant ( $P < 0.0001$ ) increases in these behaviours compared to the model control group. Although the gliclazide with selenium group showed slightly higher rearing and locomotion than the gliclazide-only group, the difference was not statistically significant [Table 1].

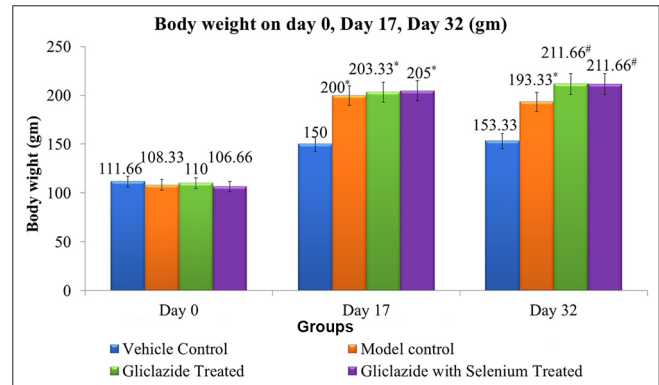


Figure 2: Change in body weight.

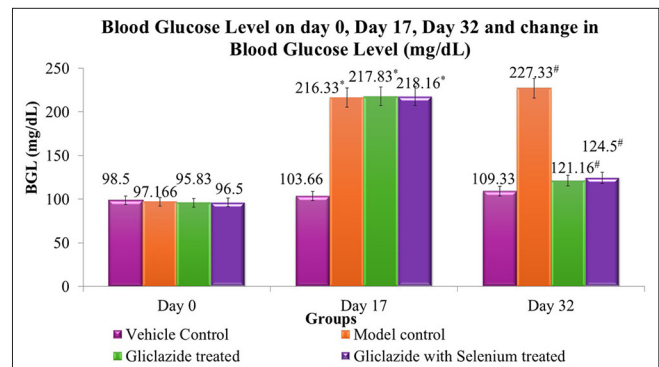


Figure 3: Blood Glucose Level (mg/dL) on Day 0, Day 17 and Day 32.

Table 1: Open field test. Effect of gliclazide and gliclazide with selenium combination on rearing and locomotion using open field test.

Groups	Rearing	Locomotion
	(No. of rearing)	(No. of crossing)
Vehicle control	20 $\pm$ 2.29	144.16 $\pm$ 2.08
Model control	13.16 $\pm$ 1.13*	133.33 $\pm$ 1.81*
Gliclazide treated	25.5 $\pm$ 1.54#	147.33 $\pm$ 2.60#
Gliclazide with selenium treated	29.66 $\pm$ 1.45#	150 $\pm$ 1.87#

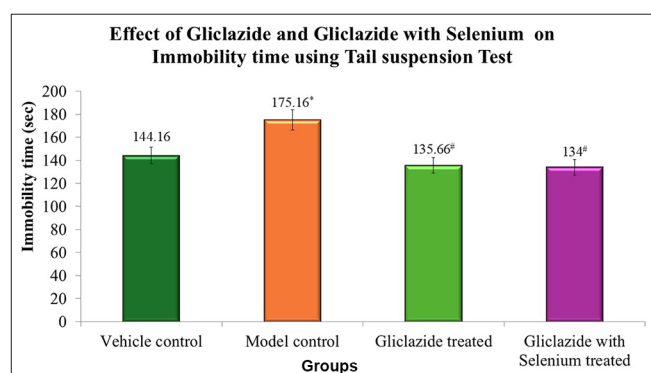
Data are expressed as mean  $\pm$  SEM, n=6. \* $p < 0.001$  When Model control group compare with Vehicle control group, # $p < 0.0001$  when Gliclazide treated group and Gliclazide with Selenium treated group compare with Model control group using by one way ANOVA followed by Dunnet's test.

### Tail suspension test (TST)

The immobility time in the model control group ( $175.16 \pm 4.20$  s) was significantly higher ( $P < 0.0001$ ) than in the vehicle control group ( $144.16 \pm 1.75$  s). The gliclazide-treated ( $135.66 \pm 4.00$  s) and gliclazide with selenium-treated groups ( $134.00 \pm 2.76$  s) exhibited significantly reduced immobility times compared to the model control group ( $P < 0.0001$ ). Although the immobility time was lower in the gliclazide with selenium combination group compared to the gliclazide-only group, the difference was not statistically significant [Figure 4].

### Sucrose preference test (SPT)

Reserpine-induced depression resulted in anhedonia, with a sucrose preference of  $0.63 \pm 0.02$ , compared to  $0.97 \pm 0.06$  in the vehicle control group, although this difference was not statistically significant. Gliclazide treatment increased sucrose preference to  $1.39 \pm 0.12$ , compared to  $0.63 \pm 0.02$  in the model control group, but this difference was also not statistically significant. However, the gliclazide with



**Figure 4:** Effect of gliclazide and gliclazide with selenium on immobility time using tail suspension test.

selenium-treated group showed a significant increase ( $P < 0.001$ ) in sucrose preference to  $2.22 \pm 0.50$  compared to  $0.63 \pm 0.02$  in the model control group. While the gliclazide with selenium group had a higher sucrose preference ( $2.22 \pm 0.50$ ) compared to the gliclazide-only group ( $1.39 \pm 0.12$ ), this difference was not statistically significant [Table 2].

### Oxidative stress markers

#### SOD activity

The SOD activity was significantly lower in the model control group ( $0.21 \pm 0.049$ ) compared to the vehicle control group ( $0.47 \pm 0.028$ ) ( $P < 0.0004$ ). Treatment with gliclazide ( $0.39 \pm 0.036$ ) and gliclazide combined with selenium ( $0.42 \pm 0.01$ ) significantly increased SOD levels compared to the model control group ( $P < 0.001$ ). Although the gliclazide with selenium group showed higher SOD levels than the gliclazide alone group, this difference was not statistically significant [Table 3].

#### Reduced GSH activity

GSH levels were significantly lower in the model control group ( $0.009 \pm 0.0001$ ) than in the vehicle control group ( $0.432 \pm 0.01$ ) ( $P < 0.0001$ ). Both the gliclazide ( $0.177 \pm 0.002$ ) and gliclazide with selenium groups ( $0.408 \pm 0.002$ ) exhibited significantly higher GSH levels compared to the model control group ( $P < 0.0001$ ). The gliclazide with selenium group also had significantly higher GSH levels than the gliclazide group ( $P < 0.0001$ ) [Table 3].

#### MDA levels

MDA levels were higher in the model control group ( $0.181 \pm 0.103$ ) compared to the vehicle control group ( $0.077 \pm 0.047$ ).

**Table 2:** % Sucrose preference. Effect of gliclazide and gliclazide with selenium combination on % sucrose preference.

Groups	Vehicle control	Model control	Gliclazide treated	Gliclazide with selenium treated
Sucrose preference (%)	$0.97 \pm 0.06$	$0.63 \pm 0.02$	$1.39 \pm 0.12$	$2.22 \pm 0.50^*$

Data are expressed as Mean  $\pm$  SEM, n=6. \* $p < 0.001$  when Gliclazide with Selenium treated group compared with Model control group by one way ANOVA followed by Dunnet's test.

**Table 3:** Oxidative stress parameters. Effect of gliclazide and gliclazide with selenium combination on oxidative stress parameters in the brain of rats of various groups.

Groups	Vehicle control	Model control	Gliclazide treated	Gliclazide with selenium treated
Superoxide dismutase (UI/g)	$0.47 \pm 0.03$	$0.21 \pm 0.05^*$	$0.39 \pm 0.04^{\#}$	$0.42 \pm 0.01^{\#}$
Glutathione (mM)	$0.432 \pm 0.01$	$0.009 \pm 0.0001^*$	$0.177 \pm 0.002^{\#}$	$0.408 \pm 0.002^{*\#}$
Malondialdehyde ( $\mu\text{mol/g}$ )	$0.077 \pm 0.05$	$0.181 \pm 0.10$	$0.046 \pm 0.00$	$0.043 \pm 0.00$

Data are expressed as mean  $\pm$  SEM, n=6. \* $p < 0.0001$  when Model Control group compared to Vehicle control group.  $\#p < 0.001$  when Gliclazide treated group and Gliclazide with Selenium treated group compared with Model control group.  $^{*\#}p < 0.0001$  when Gliclazide with Selenium treated group compare with Gliclazide treated group by using one way ANOVA followed by Dunnet's test.

Treatment with gliclazide ( $0.046 \pm 0.0035$ ) and gliclazide with selenium ( $0.043 \pm 0.0033$ ) reduced MDA levels compared to the model control group, with the gliclazide and selenium combination showing a more pronounced reduction, though the difference was not statistically significant [Table 3].

## DISCUSSION

T2DM is a long-term endocrine and metabolic condition marked by elevated BGL.<sup>[20,21]</sup> Depression is recognised as the most prevalent psychiatric mood disorder associated with diabetes mellitus as a comorbidity, with its incidence being twice as high in diabetic patients compared to non-diabetic individuals.<sup>[10,14,22-24]</sup> Insulin insufficiency or deficiency, insulin resistance-induced hyperglycaemia and reduced availability of serotonin 5-hydroxytryptamine (5-HT) in the brain are key features of both T2DM and depression, respectively.<sup>[10,14]</sup> Hyperglycaemia is also considered a primary metabolic cause in the development of depression, as it is associated with increased oxidative stress due to the overproduction of reactive oxygen species (ROS), which in turn reduces serotonin availability.<sup>[10,25]</sup> In addition, oxidative stress impairs glucocorticosteroid release and receptor function, dysregulates the polyol and glycolytic pathways, disrupts the HPA axis, overexpresses advanced glycation end-products and reduces levels of brain-derived neurotrophic factor.<sup>[10,25]</sup> These mechanisms collectively decrease serotonin synthesis and increase its reuptake, resulting in low serotonin availability in the brain and the development of depression.<sup>[10,25]</sup> The co-occurrence of depression and T2DM negatively impacts patients' health and quality of life.<sup>[10]</sup>

In the present study, a co-model of diabetes mellitus and depression in Wistar rats was utilised to evaluate the effectiveness of gliclazide and its combination with selenium. Diabetes was induced in the model control group, the gliclazide-treated group and the gliclazide-with-selenium-treated group by the fructose-fed-alloxan model.<sup>[8,9]</sup> Excessive fructose intake induces insulin resistance, obesity and compensatory hyperinsulinaemia in experimental animals, leading to  $\beta$ -cell exhaustion and impaired  $\beta$ -cell function.<sup>[8,24]</sup> Alloxan exerts its diabetogenic effect by selectively destroying pancreatic  $\beta$ -cells through ROS generation.<sup>[9]</sup> These mechanisms were evident in the model control, gliclazide-treated and gliclazide-with-selenium-treated groups, as indicated by significantly higher body weight and fasting BGL on day 17, consistent with other research findings.<sup>[8,26]</sup>

In diabetic animals, chronic administration of reserpine for 14 days depletes brain monoamine (serotonin) levels, leading to depression.<sup>[22]</sup> The model control group exhibited significant decreases in rearing and locomotion in the OFT, significant increases in immobility time in the TST on day 31, reduced sucrose preference in the SPT on day 32

and increased oxidative stress, all of which demonstrated reserpine-induced depression in diabetic animals. These results align with those of other studies.<sup>[10,22]</sup>

Gliclazide, a sulfonylurea class oral hypoglycaemic agent, demonstrated antidepressant effects in animals by significantly increasing rearing and locomotion in the OFT, significantly reducing immobility time in the TST on day 31, improving sucrose preference in the SPT on day 32 and reducing oxidative stress, indicating its effectiveness against reserpine-induced depression in diabetic animals.<sup>[27]</sup> Selenium, a trace element with antioxidant properties and neuromodulatory effects, plays a vital role in the proper functioning of selenoproteins such as GSH peroxidase, thioredoxin reductase and selenoprotein-P, which protect the brain against lipid peroxidation and oxidative cellular damage.<sup>[7,28,29]</sup> The combination of gliclazide and selenium produced a synergistic effect against depression, as evidenced by significant increases in rearing and locomotion in the OFT, significant reductions in immobility time in the TST on day 31, improved sucrose preference in the SPT on day 32 and reduced oxidative stress. These results are consistent with those of other studies.<sup>[10,13,14]</sup>

In this study, reserpine was observed to increase MDA levels and significantly reduce SOD and GSH levels in the model control group. This is likely due to the overproduction of ROS, which causes oxidative stress and contributes to depression. Co-administration of gliclazide and selenium with reserpine confirmed their effectiveness against depression compared to the model control group. Gliclazide and selenium exerted their antioxidant effects primarily by reducing systemic oxidative stress through the azabicyclo-octyl ring and selenoproteins, respectively,<sup>[7,27,29]</sup> as demonstrated by diminished MDA levels and improved SOD and GSH levels. Extensive ROS causes lipid peroxidation and increases the levels of lipid peroxides such as MDA. The elevated MDA levels, a marker of lipid peroxidation, confirmed the role of free radicals in reserpine-induced depression. Treatment with gliclazide and selenium attenuated brain MDA levels is consistent with findings reported by other researchers.<sup>[10]</sup> SOD is a key antioxidant enzyme that effectively scavenges oxygen-free radicals and inhibits lipid peroxidation in brain tissue.<sup>[10,29]</sup> Treatment with gliclazide and selenium significantly restored brain SOD levels and provided protection against reserpine-induced oxidative stress. GSH plays a vital role in suppressing oxidative stress by removing reactive species through its xenobiotic electrophiles. Gliclazide and selenium significantly alleviated oxidative stress by improving brain GSH levels. These results are consistent with other studies.<sup>[10,29-31]</sup>

Moreover, the combination of gliclazide with selenium was found to prevent weight gain in animals, as indicated by only a slight increase in body weight. This suggests that

selenium provides a protective effect against the weight gain commonly associated with gliclazide use. These findings may be attributed to selenium's impact on thyroid function. This combination also demonstrated better glycaemic control in animals compared to the gliclazide-alone group, suggesting that further research could be conducted to explore its potential in diabetes mellitus management. These effects may be due to improved insulin levels, which positively influence the serotonergic pathway and its levels. Therefore, studying this interaction could provide a deeper understanding of the mechanisms involved in depression and diabetes mellitus.

For a healthy society, preventing, identifying and treating health problems are crucial. In diabetic patients, depression often remains underdiagnosed, and diabetes specialists should be aware of this common comorbidity.

## CONCLUSION

Study findings confirm the role of gliclazide and selenium in diabetes. The restorative effect of gliclazide and gliclazide with selenium on BGL and oxidative stress acts reserpine-induced depression and fructose-fed alloxan-induced DM. Considering these results, it can be concluded that gliclazide with selenium appears to be protective. Patients who are already taking gliclazide as an oral hypoglycaemic agent can combine selenomethionine as a selenium supplement, and it can give a promising protective effect against depression in diabetes mellitus.

**Acknowledgement:** The authors would like to thank Indoco Remedies and Yarrow Chem Products.

**Ethical approval:** The research/study was approved by the Institutional Animal Ethics Committee (IAEC) at A. R. College of Pharmacy and G. H. Patel Institute of Pharmacy, approval number CPCSEA/ARCP/2022-23/01, dated 29th December 2022.

**Declaration of patient consent:** Patient's consent is not required as there are no patients in this study.

**Financial support and sponsorship:** A. R. College of Pharmacy and G. H. Patel Institute of Pharmacy.

**Conflicts of interest:** There are no conflicts of interest.

**Use of artificial intelligence (AI)-assisted technology for manuscript preparation:** The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

## REFERENCES

- Bădescu SV, Tătaru C, Kobylinska L, Georgescu EL, Zahiu DM, Zăgrean AM, *et al.* The association between diabetes mellitus and depression. *J Med Life Sci* 2016;9:120-5.
- Palagini L, Baglioni C, Ciapparelli A, Gemignani A, Riemann D. REM sleep dysregulation in depression: State of the art. *Sleep Med Rev* 2013;17:377-90.
- Berge LI, Riise T. Comorbidity between type 2 diabetes and depression in the adult population: Directions of the association and its possible pathophysiological mechanisms. *Int J Endocrinol* 2015;2015:164760.
- Rustad JK, Musselman DL, Nemeroff CB. The relationship of depression and diabetes: Pathophysiological and treatment implications. *Psychoneuroendocrinology* 2011;36:1276-86.
- Zemdegs J, Martin H, Pintana H, Bullich S, Manta S, Marqués MA, *et al.* Metformin promotes anxiolytic and antidepressant-like responses in insulin-resistant mice by decreasing circulating branched-chain amino acids. *J Neurosci* 2019;39:5935-48.
- Su WJ, Peng W, Gong H, Liu YZ, Zhang Y, Lian YJ, *et al.* Antidiabetic drug glyburide modulates depressive-like behavior comorbid with insulin resistance. *J Neuroinflammation* 2017;14:210.
- Wang J, Um P, Dickerman BA, Liu J. Zinc, magnesium, selenium and depression: A review of the evidence, potential mechanisms and implications. *Nutrients* 2018;10:584.
- Fabiyi-Edebor TD, Fasanmade AA. Evaluation of the characteristics of diabetes induced by the administration of alloxan to fructose fed wistar rat. *Int J Pharm Sci Res* 2019;10:881-9.
- Ighodaro OM, Adeosun AM, Akinloye OA. Alloxan-induced diabetes, a common model for evaluating the glycemic-control potential of therapeutic compounds and plants extracts in experimental studies. *Medicina (Kaunas)* 2017;53:365-74.
- Soliman E, Essmat N, Mahmoud MF, Mahmoud AA. Impact of some oral hypoglycemic agents on type 2 diabetes-associated depression and reserpine-induced depression in rats: The role of brain oxidative stress and inflammation. *Naunyn Schmiedebergs Arch Pharmacol* 2020;393:1391-404.
- Sarkar A, Tiwari A, Bhasin PS, Mitra M. Pharmacological and pharmaceutical profile of gliclazide: A review. *J Appl Pharm Sci* 2011;1:11-9.
- Aydoğan F, Taştan E, Aydın E, Senes M, Akgedik S, Berkem R, *et al.* Antioxidant role of selenium in rats with experimental acute otitis media. *Indian J Otolaryngol Head Neck Surg* 2013;65:541-7.
- Wang C, Wu Hm, Jing Xr. Oxidative parameters in the rat brain of chronic mild stress model for depression: Relation to anhedonia-like responses. *J Membrane Biol* 2012; 245: 675-681.
- Bampi SR, Casaril AM, Domingues M, De Andrade Lourenço D, Pesarico AP, Vieira B, *et al.* Depression-like behavior, hyperglycemia, oxidative stress, and neuroinflammation presented in diabetic mice are reversed by the administration of 1-methyl-3-(phenylselanyl)-1H-indole. *J Psychiatr Res* 2020;120:91-102.
- Gupta SK. Pharmacological screening methods in preclinical evaluation of new drugs. 2<sup>nd</sup> ed. New Delhi: Jaypee Brothers Medical Publishers; 2009. p. 392-9.
- Slattery DA, Cryan JF. Using the rat forced swim test to assess antidepressant-like activity in rodents. *Nat Protoc* 2012;7:1009-14.
- Lih-Brody L, Powell SR, Collier KP, Reddy GM, Cerchia R, Kahn E, *et al.* Increased oxidative stress and decreased antioxidant defenses in mucosa of inflammatory bowel disease. *Dig Dis Sci* 1996;41:2078-86.

18. Mihara M, Uchiyama M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. *Anal Biochem* 1978;86:271-8.
19. Fokam Tagne MA, Tchoffo A, Noubissi PA, Mazo AG, Kom B, Ngakou Mukam J, *et al.* Effects of hydro-ethanolic extract of leaves of *Maesa Lanceolata* (Mursinaceae) on acetic acid-induced ulcerative colitis in rats. *Inflammopharmacology* 2021;29:1211-23.
20. Naskar S, Victor R, Nath K. Depression in diabetes mellitus-a comprehensive systematic review of literature from an Indian perspective. *Asian J Psychiatr* 2017;27:85-100.
21. Khaledi M, Haghghatdoost F, Feizi A, Aminorroaya A. The prevalence of comorbid depression in patients with type 2 diabetes: An updated systematic review and meta-analysis on huge number of observational studies. *Acta Diabetologica* 2019;56:631-50.
22. Park BK, Kim YR, Kim YH, Yang C, Seo CS, Jung IC, *et al.* Antidepressant-like effects of Gyejibokryeong-Hwan in a mouse model of reserpine-induced depression. *Biomed Res Int* 2018;2018:5845491.
23. Iyer K, Khan ZA. Depression - a review. *Res J Recent Sci* 2012;1:79-87.
24. Prabhakar V, Gupta D, Kanade P, Radhakrishnan M. Diabetes-associated depression: The serotonergic system as a novel multifunctional target. *Indian J pharmacol* 2015;47:4-10.
25. Hosseini A, Abdollahi M. Diabetic neuropathy and oxidative stress: Therapeutic perspectives. *Oxid Med Cell Longev* 2013;2013:168039.
26. Sharma N, Saiyed M, Sachdeva P, Sharma K. Effect of gliclazide on motor and cognitive function in haloperidol induced Parkinson's disease with diabetes mellitus as co-morbidity in wistar rats. *Indian J Pharm Sci* 2024;86:1717-24.
27. Sena CM, Louro T, Matafome P, Nunes E, Monteiro P, Seiça R. Antioxidant and vascular effects of Gliclazide in type 2 diabetic rats fed high-fat diet. *Physiol Res* 2009;58:203-9.
28. Młyniec K, Gaweł M, Doboszevska U, Starowicz G, Pytka K, Davies CL, *et al.* Essential elements in depression and anxiety. Part II. *Pharmacol Rep* 2015;67:187-94.
29. Ebokaiwe AP, Okori S, Nwankwo JO, Ejike CE, Osawe SO. Selenium nanoparticles and metformin ameliorate streptozotocin-instigated brain oxidative-inflammatory stress and neurobehavioral alterations in rats. *Naunyn Schmiedebergs Arch Pharmacol* 2021;394:591-602.
30. Forman HJ, Zhang H, Rinna A. Glutathione: Overview of its protective roles, measurement, and biosynthesis. *Mol Asp Med* 2009;30:1-12.
31. Zhang Y, Fang YC, Cui LX, Jiang YT, Luo YS, Zhang W, *et al.* Zhi-Zi-Chi decoction reverses depressive behaviors in CUMS rats by reducing oxidative stress injury via regulating GSH/GSSG pathway. *Front Pharmacol* 2022;13:887890.

**How to cite this article:** Gupta P, Saiyed M. Impact of gliclazide and selenium co-treatment on depression in a diabetic rat model. *Indian J Physiol Pharmacol*. 2026;70:9-15. doi: 10.25259/IJPP\_544\_2024