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Evaluation Of Protective Effect Of Vinpocetine In Reserpine-Induced Depression In Wistar Rats

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ABSTRACT

Objective: Depression is a serious psychiatric disorder affects over 350 million peoples worldwide. The present study aimed to address the protective effect of vinpocetine in reserpine induced-depressed rats
Methods: The experimental protocol comprised of 4 groups (6 rats each), where rats received normal saline in group 1 and reserpine (0.5mg/kg, i.p) in group 2 for 14 consecutive days. Group 3 and 4 received the test drug, vinpocetine (6mg/kg) and the standard drug, fluoxetine (5mg/kg), before 30 minutes of reserpine administration for 14 days respectively. Then the effect on all groups was assessed on behavioral parameters by TST, open field test (OFT) and forced swim test (FST). While oxidative stress parameters (TBARS, GSH, SOD and CAT) were estimated in brain and Histopathological examination carried out by Hematoxylin & eosin (H&E) staining of hippocampus and cortex of brain.
Result: Result indicates that Vinpocetine significantly reversed the depression induced by reserpine in rats by increasing locomotor activity in OFT, reducing immobility time in TST, and elevating swimming time in forced swim task. Vinpocetine also reduce the oxidative stress by elevating the content of GSH and antioxidant enzymes (SOD & catalase) and decrease malondialdehyde level in the brain. Moreover, In Histopathological examination, vinpocetine significantly reversed the Histopathological alteration of reserpinized rats in hippocampus and cortex region of the brain.
Conclusion: Our result suggests that, vinpocetine possess potent antidepressant properties and can be a potential alternative drug for the treatment of depression.

Keywords: vinpocetine, reserpine, brain monoamines, oxidative stress, depression, antidepressant

INTRODUCTION

Depression is a common, debilitating mental disorder that has a significant impact on psychosocial functioning and affects millions of individuals globally.[1] Depression can be recurrent or long-lasting and is associated with persistent feeling of sadness, lack of interest, sleeplessness, suicidal thoughts, low self-esteem, anhedonia (lack of pleasure), appetite disturbances, and cognitive impairment. Depression is a widespread mental illness with 350 million sufferers around the world. The lifetime prevalence of depression is 17% (5-17%) and its incidence rate is higher in females compared to males. [2, 3] According to WHO predictions, depression will overtake all other disabilities globally by 2030.[4]

Depression is associated with deficiency of brain monoamines (nor-epinephrine, dopamine and 5-HT) in the synaptic cleft. [5] Monoamines are responsible for regulating various functions of the brain such as sleep, mood and cognition. In the pathophysiology of the depression, the level of brain monoamines, oxidative stress and inflammation are of crucial importance.[6] The exact etiology behind the depression has not been clearly elucidated; however generation of the ROS (reactive oxygen species) leads to oxidative stress which can be one of the mechanisms underlying this disease. [7]

Various pharmacological and psychological therapies are used for the management of depression.[8] Several clinically employed medications such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and selective reversible inhibitors of monoamine oxidase A (RIMAs), shows some improvement in depressive behavior but have undesirable side-effects such as insomnia, cardiac toxicity, hypopiesia etc., with long onset of therapeutic action. [9, 10] Approximately 30-40% of people with depression unable to recovered fully. Therefore, development of more effective and safer drug with lesser or no side effect is important. [11]

Reserpine is widely used as a depression inducing agent. The mechanism behind this is that reserpine acts by inhibiting VMAT2 (vesicular monoamine transporter2) irreversibly, which is necessary for the regulation of monoamine (such as norepinephrine (NE), serotonin (5-HT), (DA) dopamine) reuptake from the synapses and their accumulation into the synaptic vesicle. Therefore, by inhibiting pre-synaptic reuptake and storage of catecholamine, Reserpine leads to deficiency of monoamines and induce depression. [12] Previous research indicates that oxidative stress considered as one of the pathophysiology of depression. [13] Previous studies reveals that reserpine significantly elevates cortical and hippocampal MDA and reduces GSH content (endogenous antioxidant) and hence causes oxidative stress. [14]

The plant *Vinca minor* contains vincamine, a major alkaloid. Vinpocetine is synthetically derived from vincamine. Derivative of vincamine have been reported to treat cerebrovascular disorders like stroke and dementia in many countries for more than 30 years. [15] Vinpocetine has been extensively utilized as a neuroprotective agent. The underlying mechanism behind the protective effect against neurotoxicity is elevation of monoamines, anti-inflammatory, antioxidant effect & up regulation of mitochondrial complex-1. The marketed dietary supplement of vinpocetine used to treat impaired memory and cognitive impairment.[16,17]

2. MATERIAL AND METHODS

2.1 ANIMALS

24 wistar rats (wistar strain) weight was about 150-180 g(either sex) were obtained from the animal house facility of Jamia Hamdard University, New Delhi, after approval by the institutional Animal Ethics committee (IAEC approval no. RVNI/IAEC/2021/02). Animals were acclimatizes for one week in R. V. Northland Institute Dadri, Greater Noida before the commencement of experiment and divided into the six animals per group (4 groups) by random sampling method. All the animals had kept with good and standard laboratory condition like 12 hr light and dark cycle at maintained room temperature approx. 25±1ºC and at maintained relative humidity approx. (50±15). All the animals had diet of commercial pellet (Golden feeds, mehruli, New Delhi) and water ad libitum.

2.2 DRUGS AND CHEMICALS

Reserpine was purchased from U.K. Vet chem (Mumbai), Vinpocetine were purchased from Micro labs (Delhi), and fluoxetine was purchased from Micro labs (Delhi).

2.3 EXPERIMENTAL DESIGN

Rats were allocated into 4 groups (6 rats each) as follows: Group 1(control): Normal Control group receive 1ml/kg Normal saline intra-peritoneal for 14 days once daily; Group 2(R): In Toxic control group, Rats were administered Reserpine (0.5mg/kg, i.p) regularly for 14 days; Group 3(RV): In Test drug group, Rats received Vinpocetine (6mg/kg, p.o.) along with Reserpine (0.5mg/kg, i.p) for 14 days once daily ,Vinpocetine (test drug) was given 30 minutes prior to reserpine administration ; Group 4(RF): In standard group, Rats received fluoxetine (5mg/kg, orally) and Reserpine (0.5mg/kg, intraperitoneal) daily for fourteen consecutive days. Fluoxetine (standard drug) was given 30 minutes prior to reserpine administration. The doses of reserpine, vinpocetine and fluoxetine were considered according to prior research respectively. [2,16] [**Figure 1]**

2.4 BEHAVIORAL TESTS

2.4.1 OPEN FIELD TEST:

OFT was conducted to measure rat's movement i.e. locomotor activity (square crossing) and rearing events (standing with paws) based on previous studies. The open field apparatus(VJ Instruments, karanja) consist of chamber (50cm ×50cm ×40cm) in which rats were placed individually. The exploration surface divided into 25 identical squares with a central square. After 24 hour of the last dose of vinpocetine, reserpine and fluoxetine , each rat were positioned at the central square of the apparatus, for 5 min session and the number of rearing events and locomotor activity were recorded. Rats were returned to their cage after the end of session. The apparatus was wiped with 70% alcohol between the sessions. [18]

2.4.2 FORCED SWIM TEST:

FST was conducted according to **Porsolt et al.**, with the modifications made by **Estrada-Camarena et al; Cryan et al.** Two sessions of swimming conducted on rats in forced swim test. In Sessions, rats are placed in a vertical Plexiglas cylinder (46cm height ×23cm wide) containing 30cm of tap water (23-25°c). In the pre-test session, which was held an hour of the last dose of reserpine, vinpocetine, vehicle and fluoxetine, for 10 minutes rats were permitted to swim. After that rats were dried and returned them in home cages. After each session, the tap water was changed. After 24hour of pre-test session, the procedure repeated and rats were forced to swim for 5 minutes under same environmental conditions. The evaluated behavioral indicators were: immobility and the latency to immobility. Immobility is rat's behavior when floating on water surface and making necessary movement to maintain its head out of the water. Latency to immobility is the time duration from when rats were placed inside the cylinder to the first immobility episode. [19,20,21]

2.4.3 TAIL SUSPENSION TEST:

Each rat were hung 50cm above the floor by sticky tape positioned 1.5 cm from the tail tip after 1 hour of the last dose administration. During 6 minutes of the test, in the last 4 minutes rats were observed when they stop struggling and become immobile. The duration of immobility was considered as depression index. When animals were suspended and show no movement, they were deemed to be immobile. **[22]**

2.5 BRAIN HOMOGENATE PREPARATION:

The rats were sacrificed by cervical dislocation, one day after performing all behavioral tests. Then some brain samples of rats was removed after sacrifice and placed in neutral formalin (10%) for histological investigations. Cortical and hippocampal tissue were carefully isolated and undergoes homogenization in 10% (w/v) ice-cold phosphate buffer in homogenizer (Remi instruments Ltd India). Centrifugation of homogenate at 4000rpm for 5 minutes, and the supernatant was utilized to determine the amount of MDA and antioxidant (reduced glutathione) in the cortical and hippocampal brains.

2.6 BIOCHEMICAL ESTIMATION

2.6.1 ESTIMATION OF TBARS (thiobarbituric acid reactive substance)

Okhawa et al 1979, describe the procedure to evaluate the lipid peroxidation. The level of MDA is measured in this assay, which is a byproduct of lipid peroxidation. Prepare the 10% brain tissue homogenate, and then treat 1ml of suspension with 0.5 ml of 0.8% TBA and 30 % TCA (1:1 ratio) before placing tubes in the shaking water bath for 30 minutes. The tubes were centrifuge (Remi instruments Ltd India) for 15 minutes at 3000 rpm after 30 minutes in ice cold water. At 540nm, the absorbance was measured. [23]

2.6.2 ESTIMATION OF CAT (Catalase)

The method to estimate catalase is described by **Clairborne in 1985.** After homogenization of brain tissue in potassium phosphate buffer, 50µ L supernatant of homogenate collected after centrifugation at 10,000 rpm at 4˚c for 20 minutes. Add 2.95ml of H_2O_2 into the cuvette containing supernatant. At a wavelength of 240 nm, Absorbance was noted. The result of the activity expressed in unit (Nano moles per mg protein). The result of catalase was measured as change in absorbance per unit time. [24]

2.6.3 ESTIMATION OF SOD (superoxide dismutase)

According to **Marklund and Marklund, 1974,** to assay superoxide dismutase, tissue undergoes homogenization in 2ml of buffer and centrifuge at 10,000 round per minute in cooling centrifuge for about 20 minutes. To build up the final amount, pyrogallol and tris HCl buffer was mixed with 100 L of supernatant. Stir the solution well to mix all the chemicals well. Then, absorbance was calculated at a wavelength of 420 nm. [25]

2.6.4 ESTIMATION OF GSH (reduced glutathione)

GSH was evaluated in accordance with the methodology given by **Sedlak and Lindsay, 1968.** A mixture of 5 ml of the homogenate, 4 mL of redistilled water, and 1 mL 50% TCA was added. The tube was shaken discontinuously for 10-15 minutes and at 3000 round per minutes, centrifuged for 15 minutes. A subsequent mixture of 2 mL of supernatant, 4 mL 0.4 M Tris buffer (pH 8.9), and 0.1 mL 0.01 M DTNB was then made. Glutathione level was depicted by measurement of absorbance at a wavelength of 412 nm after 5 minutes. [26]

2.6 HISTOPATHOLOGICAL EXAMINATION:

All group (control, treatment, toxic) rats' brains were excised, washed and preserved in formalin (10%). The thick sections (4μm) of brain tissue were cutted after washing and fixing of the tissue in paraffin wax. The neuronal damage and gliosis were graded on a scale of 0 to 3. The cutted sections of tissue were stained with the dye named hematoxylin and eosin (H&E). The grades from 0-3 indicate different brain damage conditions and gliosis. The nerve cell damage and glial injury were graded on a scale of 0 to 3, with 0 indicates normal neurons, 1 indicating mild loss of neural cells and mild glial inflammation, 2 indicating substantial nerve cell injury and gliosis, and 3 indicating severe glial cell damage and diffusion.. [27]

2.7 STATISTICAL ANALYSIS

For multiple comparisons in the behavioral tests, the study data were given as Mean ±SD. Data were analyzed using one-way (analysis of variance) ANOVA following Tukey's multiple comparisons test when appropriate. The statistical tool used in the analysis was GraphPad Prism software (Version 5) & values of P less than 0.05 were considered statistically significant. To compare groups one-way ANOVA was used in biochemical and histological investigations, followed by Tukey's multiple comparison test.

3. RESULT

3.1 Results of behavioral parameters

3.1.1 Behavioral impact of vinpocetine on locomotor activity in open field test:

As shown in **table 1,** When compared to the vehicle treated rats, reserpinized rats (Daily administration of reserpine for a period of 14 days) significantly reduced the locomotor activity and number of rearing events ($p<0.05$). Test drug group (RV) and standard group (RF) shows considerable enhancement in the number of rearing and locomotor activity ($p<0.05$ & $p<0.01$) in comparison with the toxic group(R). [**Graph 1A, 1B**]

3.1.2 Behavioral impact on immobility by vinpocetine in Tail suspension task:

When compared to control rats, reserpinized rats displayed prolonged immobility duration ($p<0.001$). Vinpocetine (test drug) and Fluoxetine (standard drug) were given for 14 consecutive days, considerable decrease in immobility time has been seen on comparison to the (R) toxic group ($p<0.01$ and $p<0.01$), as given in **graph 2and table 2.**

3.1.3 Effect of vinpocetine on swimming time in forced swim test:

Daily administration of reserpine for a period of 14 days significantly decreased swimming time ($p<0.001$), on comparing with the control group. RV (test drug group) and RF (standard group) pretreatment significantly reverse the effect of reserpine by increasing the swimming time significantly as given in **table 3 & graph 3.**

3.2 Result of biochemical parameters

3.2.1 Impact on reduced glutathione (GSH) by treatment with vinpocetine in rats:

As shown in **table 4**, Reserpine administration for 14 consecutive days results in reduction of antioxidant enzyme in the hippocampus and cortical region ($p<0.001$). Vinpocetine (6mg) and fluoxetine (5mg) treatment significantly elevated GSH content ($p<0.05$ & $p<0.05$) in cortex and hippocampus, compared with the toxic control group(R). [**graph 4**]

3.2.2 Impact on lipid peroxidation (LPO Level) by treatment with vinpocetine:

Reserpine group significantly elevate cortical and hippocampal level of lipid peroxidation ($p<0.01$), in comparison with the control group. [**Graph 5**] However, administration of vinpocetine significantly reverse the effect of reserpine by decreasing the level of lipid peroxidation ($p<0.05$) in the brain, in compared with the reserpine group (R). [**Table 4**]

3.2.3 Impact on SOD (superoxide dismutase) by treatment with vinpocetine in rats:

Reserpinized rats had decrease the superoxide dismutase (SOD) content in hippocampus and cortical region of the brain ($p<0.05$) significantly in comparison to vehicle group. [**Graph 6**]Test drug group (RV) and standard group (RF) shows elevated level of antioxidant enzyme (SOD) in cortical and hippocampal region ($p<0.01$ & $p<0.05$). [**Table 4]**

3.2.4 Impact on level of catalase by treatment with vinpocetine in rats:

As given in **table 4**, Wistar rats after reserpine (0.5mg/kg) administration continuously for a total period of 14 days, had reduce the catalase level significantly ($p<0.01$). When compared with reserpine group (toxic control), Vinpocetine (6mg/kg) and fluoxetine (5mg/kg) administration reversed the effect of reserpine by attenuating decreased level of catalase ($p<0.001$ & $p<0.05$) in brain. [**Graph 7**]

3.3 Result of Histopathological examination:

Histopathological examinations of hippocampus and cortex region of brain of all group rats were done and mean pathological score has been recorded as shown in figure 2 & 3. The cortex and hippocampus of the normal control group seems normal, having big spherical neuronal cell bodies, and marked grade 0 [**Figure 2a & 3a**]. In the reserpine group (reserpine 0.5mg/kg, i.p.), significant decrease in neuronal cell (associated with proliferation of glial cell, primarily microglia and astrocytes) has been seen in both parts of the brain and hence, scored grade 3 [**figure 2b & 3b**]. The test drug group (reserpine 0.5mg/kg, i.p + vinpocetine 6mg/kg, p.o) scored grade 1 because it significantly reversed the Histopathological alteration of reserpinized rats by revealing less gliosis and mild neuronal damage, hence, reducing the pathological score of gliosis and neuronal damage in the hippocampus and cortex [**figure 2c & 3c**]. Group 4(standard group) shows normal neurons and mild gliosis in the hippocampus and mild proliferation of capillary epithelium in the cortex, after administration of reserpine (0.5mg/kg, i.p) along with fluoxetine (5mg/kg, p.o) for 14 days respectively and hence standard group scored grade 1 [**figure 2d**].

4. DISCUSSION

The research has been conducted to investigate the protective effect of vinpocetine (6mg/kg) in reserpine-induced model of depression in rats. Result showed that treatment with vinpocetine effectively ameliorates the reserpine induced depression. To the author's knowledge, this is first research to evaluate the anti-depressant potential of vinpocetine in depressive rats by assessing the interrelated role of Histopathological examination, behavioral tests and oxidative stress.[2] Depression is the mood disorder which affects the daily life activities (social & personal) of the person with high prevalence rate. [28] Currently available anti-depression medicines have shown multiple side-effects and not suitable for number of individuals. Therefore, new treatment for depression with less toxicity and high potency are needed. [29,30] Depression has a wide range of symptoms, a poor prognosis, and a varied response to treatment, making it challenging to recognize, diagnose, and treat. [31] In broad term, depression significantly affects human relationships, physical health and cognitive function of the people irrespective of age, ethnicity and gender, and increasing disease burden. [32] Depressive patients experience financial strain, domestic stress, poor workplace productivity and decreased ability to perform daily functions. The core feature of depression is cognitive impairment. According to the studies, cognitive deficit has been reported in the majority of depressive patients. It include deficit in memory, daily life functions and activities like decision making, problem solving, and judgment. [33] Herbal drugs are used traditionally from a long time due to their high potency and few side-effects. Herbal drugs are of high importance to investigating their therapeutic potential in disorders like depression. [28] Pharmacological therapy is based on the monoaminergic hypothesis that the pathophysiology behind depression is low secretion of monoamine neurotransmitters. [8] Herbal drug, Vinpocetine is obtained from the alkaloid vincamine, and is available in market for the treatment of many illnesses like stroke, cerebrovascular disease, and mainly as neuroprotective agent. [15] Previous research revealed that vinpocetine is safe and non-toxic with a wide range of novel therapeutic benefits including high fat diet induced atherosclerosis, anti-inflammation and pathological cardiac remodeling. Due to outstanding safety profile and various novel discoveries, vinpocetine could be repositioned for treatment and prevention of relevant disorders in human. [34]

In this study, Reserpine administered for 14 days to induce depression in rats, revealed by significant alterations in various biochemical, histological and behavioral parameters, which reflects reserpine exhibit depressive behavior. [35] Reserpine is a known induced drug of depression used to determine the potential of anti-depressant drugs. [36] Forced swimming task and Tail suspension task has been used for measuring the immobility time. An elevation in immobility time reflects the behaviorally depressed state and claimed to represent clinical depression. [37,38] Reserpinized rats have been shows significantly elevated immobilization time evaluated in Tail Suspension

Task and reduce swimming time in FST. Some drawbacks of FST are the chances of false negative or positive result. In addition, reserpine administration leads to declined locomotor activity evaluated in test performed in open field apparatus, which indicates motor impairment and disturbance in emotional state**.** [39,40] According to earlier studies; the behavioral despair caused by reserpine in FST is unrelated to how it affects locomotor activity. This result is consistent with a previous investigation that found the open field is a reliable animal model for assessing the general and spontaneous behavior of animals. [41]

Considerable Evidences highlighted that the main mechanism behind depression is reduction of monoamine neurotransmitters (dopamine, nor epinephrine and serotonin). Fourteen days of treatment with reserpine significantly reduce monoamine level and increased metabolites of monoamines (5-HTAA, DOPAC & HVA). [42] Reserpine (vesicle reuptake inhibitor), acts by inhibiting pre-synaptic reuptake and storage of catecholamine, leads to deficiency of monoamines and accelerates oxidative catabolism of neurotransmitter with the help of MAO (monoamine oxidase)**.** [43] These findings prove that reserpine successfully induce depression like behavior in the current study.
Interestingly, fourteen days of treatment with vinpocetine (6mg/kg) significantly enhanced the spontaneous locomotor activity, reduced the time spend immobile in TST and lengthened the time spent swimming in FST on compared with toxic group (R). It suggests that vinpocetine reverse the depressive behavior in rats induced by reserpine, which resembles its anti-depressant properties. In accordance with previous studies, vinpocetine attenuates motor functions in epilepsy induced cognitive impairment and modulate the neurotransmitter (serotonin) level in the brain. [44]

Over the past several decades, growing data has proven that the oxidative stress is also one of the depression's pathogenesis caused by reserpine. [45] It is well accepted that reserpine administration is the cause of increase formation of free radicals and lipid peroxidation resulting from oxidative metabolism of monoamines, and is marked by significant reduction in GSH (antioxidant) and increased level of MDA, which contributes to neuronal apoptosis. [46,47] Overproduction of free radicals or depletion of antioxidants can result into oxidative stress of the brain. Hence, preventing the damage of antioxidants may attenuate reserpine induce depression. [48] In our study, vinpocetine markedly suppressed the oxidative stress by elevating GSH, CAT, SOD and reducing MDA level in the hippocampus and cortex of depressed rat, suggesting that vinpocetine mediate role in anti-depressant effect due to its antioxidant activity. Interestingly, results from the Histopathological analysis also revealed that administration of reserpine for 14 days daily resulted in severe neuronal loss and gliosis in the hippocampus and cortex. Nevertheless, treatment with vinpocetine could effectively reverse the neuronal loss and gliosis by regeneration of neurons. Previous studies stated that vinpocetine possess antioxidant properties [49] and also act as neuroprotective agent. [50] These results support the fact that the drugs possess antioxidant properties could have curative role in depression. [51,52]

5. CONCLUSION

Our present data demonstrate that the investigated drug, vinpocetine mediate antidepressant- like effect in reserpinized rats, through its antioxidant effect, amelioration in altered Histopathological changes and alter depressive behavior in behavioral tests like FST, OFT and TST. However, further preclinical and clinical studies are needed to be done to investigate other underlying mechanisms of depression and to investigate the potency of vinpocetine in treating people with depression.

6. ACKNOWLEDGEMENT

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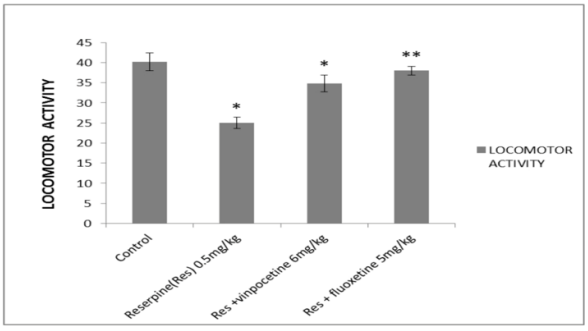
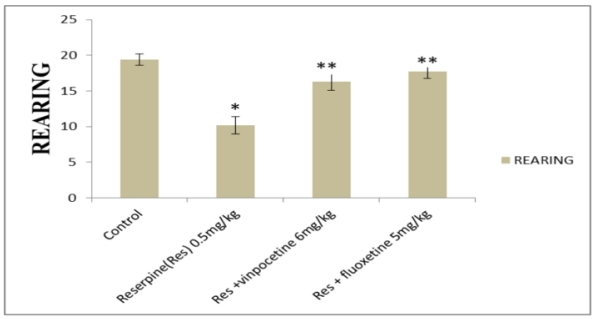
7. CONFLICT OF INTEREST

The authors declare that they have no conflicts of interests in this work.

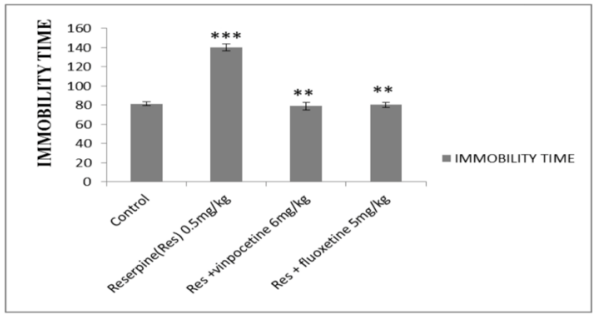
GRAPHS-



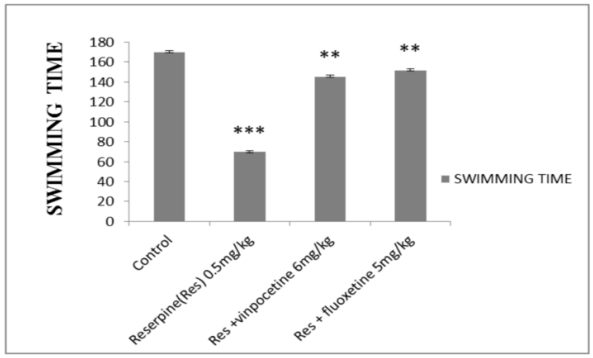
Graph 1A: Effect of vinpocetine on locomotor activity of reserpinized rats in open field test.



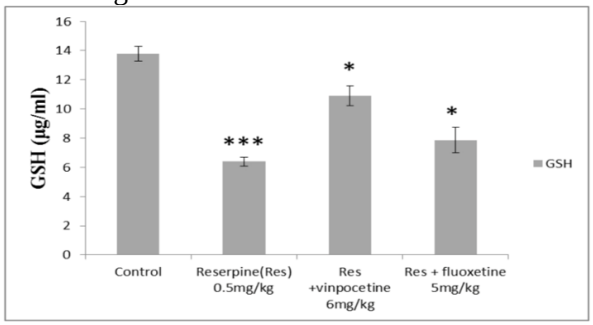
Graph 1B: Represents the vinpocetine effect on rearing events of reserpinized rats in open field test



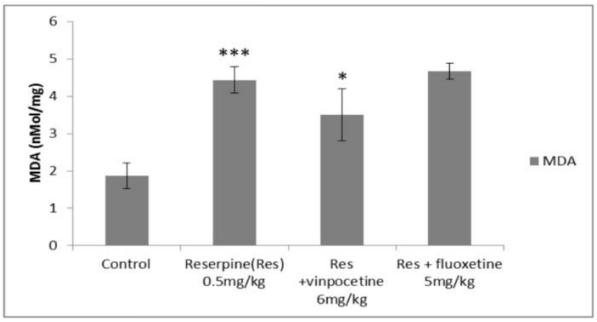
Graph 2: Effect of vinpocetine on reserpinized rat's immobility time in TST



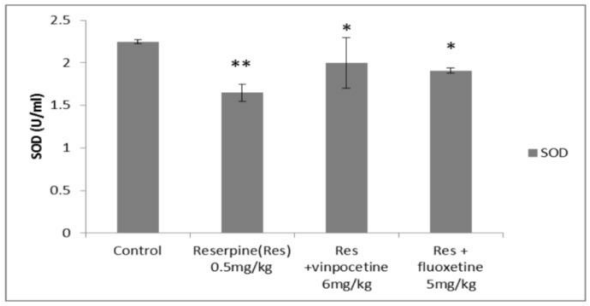
Graph 3: Represents the vinpocetine effect on swimming time in forced swim test



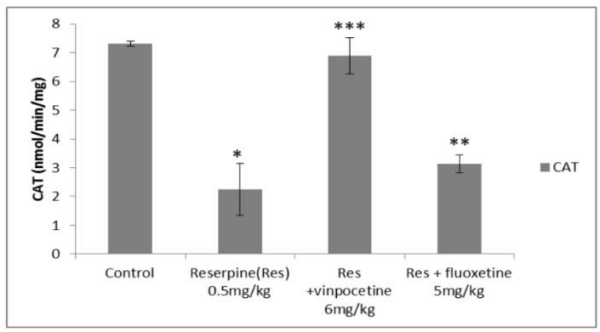
Graph 4: Effect of treatment with vinpocetine on GSH level in reserpinized rats.



Graph 5: Represents the vinpocetine effect on the level of LPO in reserpinized rats.



Graph 6: Represents the impact of vinpocetine administration on the level of superoxide dismutase in reserpinized rats.



Graph 7: Represents the impact of vinpocetine administration on the level of catalase in reserpinized rats.

FIGURES:

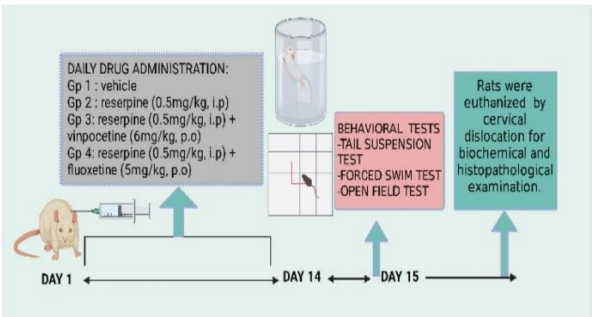


Fig 1: summary of experimental design of the study

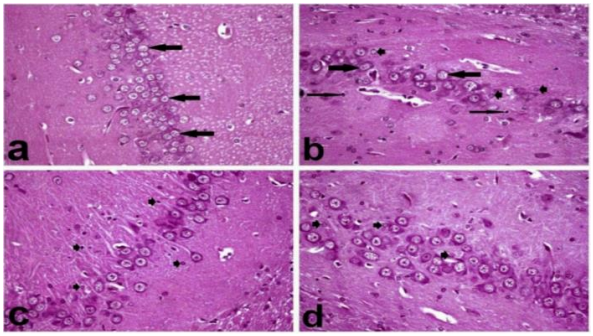


Figure 2: Represents the vinpocetine impact on histopathological changes demonstrated in rat's hippocampus. (a) Hippocampus of normal control group shows (grade 0)normal neuronal structure (thick arrows) (b) hippocampus of toxic group shows (grade 3) severe gliosis(thin arrow) and neuronal loss (thick arrow), (c) treatment group(reserpine 0.5mg/kg + vinpocetine 6mg/kg) shows (grade 1) mild proliferation of glia cells (arrows head) in the hippocampus, (e) standard group (fluoxetine 5mg/kg) shows (grade 1) normal neurons with mild proliferation of astrocytes (arrows head).

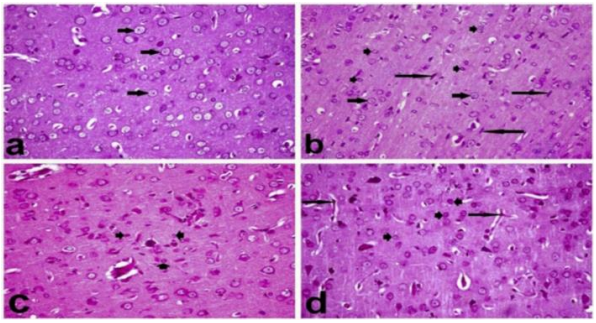


Figure 3: Represents the vinpocetine impact on histopathological changes demonstrated in rat's cortex. (a) cortex of normal control group shows (grade 0)normal neuronal structure (thick arrows) (b) cortex of toxic group shows (grade 3) severe gliosis(thin arrow) and marked reduction of neurons (thick arrow), (c) treatment group(reserpine 0.5mg/kg + vinpocetine 6mg/kg) shows (grade 1) mild proliferation of glia cells (arrows head) in the cortex, (e) standard group (fluoxetine 5mg/kg) shows (grade 1) normal neurons with mild proliferation of astrocytes (arrows head) and capillary endothelium(long thin arrow) in the cortex region of the brain.

TABLES:

Table 1: Shows the effect of vinpocetine on locomotor & rearing events of rats in OFT. Data is presented as mean±SD. One-way ANOVA was used for statistical analysis; *** p<0.001, ** p<0.01, *p<0.05.

GROUPS	LOCOMOTOR ACTIVITY	REARING
Control	40.2 ± 2.2	19.4 ± 0.8
R	25.04 ± 1.4*	10.2 ± 1.2*
RV	34.8 ± 2.04*	16.3 ± 1.2**
RF	38 ± 1.1**	17.7 ± 0.9**

Table 2: Shows the vinpocetine effect on rats Immobility time in tail suspension task. Values are represented as mean±SD. One-way ANOVA was used for statistical analysis; *** p<0.001, ** p<0.01, *p<0.05.

GROUPS	IMMOBILITY TIME
Control	81.34 ±2.2
R	40.1± 3.5***
RV	78.84± 3.7 **
RF	0.2 ±2.67**

Table 3: Shows the effect of vinpocetine on rats swimming time in forced swim test. Values are represented as mean±SD. One-way ANOVA was used for statistical analysis; *** p<0.001, ** p<0.01, *p<0.05.

GROUPS	SWIMMING TIME
Control	170.34 ±2.2
R	70.1± 3.5***
RV	145.84± 3.7 **
RF	152.2 ±2.67**

Table 4: Shows the effect of vinpocetine on biochemical parameters. Data is represented as mean±SD. One-way ANOVA was used for statistical analysis; *** p<0.001, ** p<0.01, *p<0.05.

Groups	SOD (U/ml)	CAT(nmol/min/mg)	GSH(µg/ml)	MDA(nmol/mg)
control	2.25 ±0.02	7.32± 0.09	13.8 ±0.5	1.87 ±0.34
R	1.65 ±0.1 **	2.25± 0.9 *	6.4 ±0.3 ***	4.43± 0.35**
RV	2.0 ±0.5 *	6.9 ±0.63 ***	10.9 ±0.67 *	3.5± 0.7*
RF	1.91 ±0.03*	3.14± 0.31**	7.86± 0.87 *	4.67± 0.22

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