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Assessment of Antidepressant Activity of Phosphodiesterase-4 Inhibitor Drotaverine in Swiss Albino Mice

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Abstract

Depression is a mental health disorder characterized by profound feelings of sadness and a sense of hopelessness. It is a life-threatening disorder and approximately 20% of world's population is affected by depression. Drotaverine is used as an anti-spasmodic drug. It is structurally like Papaverine. It selectively inhibits the phosphodiesterase-4 (PDE-4) enzyme.

The antispasmodic medication drotaverine was utilized as a test drug in this investigation, and its effects as an antidepressant were examined. Compared to the standard drug imipramine used for depression therapy, it has fewer negative effects. For a variety of behavioral (in vivo) and non-behavioral (in vitro) investigations, we have employed Swiss Albino mice. The Forced Swim Test, Tail Suspension Test, and Elevated Plus Maze Model Test are three behavioral models that were applied to estimate the antidepressant influence of drugs. The non-behavioral techniques of MAO-A and MAO-B inhibition were employed to assess the antidepressant action of medications. We have also conducted an antioxidant investigation using the Nitric Oxide Scavenging Assay and Glutathione (GSH) estimate. Additionally, histopathological investigations and protein measurements were carried out. The outcomes were noteworthy and excellent.

The test drug has shown considerable efficacy and promise as an antidepressant agent in the Tail Suspension Test (TST) (*$p<0.05$), Elevated Plus Maze Model Test (EPM) (*$p<0.05$), as well as Forced Swim Test (FST) (*$p<0.01$). The results were compared to the reference drug. The test medication had little to no effect on MAO inhibition, in accordance with assessment of MAO-A alongwith MAO-B. Nitric oxide (*$p<0.05$), glutathione (GSH) estimation (****$p<0.0001$), and total protein estimation (****$p<0.0001$) all showed considerable scavenging effects. The histopathological results provided a quick overview of the effects of both experimental and prescription medications, as well as the alterations to the cerebellar granular neurons, Purkinje cells, and cerebrum cell bodies. This points to the drug's protective function in the brain.

Keywords: Antidepressants; Drotaverine; PDE-4; Depression; Neurological; Anxiety; Neuropsychiatric disorders.

1. Introduction

Feelings of extreme hopelessness and despair are hallmarks of the mental illness known as depression [1]. It is a serious mental illness that has the potential to be fatal and a global public health emergency. Depression is considered a significant risk factor for various conditions, such as metabolic, CV and neuropsychiatric disorders. It is also linked to disability, a lower quality of

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life, and higher health-related expenses. Major Depressive Disorder is the term commonly used to describe it. The patient exhibits a generalized depressed mood with low self-esteem. The patient may also lose interest in everyday social activities and life, as well as experience fatigue, remorse, a sense of worthlessness, difficulty concentrating, and suicidal thoughts [2].

The traditional medications used to treat depression either work on serotonin (5HT) or noradrenaline (Noradrenaline). Numerous severe adverse effects, including nausea, weight gain, decreased libido, exhaustion, difficulty sleeping, dry mouth, impaired vision, constipation, dizziness, and anxiety, are associated with them.

Drotaverine acts by inhibiting the phosphodiesterases (PDEs) by hydrolysing cAMP, and increase the concentration of cAMP thus, a decrease of Ca^{++} uptake of the cells and changes the allocation of calcium amidst the cells can be seen. Drotaverine also has some minor allosteric calcium channel blocking properties. The anti-spasmodic medication of drotaverine shares structural similarities with papaverine. It doesn't inhibit cholinergic function. Dry mouth, headache, nausea, and vomiting are less frequent side effects.

The intracellular non-receptor enzyme phosphodiesterase-4 (PDE4), which is mostly present in immune cells, cells of epithelial tissue, and neurons, controls inflammation and preserves the integrity of epithelium. By raising cAMP (cyclic adenosine monophosphate) levels, which in turn alter a variety of genes and proteins, inhibiting PDE4 is anticipated to have a number of consequences. PDE4 has been identified as a viable therapeutic target for the treatment of severe neurological, dermatological, and pulmonary disorders. [3]

As a PDE-4 inhibitor, this medication functions differently from conventional treatments that work on noradrenaline and serotonin. This allows us to investigate a new class of drugs with fewer side effects.

2. Materials and Methods

2.1. Chemicals and Equipments

Concerning this investigation, a variety of substances, medications, equipment, and biochemical reagents were used. The standard medication Imipramine was utilized as Imipramine Hydrochloride (CAS No.: 113-52-0) by Central Drug House (CDH), while the test drug Drotaverine was obtained from the market (Drotaverine HCl injection, DROTIN® Walter Bushnell Pvt. Ltd.).

2.2. Experimental Animals

The Central Drug Research Institute (CDRI) in Lucknow provided healthy male Swiss albino mice (25–30g, 10–12 weeks old). Following CPCSEA standards, the mice acclimated for a week in polypropylene cages with regulated conditions: 23±2ºC, 55±5% humidity, and a 12-hour light/dark cycle. They were housed in groups of four, with husk bedding, and had admittance to commercial food and water ad libitum. Food was restricted one hour before and during behavioral studies. Procedures were approved by CPCSEA or the IAEC at the Institute of Pharmacy; Approval Number (AUUP/AIP/M.Pharm/009/2018).

2.3. Experimental Design

After testing, mice were grouped in four and housed in cages. The control group and negative control group acquired 0.25 ml of vehicle (water for injection, i.p.), with the negative control group having disease induction but no treatment. The test drug group received drotaverine HCl (10 mg/kg bw, i.p.) [4], and the standard drug group received imipramine HCl (10 mg/kg bw, i.p.).

2.4. Methods

2.4.1. Locomotor Activity

Each mouse was tested one at a time. The interruption of a light beam by the mouse, detected by photocells, recorded its movement horizontally for about five minutes [5].

2.4.1.1. Experimental Design for Forced Swim Test (FST)

Following the acclimatization phase, the negative control group received an intraperitoneal injection of 0.25 ml water for injection every day for 14 days. For a duration of 14 days, imipramine HCl (10 mg/kg bw, i.p.) dissolved in WFI was given to the standard group. Drotaverine HCl (10 mg/kg bw, i.p.) dissolved in WFI was given to the test group for a duration of 14 days. FST took place on the fourteenth day.

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2.4.1.2. Experimental Design for Tail Suspension Test (TST)

Post-acclimatization, the control group received 0.25 ml WFI daily for 14 days. The standard and test groups received 10 mg/kg imipramine HCl and drotaverine HCl, respectively, in WFI for 14 days.

2.4.1.3. Experimental Design for Elevated Plus Maze Model Test (EPM)

Following a 15-day wash-off, animals were treated for 14 days with 0.25% WFI (negative control), imipramine HCl (10 mg/kg bw, standard), or drotaverine HCl (10 mg/kg bw, test) intraperitoneally. EPM Test trials occurred on Days 15 and 16, with the test conducted on Day 17.

2.4.2. Behavioural Model Study (in-vivo study)

The behavioural model study (*in-vivo* study) was done with the help of FST, TST and EPM Model Test.

2.4.2.1. Forced Swim Test in Mice

The FST used clear cylindrical jar (20 cm in diameter, 30 cm in height) brimmed with water at 25° ± 1 ℃. Mice were habituated for 15 minutes the day before the test and acclimatized to the test environment for 30 minutes on the test day [6]. Each mouse underwent a 6-minute swim session, during which immobility time, defined as floating passively, was recorded [7]. After testing, mice were dried in a heated enclosure at 32ºC for 15 minutes, and the water was changed between tests to prevent behavioral changes. Initially, mice showed vigorous movement for the first 2 minutes [8].

2.4.2.2. Tail Suspension Test in Mice

An elevated laboratory slab, 60 cm above the floor, was used for the TST. Each rodent was raised 50 cm above the ground using adhesive tape attached near the tip of its tail. The mice acclimated to the test setting for 30 minutes before testing on day 14 [9]. During the six-minute test, immobility time, defined as hanging motionlessly, was recorded with a stopwatch. Antidepressant activity was assessed by comparing the reduction in immobility duration across the test, standard, and negative control groups [10].

2.4.2.3. Elevated Plus Maze Model Test

Subsequent to 14th day, mice were timed moving from an open to a closed arm in a maze over the next two days (15th and 16th). If a mouse took over 90 seconds, it was prodded, then given two minutes to explore. After a 30-minute acclimation, the test was repeated for 90 seconds on the 17th day. Reported times were compared for analysis [11].

2.4.3. Non-Behavioural Model Study (in-vitro study)

The non-behavioral in-vitro study involved preparing brain tissue homogenate to estimate MAO-A, MAO-B, antioxidant activity (including nitric oxide scavenging), and glutathione (GSH) and protein levels. The study concluded with a histopathological investigation of the brain tissue.

2.4.3.1. MAO-A and MAO-B Estimation

Ketamine (80 mg/kg, i.p.) was used as an anesthetic for the mice and atropine (0.02 mg/kg, s.c.) after the Forced Swim Test. Brain tissue was homogenized in cold SET buffer, cleaned, and centrifuged twice at 800 rpm to remove debris. The supernatant was subjected to centrifugation at 12,000 rpm, and mitochondrial precipitate was washed and subjected to final centrifugation at 15,000 rpm. Protein content was measured using the Lowry method with bovine serum albumin as the standard [12].

Procedure for MAO-A

MAO-A activity was assessed by mixing 5-hydroxytryptamine (4 mM) with sodium phosphate buffer (0.03 M, pH 7.0) and injecting a mitochondrial fraction to initiate the reaction. Absorbance changes at 280 nm were monitored using a SHIMADZU UV-visible spectrophotometer, with blank readings obtained from the mixture of 5-hydroxytryptamine and buffer only.

Procedure for MAO-B

To measure activity of MAO-B, 2.75 ml of sodium phosphate buffer (0.03 M, pH 7.0) along with 100 µl benzylamine (0.1 N) were entwined. The reaction started with 150 µl of mitochondrial fraction, and absorbance

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changes at 249.5 nm were tracked using a SHIMADZU double beam UV-visible spectrophotometer. Blank readings used benzylamine and buffer, with each measurement repeated three times.

2.4.3.2. Antioxidants Activity

The antioxidant activity was done by scavenging of Nitric Oxide with the help sodium nitroprusside and Griess reagent.

2.4.3.3. Nitric Oxide Scavenging Assay

Sodium Nitroprusside (10 mM) was intermingled with distinct amounts of mice brain homogenate in ethanol with incubation to 180 minutes. After adding Griess reagent, NO production was detected via a diazotization reaction, yielding a chromophoric azo product measurable at 546 nm. Butylated Hydroxy Toluene (BHT) was used as a control, and absorbance at 546 nm was measured with a UV spectrophotometer [13-14].

2.4.3.4. Estimation of Glutathione (GSH)

For GSH estimation, 500 µl of brain homogenate mixed with 10% TCA was whirled at 2000 rpm (10 minutes) with the cold setting of 4°C. The supernatant was combined with DTNB (50 µl, 0.2% in buffer), sodium phosphate buffer (2 ml, pH 8.4), and water (950 µl), vortexed, and absorbance at 412 nm was measured. GSH concentration was calculated using a standard curve [15].

2.4.3.5. Estimation of Total Protein

Following the addition of 400 µl of Lowry reagent, 1700 µl of distilled water, and 300 µl brain tissue homogenate, the mixture was permitted for incubation at room temperature for 20 minutes.

Subsequent to adding Folin & Ciocalteu's Phenol Reagent, the mixture was given a further 30 minutes to incubate. Using a UV spectrophotometer, absorbance measurements were made at 760 nm to determine the protein amount [16].

2.5. Histopathological Investigations

In a beaker, 10 ml of a solution of formaldehyde (FISCHER SCIENTIFIC) was added, and the amount was increased to 100 ml using distilled water to create formalin (10%). Subsequently, the brain of the mice was removed and allowed to set in 10% formalin.

2.6. Statistical Analysis

Using a one-way ANOVA, the mean value as well as standard error for the mean (S.E.M.) among the results were calculated, and then the post-hoc tests for Dunnett and Tukey were applied. Graph Pad Prism Ver. 8.0.2 software was used to calculate all of the statistical data.

3. Results and Discussion

3.1. Behavioural Study Results

*3.1.1. Antidepressant effects of Drotaverine on immobility period of Swiss Albino Mice in Forced Swim Test (FST) (**Figure 1**)*

Values are represented in terms of Mean ± S.E.M.; n = 5 one-way ANOVA with Dunnett's post-hoc test in between. [**(p<0.01) in contrast with negative control group].

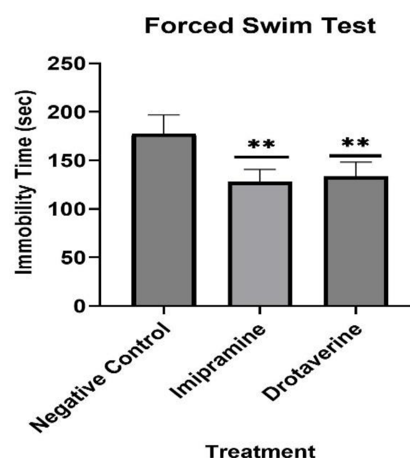

Figure 1: Effect of drotaverine and imipramine on immobility period of mice in forced swim test.

Each value is represented as Mean ± S.E.M.; n = 5, **(p<0.01) in contrast with negative control group. (one- way ANOVA followed with Dunnett's post-hoc test)

*3.1.2. Antidepressant effects of Drotaverine on Immobility Period of Swiss Albino Mice in The Tail Suspension Test (TST) (**Figure 2**)*

After a one-way ANOVA and Dunnett's post-hoc test, all values are shown as Mean ± S.E.M. for n = 5. [*(p<0.05), **(p<0.01) in contrast to group under negative control].

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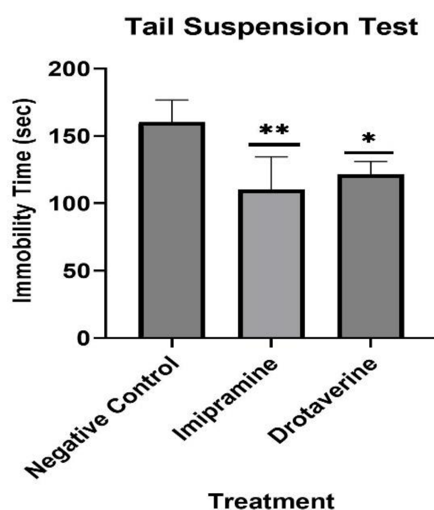

Figure 2: Effect of drotaverine and imipramine on immobility period of mice in tail suspension test.
Each values are shown as Mean ± S.E.M. for n = 5. **(p<0.01), *(p<0.05), in comparison with negative control group (After a one-way ANOVA followed by Dunnett's post-hoc test).

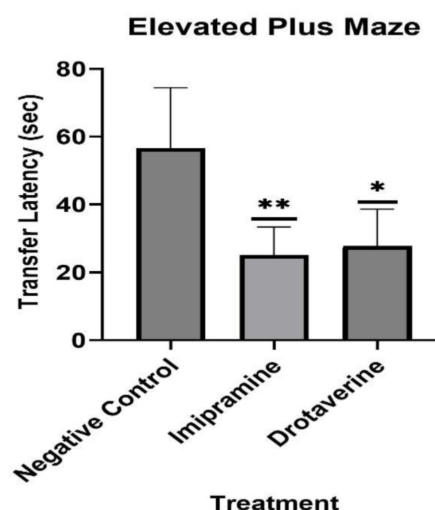

Figure 3: Effect of drotaverine and imipramine on transfer latency (TL) of mice in elevated plus maze (EPM) model test.
Each value is shown as Mean ± S.E.M. for n = 5. **(p<0.01), *(p<0.05) in comparison with negative control group (After a one-way ANOVA followed by Dunnett's post-hoc test).

*3.1.3. Antidepressant effects of Drotaverine on Transfer Latency (TL) of Swiss Albino Mice Using Elevated Plus Maze (EPM) Model Test (**Figure 3**)*

After a one-way ANOVA and Dunnett's post-hoc test, all values are shown as Mean ± S.E.M. for n = 5. [*(p<0.05), **(p<0.01) in parity with the group under negative control].

3.1.4. Effect of Drotaverine on Brain MAO-A & MAO-B Activity of Swiss Albino Mice

Table 1 Effect of drotaverine and imipramine on MAO-A & MAO-B estim–ation of mice brain

3.1.5. Antidepressant Effect of Drotaverine on Nitric Oxide (NO), Reduced Glutathione (GSH) & Total Protein in Swiss Albino Mice

Table 2: Effect of drotaverine and imipramine on Nitric oxide (NO), GSH & total protein estimation of mice.

Table 1: Effect of drotaverine and imipramine on MAO-A & MAO-B estimation of mice brain.

Sr. No.	Groups	Treatment	MAO-A Mean ± S.E.M (µmol/mg Protein)	MAO-B Mean ± S.E.M (µmol/mg Protein)
1	Normal Control	Vehicle (water for injection, 0.25ml, i.p.)	46.266 ±4.454	39.704 ±2.585
2	Negative Control	Vehicle (water for injection, 0.25ml, i.p.)	79.862 ±4.047####	52.102 ±4.442###
3	Test Drug	Drotaverine HCl in Vehicle (10 mg/kg bw, i.p.)	73.918 ±3.776****	50.016 ±1.288***
4	Standard Drug	Imipramine HCl in Vehicle (10 mg/kg bw, i.p.)–	76.594 ±3.770****	51.140 ±2.821***

Each value is represented as Mean ± S.E.M.; n = 5, ####p<0.0001 when compared with normal control group, **** (p<0.0001) when compared with negative control group, ###p<0.001 when compared with normal control group, *** (p<0.001) when compared with negative control group (one-way ANOVA followed with Tukey's post-hoc test)

Table 2: Effect of drotaverine and imipramine on Nitric oxide (NO), GSH & total protein estimation of mice.

Sr. No.	Groups	Treatment	NO (µg/ml)	GSH (µmol/mg Protein)	Total Protein (µg/ml)
1	Normal Control	Vehicle (water for injection, 0.25ml, i.p.)	1806.95 ±454.17	10.880 ±0.880	1448.232 ±23.282
2	Negative Control	Vehicle (water for injection, 0.25ml, i.p.)	1099.82 ±324.08#	4.486 ±0.520###	2092.552 ±53.634##
3	Test Drug	Drotaverine HCl in Vehicle (10mg/kg bw, i.p.)	1917.83 ±383.36**	15.394 ±2.057***	992.704 ±279.965***
4	Standard Drug	Imipramine HCl in Vehicle (10mg/kg bw, i.p.)	2130.74 ±319.70**	20.906 ±1.394***	1182.364 ±105.952***

Each value is represented as Mean ± S.E.M.; n = 5, #p<0.05 when compared with normal control group, ** (p<0.01) when compared with negative control group, ###p<0.0001 when compared with normal control group, *** (p<0.0001) when compared with negative control group, ##p<0.001 when compared with normal control group (one-way ANOVA followed with Tukey's post-hoc test)

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3.1.6. Histopathological Investigation

(**Figure 4**) Histopathological Investigation results of the mouse brain (Cerebrum).
Normal Control: Normal cell bodies, Negative Control: Cell bodies were degenerated (arrow), Standard: Majority of neurons were protected. Arrow indicates degenerated neurons. Test Group: Cell bodies were bodies. (H. & E. X 400)

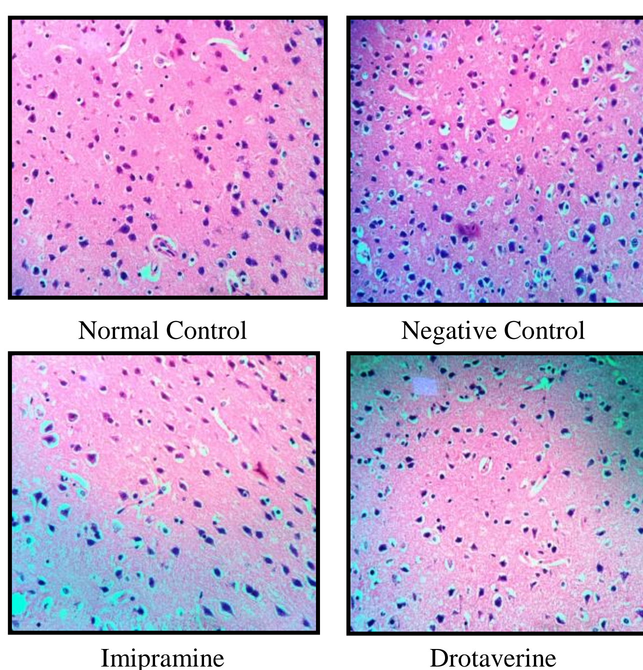

Figure 4. Histopathological Investigation results of the mouse brain (Cerebrum).
Normal Control: Normal cell bodies, Negative Control: Cell bodies were degenerated (arrow), Standard: Majority of neurons were protected. The arrow indicates degenerated neurons. Test Group: Cell bodies were bodies. (H. & E. X 400)

(**Figure 5**) Histopathological Investigation results of mice brain (Cerebellum).

Normal Control: Normal Purkinje cells and granular neurons, Negative Control: Majority of Purkinje cells were degenerated (arrow). Granular neurons were also degenerated, Standard: Majority of Purkinje cells were protected (arrow). Granular neurons were also protected (arrowhead), Test Group: Purkinje cell as well as granular neurons were protected (arrow). (H. & E. X 400).

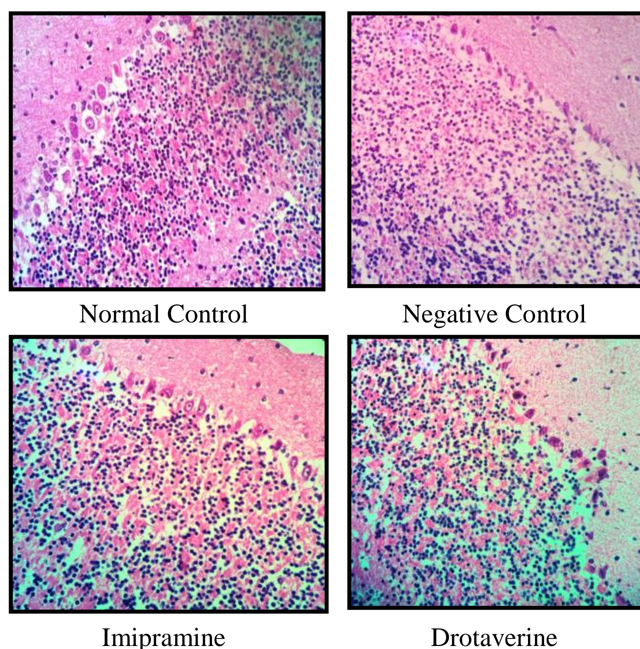

Figure 5. Histopathological Investigation results of the mouse brain (Cerebellum).
Normal Control: Normal Purkinje cells and granular neurons, Negative Control: Majority of Purkinje cells were degenerated (arrow). Granular neurons were also degenerated, Standard: Majority of Purkinje cells were protected (arrow). Granular neurons were also protected (arrowhead), Test Group: Purkinje cell as well as granular neurons were protected (arrow). (H. & E. X 400)

3.2. Discussion

Drotaverine, an anti-spasmodic drug structurally related to Papaverine, works by inhibiting phosphodiesterase that hydrolyze cAMP, increasing cAMP concentration and consequently decreasing calcium uptake by cells. Its method of action is centered on this change in the distribution of calcium within cells. Drotaverine's potential as an antidepressant was investigated in this study using a range of behavioral and biochemical investigations.

Rodents' behavioral despair was analyzed using the FST, where immobility is indicative of an acute depressive episode. According to the findings, Drotaverine and the standard medication both considerably decreased the immobility of the mice, suggesting possible antidepressant effects [16]. In the same direction, the usual medication and Drotaverine both markedly shortened the duration of immobilization in the Tail Suspension Test (TST), which evaluates behavioral despair by measuring the immobility that mice exhibit during inevitable stress [17]. This finding raises the possibility that Drotaverine's antidepressant

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potential is on par with that of the prescribed medication. Drotaverine's antidepressant efficacy was further supported by the discovery that both medications shortened the Transfer Latency period in mice on the Elevated Plus Maze Model Test, which is used to evaluate learning and memory impairment [18].

Abnormal enzyme activity that results in dysfunctional monoaminergic neurotransmission in CNS is frequently linked to depression pathophysiology. But neither conventional medication nor drotaverine enormously suppressed MAO-A or MAO-B enzymes in the trial, suggesting that MAO inhibition is not a factor in the antidepressant effects of these drugs. This implies that the mechanism of action of drotaverine may be different from that of conventional MAO-inhibiting antidepressants.

Sodium nitroprusside (SNP) was converted to nitric oxide (NO), which was then quantified with the Griess reagent [18]. Diseased animals in this study had reduced scavenging activity for nitric oxide. Attributable to regular NO concentration in lack of disease, the control group showed somewhat increased scavenging in contrast. Both the test and the standard groups showed substantial scavenging of nitric oxide.

In addition to neutralizing free radicals, GSH, a crucial intracellular antioxidant that is highly abundant in the brain, keeps additional antioxidants notably vitamin C as well as vitamin E in their active states [19]. GSH levels were lower in diseased animals than in control groups, but GSH depletion was avoided in standard and test groups. Due to its protective nature, GSH levels decrease with illness and increase with intervention.

Bovine serum albumin was used as the standard to assess the amount of protein in brain tissue homogenates. [20] The protein content of both the standard and the test groups was much lower than that of diseased animals. Following treatment, there was a drop in the levels of the main proteins' albumin and globulin in the test group animals unlike to negative control group.

Additional validation of results came from brain histopathological examinations. The bulk of neurons within the cerebrum as well as cerebellum, including granular neurons and Purkinje cells, were protected in the group administered the conventional medication. In the cerebellum, the Drotaverine-treated group also showed preservation of granular neurons, Purkinje cells, and cerebrum cell bodies.

To sum up, the research offers strong proof that Drotaverine has strong antidepressant potential, on par with the conventional medication employed in the investigation. Though it does not block MAO enzymes, it significantly lowers immobility in behavioral tests, avoids GSH depletion, reduces total protein content, demonstrated good Nitric Oxide Scavenging and protects brain neurons [19-20]. These results demonstrate the potential of drotaverine as a powerful antidepressant.

Imipramine being a tricyclic antidepressant (TCA) acts on norepinephrine and increases its level. On the other hand, Drotaverine also acts on norepinephrine. The monoamine oxidase enzyme also acts on norepinephrine and reduces its level in case of Depression. The drug is a PDE-4 inhibitor, giving a new class of drugs for future treatment of Depressive syndromes. The drug can be used as an antidepressant medication under supervision. The drug Drotaverine decreased severity of depression, but it cannot inhibit the levels of MAO-A and MAO-B, significantly concluding that it has no MAO inhibitory action. It only acts on NE and can be used for antidepressant therapy.

4. Conclusion:

Depression can be treated with drotaverine because of its potent antidepressant properties. It has the ability to inhibit phosphodiesterase 4 (PDE-4) and so prevent the brain from losing its supply of norepinephrine (NE), which is related to depression brought on by a drop in monoamine levels (NE, serotonin, and dopamine). With fewer adverse effects, drotaverine exhibits efficacy comparable to that of conventional antidepressants. Despite being in a distinct class of medication, this trial effectively illustrated its potential for use as an antidepressant.

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Conflict of Interest:

We report no conflict of interest.

Authors Contributions

Vivek Srivastava: conceptualization, formal analysis, methodology, validation, writing–review and editing. **Prabhat Kumar Yadav**: data curation, formal analysis, manuscript writing. **Rudrakshri Kaushik**: visualization,

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writing–original draft, writing–review and editing. **Kapil Goel**: visualization, writing–review and editing.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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