View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Journal of Drug Delivery and Therapeutics (JDDT)

Available online on 15.04.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited

Research Article

Evaluation of Antioxidant and Anti Parkinsonism Activity of Betaine in Experimental Rats

Milind V. Masule[1], Sachin D. Shinde[2], Sujata S. Kurkute[3], Balu U. Salve[1]*

[1] Department of Pharmacology, Sinhgad Technical Education Society's, Sinhgad Institute of Pharmacy, Narhe, Pune-411041, Maharashtra, India

[2] Department of Pharmacology, Shri. R. D. Bhakt College of Pharmacy, Jalna Maharashtra, India-431203

[3] Department of Pharmacology, Dr. D. Y. Patil Institute of Pharmaceutical sciences and research, Pimpri, Pune-411018, Maharashtra, India

ABSTRACT

Aim and Objectives: The present study was aimed to evaluate anti parkinsonium effect of Betaine for its Applications in trigger factors in pathogenesis of Parkinson's disease and to understand development of new treatments approaches for PD. Betaine is naturally obtained product. It has antioxidant, neuroprotective activity. Hence, we inspected whether betaine can act as a protective agent in 6-OHDA induced oxidative stress on cerebellum of Sprague-Dawleyrats.
Material and Methods Thirty-six adult Sprague-Dawley rats were dived into six groups. Rats were received unilateral 6-hydroxydopamine lesions for induction except normal and rats were treated with respective treatment. At the day of 21 rats were sacrificed. Prepared brain homogenate was used for further Biochemical estimation.
Result: Betaine showed marked rise in SOD and Catalase activity as well as GSH content subsequently decreasing in the lipid peroxidation process. Our result suggests Betaine to be potent antioxidant at dose 12.5 and 25 mg/kg as compared to standard (L-dopa+Benserazide) and pro-inflammatory cytokines viz: TNF-α, IL-1β and IL-6 were significantly reversed by Betaine as compared to that of standard group (L-dopa+ Benserazide).
Discussion and Conclusion: Betaine showed dose dependent effect by reducing LPO level as increasing SOD, GSH and Catalase activity and marked reduced proinflammatory cytokine, hence we conclude that betaine has good anti parkinsonism activity.

Keywords: 6-OHDA, Antioxidant, Betaine, Pro-inflammatory cytokines.

Article Info: Received 28 Feb 2019; Review Completed 07 April 2019; Accepted 11 April 2019; Available online 15 April 2019

Cite this article as:

Masule MV, Shinde SD, Kurkute SS, Salve BU, Evaluation of Antioxidant and Anti Parkinsonism Activity of Betaine in Experimental Rats, Journal of Drug Delivery and Therapeutics. 2019; 9(2-s):417-421

http://dx.doi.org/10.22270/jddt.v9i2-s.2717

***Address for Correspondence:**

Prof. Balu U. Salve, Department of Pharmacology, Sinhgad Technical Education Society's, Sinhgad Institute of Pharmacy, Narhe, Pune-411041, Maharashtra, India.

INTRODUCTION

Parkinsonism (PD) is slowly progressive neurodegenerative disease caused due to die of brain cell that control body movements. It is described by James Parkinson in 1817. It is mainly characterised clinically by bradykinesia, tremor, rigidity and postural instability[1]. Prevalence of PD increase with age near about 1% people with above 60 age affected by parkinsonism[2]. In pathophysiology of PD increase in cytokine level as increases the oxidative stress as well as change in behavioural changes occurs[3]. 6-Hydroxydopamine (6-OHDA)-induced neurodegeneration is a well known experimental model for PD. It is selectively taken up by the dopamine transporters of dopaminergic neurons, and it induces retrograde neurodegeneration. Thus, 6-OHDA injections into the striatum or medial forebrain bundle induce nigral degeneration that then results in characteristic behavior abnormalities with change biochemical parameters in experimental animals[4,5].

Betaine is found in plants, animals and microorganisms and is a significant component of many foods, including wheat, shellfish, spinach, and sugar beets[6]. It is a zwitter ionic quaternary ammonium compound that is also known as trimethylglycine, glycine betaine, lycine, and oxyneurine. It has physiologic function either as an organic osmolyte to protect cells under stress. The principle role of Betaine is to protect cells against osmotic inactivation in plants and microorganisms. Betaine synthesis is triggered due to exposure to drought, high salinity, or temperature stress, which results in its accumulation in the cells. It increases the water retention of cells, replaces inorganic salts, and protects intracellular enzymes against temperature-induced or osmotically induced inactivation as it is a compatible osmolyte[7]. It has been reported as Betaine is for the number of several conditions of disease

involving brain, heart and kidney. It also has potential as a neuroprotective agent for prevention of LD induced oxidative damage in brain tissue of rats. It has been demonstrated that Betaine may have a potential as a neuroprotective agent for prevention of LD induced oxidative damage in cerebellum and Benserazide mediated hyperhomocysteinemia in rats[8]. It prevents ethanol-induced oxidative stress and reduces total homocysteine in the rat cerebellum[7]. In suggesting Betaine may have a therapeutic neuroprotective effect of PD. It is also has been used in the treatment of elevated homocysteine[10].

MATERIAL AND METHODS

Animals and groups

Sprague-Dawley male rats with 200-250 gm were used for this study. Animal were procured from National Institue of Bioscience (CPCSEA reg. no. 1139/a/07/CPCSEA) and housed at the Institute Animal House at standard laboratory conditions with a temperature of 25±1°C, relative humidity of 50–65% and 12:12 h dark and light cycle. Animals had free access to food (Standard chaw pellets, Nutrivet life sciences, Pune) and water with *ad libitum*. The experimental protocol (Protocol approval no. SIOP/IAEC/2017/02/03) was approved by the Institutional Animal Ethics Committee (IAEC) constituted in accordance with the rules and guidelines of the Committee for the Purpose of Control and Supervision on Experimental Animals, India (CPCSEA).

Chemicals and Drugs

Betaine, Apomorphine hydrochloride hemihydrates, Desipramine HCL, 6-Hydroxydopamine Hydrochloride, Benserazide Sigma Aldrich), Ketamine (Themis Medicare), Xyalazine (Indian Immunological LTD. Telangana.), L-Dopa, Dopamine (Aqua Fine Injecta PVT. LTD. Pune), Haloperidol (RPG Lifescience).

Experimental Protocol

Two weeks after surgery, rats were randomly divided into six groups based on the number of contralateral rotations

Group 1: Normal- received vehicle for 21 days

Group 2: Control- Rats received unilateral 6-hydroxydopamine

Group 3: Standard - received 6- hydroxydopamine + L-Dopa 10mg/kg along with Benserazide 2.5 mg/kg orally

Group 4 to 6: Test-I, II and III- received 6-hydroxydopamine + 12.5mg/kg, 25 mg/kg, 50 mg/kg betaine orally for 21 days.

6-Hydroxydopamine (6-OHDA) lesioning

Rats received unilateral 6- hydroxydopamine lesions medial forebrain bundle to destroy DA neurons. Desipramine HCL (25mg/kg, i.p.) was given prior to the 6-OHDA injection to protect norepinephrine (NE) neurons. Rats were anesthetized with Ketamine (80 mg/kg, i.p.) and then placed in a stereotaxic apparatus (Inco Ambala, India). The coordinates for 6-OHDA injections were AP: -2.5mm, ML: + 2.0 mm, DV: -9 mm relative to bregma with the incisor bar positioned 3.3 mm below the interaural line. Using a 10µl Hamilton syringe attached to a 26 gauge needle, 6-OHDA (12 µg) dissolved in 0.9% NaCl + 0.1% ascorbic acid was infused through a small blur hole in the skull at a rate of 2 µl/min for a total volume of 4 µl. The needle was withdrawn 1 m later. Two weeks after the surgery rats were challenged with apomorphine hydrochloride (0.2 mg/kg, s.c.) and contralateral rotation was monitored. Animals showing fewer than 20 rotations per 5 min were excluded from further studies[10-12].

Behavioural Parameter

Grid test

Gridiron of 30 cm wide and 35 cm high with a space of 1.2 cm between each wire was used. Each rat was hung by all four paws on the vertical grid and stopwatch was started as the rat was held on the grid. A stopwatch was stopped and time taken by the rats was noted as descent latency. The maximum cut of time was 180 seconds [13].

Catalepsy Bar test

A rat was placed with both forepaws on a bar, which was 10 cm above the surface in half rearing position (Catalepsy Bar Test, VJ Instruments India). The maximum cut of time for 180 seconds[14].

Locomotor Activity

Spontaneous locomotor activity was assessed in the Actophotoactometer. Rats were placed in Digital Photoactometer the center allowed to freely explore it for 5 min. Evaluate the total no. of counts as an indicator of spontaneous locomotor activity[15].

Evaluation of the oxidative stress

Estimation of Reduced Glutathione

GSH was estimated by the method with add 0.1 ml supernatant into 0.9 ml of 0.001 mol/l 5, 5'-dithiobis-2-nitrobenzoic acid (in 0.1 mol/l phosphate buffer, pH 8.0). The yellow color that developed was read immediately at 412 nm (endpoint) using PowerWave™ XS Microplate Spectrophotometer. GSH (Sigma Chemicals, USA) was used as the standard. The amount was expressed as mg of GSH /g of wet tissue[16].

Estimation of lipid peroxidation

Lipid peroxidation in the brain was determined by measuring MDA content using the method reported by0.5 ml homogenate added into the mixture of 3ml of 1% w/v Phosphoric acid and 1ml of 0.6% w/v Thiobarbituric acid. Heat for 45 min (boiling water bath 85°C), cool immediately in ice bath. Add 4ml n-butanol and vortex and centrifuge at 5000 rpm for 10 min. Take the absorbance of organic layer at 535 nm (endpoint method) using PowerWave™ XS microplate spectrophotometer. 1, 1, 3, 3-tetraethoxypropane (Sigma Chemicals, USA) was used as the standard MDA and levels were expressed as µg/g tissue[17].

Estimation of catalase

Catalase activity was estimated with the supernatant (0.5 mL) was added to a quartz cuvette containing 2.mL 10 mM H_2O_2 prepared in potassium phosphate buffer (50 mM, pH 7.0). The change in absorbance was monitored at 240 nm from 00 sec. to 210 sec. using a Shimadzu spectrophotometer (UV-1201, Japan). Catalase levels were expressed as U/mg protein[16].

Estimation of superoxide dismutase

SOD activity was determined with slight modifications. To 150 µl of tissue supernatant, 2.85 ml of 0.1 M phosphate buffer (pH 8.4) and 50 µl of 7.5mM pyrogallol were added and absorbance was measured at 420 nm for 3 min at 30 s intervals. Enzyme levels were expressed as U/mg protein[17].

Evaluation of Pro-inflammatory cytokines.

Proinflammatory cytokine were determined in brain tissue homogenate. Cytokines like Tumor Necrosis Factor- alpha (TNF-α), Interleukin-1-beta (IL-1β), Interleukin-6 (IL-6) was estimated by sandwich ELISA by using commercially available ELISA kits[18].

Statistical analysis

Data was analysed by One way ANOVA followed by Bonferroni multiple comparison test. Data were expressed as mean ± SEM

RESULTS

Effect of Betaine (12.5, 25 and 50 mg/kg., p.o.) on Locomotors Activity.

Decreased locomotion count was observed in control group ($^{a}p<0.001$) as compared to the normal. Whereas significant increase in locomotion count was observed from day 7 onwards in Test-II groups as compared to control group ($^{d}p<0.001$) as shown in table 1.

Table 1: Effect of Betaine (12.5, 25 and 50 mg/kg., p.o.) on Locomotor Activity

Groups	Day 0	Day 7	Day 14	Day 21
Normal	764 ±2.057	749.5±1.84	709.5±21.07	780.33±1.98
Control	710.5±2.09^{a}	405.83 ±0.68^{a}	385.8±0.76^{a}	206.83±0.73^{a}
Standard	759.5±1.92^{c}	566±0.87^{d}	649.33±3.97^{d}	777.67±2.026^{d}
Test-I	750.83±1.82^{b}	379.67±0.85^{ns}	362.5±0.78^{ns}	180.167±0.37^{ns}
Test-II	754.5±1.83^{b}	555.16±0.72^{d}	630.67±4.06^{d}	758.33±2.30^{d}
Test-III	740.5± 1.80^{ns}	369.3±0.98^{ns}	349.83±0.67^{ns}	169.667±0.46^{ns}

Effect of Betaine (12.5, 25 and 50 mg/kg., p.o.) on the cataleptic score.

The graph shows significant increase in cataleptic score in 6-OHDA treated animals in control ($^{a}p<0.001$) group as compare to normal group. Whereas significant decrease in cataleptic score was observed in test test-I, test-II and test-III group on day 0 and 7 ($^{d}p<0.001$), as compare to control group as shown in table 2.

Table 2: Effect of Betaine (12.5, 25 and 50 mg/kg., p.o.) on the cataleptic score

Groups	Day 0	Day 7	Day 14	Day 21
Normal	2.83±0.19	3.83±0.34	3.33±0.29	2.83±0.28
Control	26.17±0.48^{a}	27.33±0.51^{a}	28.5±0.65 ^{a}	30±0.83^{a}
Standard	12.83±0.56^{d}	19.33±0.40^{d}	22.83±0.54^{c}	26.67±0.46^{ns}
Test-I	13.83±0.51^{d}	17.17±0.45^{d}	22.5±0.30^{c}	25.17±0.71^{b}
Test-II	17.17±0.51^{d}	21.5±0.44^{c}	24.17±0.58^{ns}	27±0.65^{ns}
Test-III	17.83±0.46^{d}	19±0.27^{d}	25.17±0.59^{ns}	29.5±0.78^{ns}

Effect of Betaine (12.5, 25 and 50 mg/kg., p.o.) on decent latency.

The graph shows effect of Betaine on descent latency i.e. the time taken by the rats to remove the grip from the iron grid. The 6-OHDA treatment significantly ($^{a}p<0.001$) reduced descent latency on day 0, 7, 14 and 21 as compare to normal. Whereas significantly ($^{d}p<0.001$) increase in decent latency was observed in test-I, test-II and test-III on day 0 onwards up to day 21 except test-III on day 14. As shown in table 3.

Table 3: Effect of Betaine (12.5, 25 and 50 mg/kg., p.o.) on decent latency

Groups	Day 0	Day 7	Day 14	Day 21
Normal	23.17±0.20	37.33±0.90	33.5±0.83	32.33±0.75
Control	5.83±0.19^{a}	4.33±0.20^{a}	3.83±0.12^{a}	3±0.23^{a}
Standard	21.67±0.39^{d}	27.83±0.59^{d}	31.33±0.39^{d}	28.67±0.49^{d}
Test-I	25.83±067^{d}	26.17±0.39^{d}	31.67±0.91^{d}	32.33±0.84^{d}
Test-II	16±0.3^{d}	27.67±1.02^{d}	28.83±0.51^{d}	30.17±1.04^{d}
Test-III	23.33±0.52^{d}	24±0.0.23^{d}	24.67±0.36^{d}	25.5±0.31^{d}

Effect of betaine on activities of Effect of Betaine (12.5, 25 and 50 mg/kg., p.o.) on antioxidant.

The control group shows significantly decrease in catalase activity as compare to normal ($^{a}p<0.01$). Betaine test-I, test-II and test-III counteracted the deleterious effect of 6-OHDA by increasing level of this antioxidant. SOD activity is increased by test-II, which is less significant ($^{c}p<0.01$). MDA content is significantly increased in control as compare to normal ($^{a}p<0.001$). MDA content significantly decreased by Betaine test-I, test-II and test-III ($^{d}p<0.001$). GSH content is found to be decreased in control as compare to normal ($^{a}p<0.01$) Betaine test-II increased GSH content as compared to control ($^{c}p<0.01$) as shown in table 4.

Table 4: Effect of Betaine (12.5, 25 and 50 mg/kg., p.o.) on antioxidant

Groups	Conc. of Catalase (U/mg of protein)	Conc. of SOD (U/mg of protein)	MDA (µg/mg protein)	GSH µg/mg of protein
Normal	22.03±1.39	22.79±1.077	0.08±0.0022	4.70±0.11
Control	3.151±0.16[a]	8.388±0.26[a]	0.86±0.016[a]	2.96±0.033[a]
Standard	11.09±0.27[d]	16.38±0.77[ns]	0.14±0.0076[d]	4.57±0.10[c]
Test-I	20.83 0.47[d]	14.36±0.12[ns]	0.19±0.001[d]	2.52± 0.14[ns]
Test-II	21.61± 0.54[d]	22.08±0.54[c]	0.10±0.0011[d]	4.38±0.11[c]
Test-III	20.82±0.32[d]	14.60±0.17[ns]	0.19±0.00151[d]	2.50±0.15[ns]

Effect of Betaine (12.5, 25 and 50 mg/kg., p.o.) on pro-inflammatory cytokines.

The effect of Betaine on pro-inflammatory cytokines in control groups showed a significantly ([a]$p<0.001$) increased in TNF-α, IL-1β and IL-6 level as compared to normal groups. Twenty one days of Betaine treatment in test-I, test-II and test-III is decreased significantly ([d]$p<0.001$) in TNF-α, IL-1β and IL-6 level as compared to control groups as shown in table 5.

Table 5: Effect of betaine on pro-inflammatory cytokines

Sr. No.	Groups	IL-6	IL-1β	TNF-α
1	Normal	50.61±0.23	50.56±0.21	77.40±0.74
2	Control	162.68±1.48[a]	143.62±0.64[a]	145.35±0.76[a]
3	Standard	51.54±0.07[d]	51.37±0.09[d]	86.61±0.87[d]
4	Test-I	59.21±0.63[d]	71.28±0.31[d]	97.24±2.11[d]
5	Test-II	143.78±0.71[d]	58.50±0.63[d]	121.02±0.43[d]
6	Test-III	142.80±0.54[d]	70.96±0.30[d]	119.69±0.57[d]

DISCUSSION

In present study we have evaluated aanti-parkinsonium effect of betaine in experimental rats. Parkinsonism is neurodegenerative disease associated with loss of dopaminergic neurons in substantia nigra pars compacta[19]. PD is characterized by tremor, akinesia and muscle rigidity. it has been proved that in PD there is increase in the content of TNF- α, IL-1β, IL-6 and many more in striatal dopaminergic region of Parkinson's brain. Numerous studies support that administration of 6-OHDA induces neuronal toxicity. It is a hydoxylate analogue of dopamine which uses the same transport system as dopamine and nor- epinephrine to produce specific degeneration of catecholaminergic neurons. On ICV administration, 6-OHDA causes degeneration of dopaminergic neurons with dramatic loss of DA in striatum. The toxic mechanism of this compound is dependent on its oxidation with concomitant production of ROS, para and semiquinolone products[201,21]. Brain being deficient in oxidative defence mechanism is at greater risk of cellular damage caused by free radicals. 6-OHDA undergo metabolism and forms ROS. The para and semiquinolone products formed during oxidation of 6-OHDA are capable of inducing cellular damage through reaction with nucleophile such as protein and DNA, they do not appear to be primarily responsible for toxic effects. ROS formed during its metabolism has shown to exhibit potential role in neurotoxicity[22]. This acute model has been used in the efficacy testing of many pharmacological, anti-Parkinsonism drugs. In order to understand the mechanism of action, we evaluated the effects of Betaine in 6-OHDA induced PD as evident by the grip strength, locomotion and catalepsy score (akinesia with muscle rigidity) parameters. 6-OHDA treatment showed deterioration of above mentioned behavioural parameters in rats. Betaine restored these behavioural changes significantly. Administration of Betaine showed significant improvement in grip strength, catalepsy and restored locomotor activity in rats; these effects were comparable to that of standard group (L-dopa + Benserazide). Brain homogenates of 6-OHDA treated rats were subjected to biochemical estimationin terms of levels/ activity. Analysis of post-mortem brains from PD rats confirms the high level of oxidative stress in the SNPc marked by increase iron concentrations, decreased levels of GSH and increased lipid peroxidation. Betaine has showed marked rise in SOD and Catalase activity as well as GSH content subsequently decreasing in the lipid peroxidation process. Our result suggests Betaine to be potent antioxidant at dose 12.5 and 25 mg/kg as compared to standard (L-dopa+Benserazide). Elevated inflammatory cytokines in the brain, cerebral spinal fluid (CSF) and plasma of PD patients supports the existence of functional interconnections between the immune and nervous systems[23]. Recent reports indicate that a pro-inflammatory event in the periphery can induce chronic, self-propelling neuroinflammation in the brain, and that systemic cytokines are critical for CNS effects in response to peripheral immune activation show that the entry of pro-inflammatory factors, such as TNF- α, to the brain will cause the activation of microglia to produce more inflammatory factors[24]. The factors may cause neuronal death, suggesting a clinical implication for the link between peripheral inflammation and neuroinflammation[25]. The stimulation of immune-competent cells and hyper production of cytokines are considered to play a role in the development and progression of multiple neurodegenerative diseases. Peripheral inflammation may amplify the neuro-inflammation contributing to disease pathogenesis[26]. The augmented expression of pro-inflammatory cytokines viz: TNF-α, IL-1β and IL-6 were significantly reversed by Betaine as compared to that of standard group (L-dopa+ Benserazide). As per literature review, Betaine is a safer drug possessing wide therapeutic window. It can also act as antioxidant agent versus oxidative stress mediated by antiparkinsonian drugs viz L- dopa and L-dopa+ Benserazide. Betaine also demonstrated a methyl donor

effect to reduce hyperhomocysteinemia. It appears that antioxidant and methyl donor properties of Betaine are promising particularly in management of plasma total homocysteine (tHcy) and oxidative stress in dopaminergic neurons of the brain. Betaine can be better adjuvant in pharmacotherapy of PD and/or to manage extrapyramidal side effects of anti-parkinsonian drugs like L-dopa.

CONCLUSION

The present study provides proof of concept for potential use of Betaine as an adjuvant in pharmacotherapy of PD. Additionally Betaine is safer drug with wide therapeutic window.

REFERENCES

1. Banu Z, Fatima, SJ, Fatima A, Fatima S, Zohra SF, Sultana T, Phytochemical Evaluation and Pharmacological Screening of Antiparkinson's Activity of Allium Sativum In Swiss/Albino Mice. IOSR Journal of Pharmacy, 2016; 6(6):1-12.
2. De Lau LM, Breteler MM, Epidemiology of Parkinson's disease. The Lancet Neurology, 2006; 5(6):525-535.
3. Lundblad M, Anderson M, Winkler C, Kiric D, Wierup N, Cenci M, Pharmcolological validation of behavioural measures of akinesia and dyskinesia in rat model parkinson's disease. European Journal of Neuroscience, 2002; 15:120-32.
4. Goes AT, Jesse CR, Antunes MS, Ladd FVL, Ladd AAL, Luchese C, Paroul N, Boeira SP, Protective role of chrysin on 6-hydroxydopamine-induced neurodegeneration a mouse model of Parkinson's disease: Involvement of neuroinflammation and neurotrophins. Chemico-biological interactions, 2018; 279:111-120.
5. Lai CL, Lu CC, Lin HC, Sung YF, Wu YP, Hong JS, Peng GS, Valproate is protective against 6-OHDA-induced dopaminergic neurodegeneration in rodent midbrain: A potential role of BDNF up-regulation. Journal of the Formosan Medical Association, 2019; 118(1):420-428.
6. Craig S, Betaine in human nutrition, American Journal of Clinical Nutrition, 2004; 80:539–49
7. Alirezaei M, Khoshdel Z, Dezfoulian O, Rashidipour M, Taghadosi V, Beneficial antioxidant properties of betaine against oxidative stress mediated by levodopa/benserazide in the brain of rats'. Journal of Physiology and Science 2015; 65:243-52.
8. Alirezaei M. Betaine protects cerebellum from oxidative stress followinglevodopa and benserazide administration in rats'. IJBMS 2004; 18:950-957.
9. Alirezaei M, Jelodar G, Niknam P, Ghayemi Z, Nazifi S, Betaine prevents ethanol-induceed stress and reduce total homocysteine in the rat cerebellum Journal of Physiology and Biochemistry 2011; 67:605-612.
10. Lawson A, Levy H, The use of betaine in the treatment of elevated homocysteine, Molecular Genet Metabolism Report 2006; 88:201-07.
11. Zhang H, Liqun M, Chen J, Zhen X, Chronic SKF 83959 Include less sever dyskinesia and attenuated L-DOPA induced dyskinesia in 6-OHDA lesioned rat model of Parkinson's disease'. Journal Neuropharmacy 2007; 53:125-33.
12. Eskow K, Gupta V, Alam S, Park J, Bishop C, The partial 5-HT1A agonist buspirone reduces the expression and development of L-DOPA induced dyskinesia in rats and improves L-DOPA efficacy'. Pharmacology and Biochemistry Behaviour 2007; 87:306–314.
13. Bishop C, Taylor J, Ullrich T, Kuhn D, Eskow K, Park J, Walker P, MDMA and fenfluramine reduce L-DOPA induced dyskinesia via indirect 5-HT1A receptor Stimulation European Journal of Neuroscience 2006; 23:2669-76.
14. Matheus F, Rial D, Real J, Lemos C, Ben J, Guaita G, Decreased synaptic plasticity in the medial prefrontal cortex underlies short-term memory deficits in 6-OHDA-lesioned rats'. Behav Brain Research 2015; 301:43-54.
15. Sadekar S, Chauhan V, Shirole R, Salve B, Kasture S, Antidopaminergic activity of VitexnegundoLinn leaves Journal of Natural Remedies 2006; 6(2):165–69.
16. Jain PG, Mahajan UB, Shinde SD, Surana SJ, Cardioprotective role of FA against isoproterenol induced cardiac toxicity. Molecular biology reports, 2018; 45(5):1357-1365.
17. Sonawane VK, Mahajan UB, Shinde SD, Chatterjee S, Chaudhari SS, Bhangale HA, Ojha S, Goyal SN, Kundu CN, Patil CR, A chemosensitizer drug: Disulfiram prevents doxorubicin-induced cardiac dysfunction and oxidative stress in rats. Cardiovascular toxicology, 2018; 18(5):459-470.
18. Khairnar SI, Mahajan UB, Patil KR, Patel HM, Shinde SD, Goyal SN, Belemkar S, Ojha S, Patil CR, Disulfiram and Its Copper Chelate Attenuate Cisplatin-Induced Acute Nephrotoxicity in Rats Via Reduction of Oxidative Stress and Inflammation. Biological trace element research, 2019; 2:1-11.
19. Nair V, Arjuman A, Dorababu P, Gopalkrishna H, Chakradhar-rao U, Mohan L, Effect of NR-ANX-C (a polyherbal formulation) on haloperidol induced catalepsy in albino mice Indian Journal of Medical Research, 2007; 126:480-84.
20. Deumens R, Blokland A, Prickaerts J, Modeling Parkinson's disease in rats: an evaluation of 6-OHDA lesions of the nigrostriatal pathway Exp Neurol 2002; 175:303-17.
21. Schober A, Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP Cell Tissue Research 2004;318:215-24.
22. Gopal krishna C, Shankarnarayan D, Nazimudeen Sk, Kameswara L, Effect of tylophorine, a major alkaloid of Tylophoraindica, on immunopathological and inflammatory reactions. ijmr 2008; 71:940-48.
23. Zbarsky V, Datla P, Parkar S, Rai K, Aruoma I, Dexter T. Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease Free Radical Research 2005;39:1119-25.
24. Reale A, Iarlori C, Thomas A, Gambi D, Perfetti B, Di Nicola M, Onofrj M, Peripheral cytokines profile in Parkinson's disease Brain, Behavioural Immunology 2009; 23:55–63.
25. Qin L, Wu X, Block L, Liu Y, Breese R, Hong J, Knapp J, Crews T, Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration, Glia 2007; 55:453–62.
26. Iarlori C, Reale M, Lugaresi A, Luca G, Bonanni L, Di Iorio A, Feliciani C, Conti P, Gambi D, RANTES production and expression is reduced in relapsing-remitting multiple sclerosis patients treated with interferon-beta-1b, Journal Neuroimmunology, 2000; l107:100–07.