NSAIDs ameliorate cognitive and motor impairment in a model of parkinsonism induced by chlorpromazine

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Abstract: Parkinson's disease (PD) is a long-lasting neurodegenerative brain disease. It is characterized by a gradual decline in motor and non motor symptoms especially postural instability, tremors and memory impairment with localized loss of neurons mainly in the Substantia nigra. In the current research we evaluated the effects of Non-steroidal anti inflammatory drugs (NSAIDs) on motor coordination and memory in chlorpromazine (CPZ) induced Parkinson's experimental model. Intraperitoneal (i.p.) injection of CPZ (3 mg/kg) was given to all rats for 21 days to induce Parkinson like symptoms; ibuprofen (40mg/kg/day) and celecoxib (20mg/kg) were administered 30 minutes after CPZ injection. Behavioral parameters like Catalepsy, muscle strength (wire hanging test), locomotor activity (open field test) were observed. Moreover, its effect on memory was explored by the use of water maze and passive avoidance test. Our results showed CPZ significantly induced motor fluctuation and cognitive impairment in a period of 21 days. Celecoxib and ibuprofen significantly improved cataleptic scores ($P<0.01$), locomotion and muscular coordination in open field ($P<0.01$) and in wire hanging test ($P<0.01$). Significant improvement in memory was observed with celecoxib ($P<0.01$) and ibuprofen ($P<0.05$) in water maze test as well as in passive avoidance test. Therefore, the present study showed neuroprotective and memory enhancing effect of ibuprofen and celecoxib against CPZ induced Parkinson's model.

Keywords: Parkinson's disease (PD), memory impairment, chlorpromazine (CPZ), anti inflammatory drugs (NSAIDs), Neuroprotection.

INTRODUCTION

Parkinson's disease (PD) is characterized by a pattern of neuropathological alteration such as dopaminergic neuronal loss, presence of lewy bodies and α-synuclein (Vasant-more *et al*, 2013). Motor dysfunction, cognitive impairment, delirium and depression are most common symptoms related to Parkinson disease (Fahn and Perzborski, 2000). Chronic inflammatory process may play an important role in the pathogenesis of PD (Savitt *et al*, 2006; Glass *et al*, 2010). Reactive gliosis and presence of inflammatory cytokines may contribute to the pathology of alzheimer and parkinsons disease (PD) (Tansey *et al*, 2006; Whitton, 2007). Inflammatory cytokine like prostaglandins (PGs) are not only involved in the pathogenesis of neurodegenerative disorders but also play a vital role in different brain functions such as memory, sleep and depression (McAfoose *et al*, 2009). Both COX-1 and COX-2 are constitutively expressed in the brain and play a major role to regulate normal CNS physiological functions such as memory, sleep and mood (Graffin, 2006; McGeer *et al*, 2000; Yermakova *et al.*1999; Hoozemans *et al*, 2005; Teismann *et al*, 2003). Over expression of COX enzymes appear to be involved in noradrenergic stimulation by producing IL-1 and TNF-α (Hoozemans *et al*, 2008; Lima *et al*, 2012). Several clinical and experimental studies on the pathogenesis of PD have proposed a key role of COX2 in the activation of microglia and in the production of toxic free radicals (Zhang *et al*, 2005, Choi *et al*, 2009). Elevated PGE2 levels in mid brain and hypothalamus activates NADPH oxidase enzyme system which creates reactive oxygen and reactive nitrogen species (ROS, RNS), hence generates oxidative stress (Whitton, 2007; Kim andJoh, 2006; Ransohof and Perry, 2009).

Oxidative stress deregulates the glutathione system and is responsible for reducing glutamatergic and serotenergic activity at the glutamate NMDA receptor (Johansson *et al*, 2012). This results decreased expression of neurotrophin in cortex and hippocampus and ultimately leads to cognitive and mood disorders in PD patients (Shungu *et al*, 2012). In this regard motor and non motor signs of PD patients are being understudied and inadequately understood. Latest researches suggest inhibition of COX pathway as an alternate treatment option and as neuroprotective agent in PD (Menza *et al* 2010; Mrak and Griffin, 2005; Choi *et al*, 2010; Warner-Schmidt *et al*, 2011). COX initiate cytokines production from activated glial cells (Parepally *et al*, 2006), and NSAIDs inhibits cytokine production by inhibiting neuronal COX enzymes (Kotilinek *et al*, 2008; Choi *et al*, 2013). It also acts as an antioxidant and activate the nuclear factor PPARγ which is neuroprotective in PD (Episcopo *et al*, 2010; Yinxia *et al*, 2014).

The present study was designed to assess the role of ibuprofen and celecoxib in improving motor deficits and cognitive functions in chlorpromazine induced rat model of PD. The main purpose of our research was to explore

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the comparative effect of ibuprofen and celecoxib in improving motor and cognitive functions in chlorpromazine induced parkinson's disease model.

MATERIALS AND METHODS

Chlorpromazine

(Sigma-Aldrich, MO, USA), (3 mg/kg,i.p.). L-dopa/Carbidopa (OBS-Pharma Company, pakistan), Ibuprofen (Novartis Pharma (Pak) LTD) and Celecoxib (Getz Pharma Pakistan (PVT) LTD**). A**ll drugs were freshly prepared daily by dissolving in physiological saline (0.9% NaCl) and given orally.

Experimental animals

Induction of parkinsonism by chlorpromazine (CPZ) and administration of ibuprofen, celecoxib and standard drug (L-dopa/carbidopa) was carried out on healthy albino wistar rats. CPZ and other test drugs were given to 6-8 weeks old rats of 150-250 grams weight with equal sex distribution. Animals were kept under standard environmental settings (22±2°C, 60±10% humidity) with twelve/twelve hours light and dark cycle at the department of Pharmacology, University of Karachi. All animals were housed in a group of 2 rats per cage and provided with normal rat pellet diet (rat chow) in morning and evening as well as drinking water was available throughout a day. Rats were divided in five groups after one week of acclimatization. Specifications of Helsinki Resolution 1964 were followed in the animal handling procedure. The plan followed for animal experiments was approved by BASR University of Karachi under resolution No.02(50).

Dosing protocol

All rats were randomly allocated into 5 groups, containing 10 animals each. Grouping of animals was as follows:

Group I. control group received only saline water

Group II. Parkinson disease control group received i.p 3mg/kg/day CPZ only (Bishoni *et al*, 2006).

Group III. Standard group received CPZ i.p 3mg/kg/day and after 30 minutes received L-dopa/Carbidopa (1:10 ratio) combination orally 30mg/kg/day (Sandhu and Rana, 2013).

Group IV. Test group received CPZ i.p 3mg/kg/day and after 30 minutes received 40mg/kg/day oral suspension of ibuprofen (De La Garza and Asnis, 2003).

Group V. Test group received CPZ i.p 3mg/kg/day and after 30 minutes received 20mg/kg/day oral suspension of celecoxib (Kaizaki *et al*, 2013).

Methodology

Parkinson was experimentally induced by giving 3mg/kg/day chlorpromazine for 21 days (Sandhu and Rana, 2013). After 30 minutes of chlorpromazine administration animals were tested for induction of severity of parkinsonism by measuring cataleptic scores. In other groups 30 min before the administration of standard and test drugs, CPZ was also given for a period of 21 days. Different memory and motor activity parameters like open field test, grip strength activity, catalepsy, water maze and passive avoidance test were performed in all animals after 10 and 21 days (Shin and Chung, 2012).

Motor evaluations

Catalepsy test

Assessment of catalepsy behavior (inability to correct abnormal posture) was done by using the standard Bar test. It is defined as the time the animal sustained an imposed position with both front limbs extended and resting on a 9-cm high round wooden bar. The end point of catalepsy was considered to occur when both front paws were removed from the bar or if the animal moved its head in an exploratory manner. The cut-off time of the test was 720 sec (Pires, 2005).

Open field activity

To assess the spontaneous locomotor activity of animals, Open Field Test was conducted. It consisted of wooden Board (76cm length x 40cm height x 76cm width) with the uniformly sized 25 squares with square open arena. Escaping of the animals was prevented by the surrounded walls which were painted in black (Sestakova *et al*., 2013). Albino Wistar rats control and test groups were kept individually in the central square of the Open Field. Animals were kept for 10 minutes and number of squares crossed was counted in both groups control and test (celecoxib, ibuprofen, L-dopa and CPZ) after 10 and 21 days of dosing. All test drugs were administered to animals and after 15 min of the dosing the activity was recorded.

Grip strength

Griping strength of animals was assessed by using wire hanging test. Apparatus consisted of stainless steel bar with two platforms, rats (control, CPZ, standard and test groups) were briefly trained before test session. The animals were placed separately on stainless steel bar and allow gripping the bar to observe their grip strength and muscular tone. The length of time the rat was able to hold the bar till it fell was recorded after 10 and 21 days of treatment, with cut-off time of 300 seconds (Takahashi *et al*, 2009).

Cognitive measures

Water maze test

This test is used to assess the spatial learning behavior of the rodents. The Water Maze apparatus consisted of a rectangular transparent Plexiglas tank (60x30cms) that was filled with tap water. Water was maintained at room temperature. The depth of maze was 12cm. The water was made opaque in order to hide the platform from animal via dissolving starch in it. A platform (15x13cms) made of Plexiglas was fixed; the water level was kept 2cm above the surface of platform.

Table 1: Effect on Catalepsy

Test	Time	Groups				
Catalepsy (sec)		Control	Chlorpromazine 3mg/kg/day	Ibuprofen 40mg/kg/day	Celecoxib 20mg/kg/day	L-dopa/Carbidopa 30mg/kg/day
	5 Minute	##1.2±0.4	**11.6±10.1	9.2±5.83	9.3±7.2	5.9±3.03
	60 Minutes	##1.4±0.5	**109±25.8	**70.6±22.8	**91.7±64.2	**72.4±34.2
	120 Minutes	##1.3±0.67	**321.5±83.7	**##58.8±16.6	**##56.9±34	**##35.5±11.5
	180 Minutes	##1.3±0.48	**183.9±56.7	##27.3±9.28	##18.9±8.97	##12.1±7.97

n=10 df=(1, 54) Results are mentioned as average ± standard deviation p-values are calculated by post hoc analysis using Bonferroni test when compared with control. **p≤0.01= moderately significant; when compared with Chlorpromazine. ##p≤0.01= moderately significant among the groups

Table 2: Effect on Open Field activity

Activity	Days	Drugs				
Open field activity		Control	Chlorpromazine 3mg/kg/day	Ibuprofen 40mg/kg/day	Celecoxib 20mg/kg/day	L-dopa/Carbidopa 30mg/kg/day
	10 Days	81.60±2.4	**29.10±6.1	**21.70±5.90	**22.80±3.91	**23.30±6.78
	21 days	80.50±2.4	***6.60±3.77	**##30.70±6.43	**##37.10±6.60	**##41.70±13.1

n=10 df=(1, 54) Results are mentioned as average ± standard deviation, p-values are calculated by post hoc analysis using Bonferroni test when compared with control/CPZ. *p≤0.05= significant, **p≤0.01= moderately significant, ***p≤0.001= highly significant when compared with Chlorpromazine. #p≤0.05= significant, ## p≤0.01= moderately significant among the groups

Table 3: Effect on Wire Hanging test

Activity	Days	Drugs				
Wire Hanging Test Latency time (sec)		Control	Chlorpromazine 3mg/kg/day	Ibuprofen 40mg/kg/day	Celecoxib 20mg/kg/day	L-dopa/ Carbidopa 30mg/kg/day
	10 Days	213.40±64.97	* 64.50±12.7	* 71.3±10.66	*72.16±10.18	* 76.90±12.13
	21 days	225.20±40.33	*** 6.10±1.66	**## 92.1±13.23	**## 96.5±10.06	**## 108.8±16.39

n=10 df=(1, 54) Results are mentioned as average ± standard deviation, p-values are calculated by post hoc analysis using Bonferroni test when compared with control/CPZ. *p≤0.05= significant, **p≤0.01= moderately significant, ***p≤0.001= highly significant when compared with Chlorpromazine; ## p≤0.01= moderately significant among the groups

Table 4.1: Effect on short term memory by Water Maze test

Activity	Days	Drugs				
Water Maze activity (short term)		Control	Chlorpromazine 3mg/kg/day	Ibuprofen 40mg/kg/day	Celecoxib 20mg/kg/day	L-dopa/Carbidopa 30mg/kg/day
	10 Days	25.40±5.91	*37.60±8.42	33.5±5.5	31.8±7.68	33.1±7.14
	21 days	20.2±2.8	**69.90±8.86	***##16.30±4.37	***##13.20±5.67	***##9.20±4.54

n=10 df=(1, 54) Results are mentioned as average ± standard deviation, p-values are calculated by post hoc analysis using Bonferroni test when compared with control/CPZ. *p≤0.05= significant, **p≤0.01= moderately significant**,** ***p≤0.001= highly significant when compared with Chlorpromazine; ## p≤0.01= moderately significant among the groups

Table 4.2: Effect on Long term memory by Water Maze test

Activity	Days	Drugs				
Water Maze activity (long term)		Control	Chlorpromazine 3mg/kg/day	Ibuprofen 40mg/kg/day	Celecoxib 20mg/kg/day	L-dopa/Carbidopa 30mg/kg/day
	10 Days	28.90±2.76	*43.30±7.60	38.60±6.07	36.70±8.433	39.50±7.80
	21 days	23.50±3.2	**82.60±14.99	***##20.60±4.35	***##17.50±5.54	***###12.50±4.08

n=10 df=(1, 54) Results are mentioned as average ± standard deviation, p-values are calculated by post hoc analysis using Bonferroni test when compared with control/CPZ. *p≤0.05= significant, **p≤0.01= moderately significant**,** ***p≤0.001= highly significant when compared with Chlorpromazine; ## p≤0.01= moderately significant, ### p≤0.001= highly significant among the groups

Table 5: Effect on passive avoidance test

Activity	Days	Drugs				
Passive Avoidance test		Control	Chlorpromazine 3mg/kg/day	Ibuprofen 40mg/kg/day	Celecoxib 20mg/kg/day	L-dopa/Carbidopa 30mg/kg/day
	10 Days	138.80±53.27	*51.30±14.85	*71.10±19.59	*84.70±14.04	*81.50±36.64
	21 days	149.50±53.59	**24.60±5.85	**#90.0±19.44	***##115.90±33.03	***##115.80±31.36

n=10 df=(1, 54) Results are mentioned as average ± standard deviation, p-values are calculated by post hoc analysis using Bonferroni test when compared with control/CPZ. *p≤0.05= significant, **p≤0.01= moderately significant, ***p≤0.001= highly significant when compared with Chlorpromazine; # p≤0.05= significant, ## p≤0.01= moderately significant among the groups

Initially the rats were trained before the test session. During the training period each animal was individually placed in the water facing the wall of the tank. Rats were allowed to locate and climb onto the submerged platform and allowed to stay on the platform for 10 seconds. Cut-off time for the test is 2 minutes. If the animal failed to find the platform within the allowed time it was guided gently onto the platform. Memory of the animals was evaluated by recording retention latency. The time that animal takes to reach the platform is taken as "retention latency". Retention latency (in seconds) was noted during the test session after 1 hour (short term memory) 24 hours (long term memory) after the training of animals. All the rats of control, CPZ, standard and test groups were tested for their short and long term memory after 10 and 21 days of treatment (Vorhees and Williams, 2006).

Passive avoidance test

This test is used to assess fear aggravated learning and memory behavior in animals. It consisted of two illuminated and non-illuminated compartments i.e. light compartment and dark compartment. Foot shock is given to animals in non-illuminated box termed as punishable box and illuminated box is safe and enlightened with bulb. Rats can freely move between these 2 compartments due to the sliding door which separate these compartments. The floor of the passive avoidance apparatus is grid with steel bars. 1.5mA foot shock for five seconds was given to all rats when arrived to the non-illuminated box. As a result animal rapidly come back to the safe illuminated box.

Rats go through test trial session that followed 24 h later to the training session. Latency time was noted down in the test session One hour before the test trial, rats were given CPZ, standard and test drugs, (L-dopa/carbidopa, ibuprofen and celecoxib) (Lee *et al*., 2012).

Data analysis

All the data is presented as Mean ± S.D. (n=10). Results from the open field activity, grip strength, Morris water maze and passive avoidance tests were analyzed by using one-way analysis of variance (ANOVA). When significant values were obtained, Bonferroni test was used for post hoc analysis. All the analysis were performed using Social Sciences version 22 (SPSS, Inc., Chicago, IL, USA)

RESULTS

Open field test

In the present study it was observed that i.p administration of CPZ produced significant deteriorated motor performances in open field test after 10 days (29.10±6.1, P<0.05) as compared to control group and showed highly reduced motor performances (6.60±3.77, P<0.001) after 21 days of treatment as compared to control, standard and test groups (ibuprofen and celecoxib). Animals of standard and test groups (ibuprofen and celecoxib) showed nonsignificant effect in motor activity after 10 days as compared to control group and CPZ group however, we observed significantly improved motor activity in open field test after 21 days of treatment with standard (41.70±13.1, P<0.001), ibuprofen (30.70±6.43, P<0.01) and celecoxib (37.10±6.60, P<0.001) treated groups as compared to CPZ group.

Grip strength

Wire hanging test is used to determine grip and muscular tone in rodents. In present study i.p administration of CPZ produced significantly reduced muscular tone and hanging time during cut-off time of 5 minutes in rats (64.50±12.7, P<0.01) as compared to control group after 10 days which further gradually decreased during 21 days of treatment (6.10±1.66, P<0.001) as compared to control and test drugs. Post hoc analysis showed nonsignificant effect in muscular tone and grip in test groups (ibuprofen and celecoxib) in comparison to control group after 10 days of treatment. After 21 days of treatment we found significantly improved muscular tone and grip with ibuprofen (92.1±13.23, P<0.01) and celecoxib (96.5±10.06, P<0.001) treated groups as compared to control and CPZ treated groups (table # 3).

Effect on memory in water maze test

Effect on short term memory in water maze test

The short term learning and memory behavior of rats were assessed by water maze activity. In this activity it was observed that CPZ administration produces significantly increased escape latency time which shows more time taken to reach the platform (37.60±8.42, P<0.01) after 10 days. On 21st day in CPZ group highly significant increase in escape latency was observed (69.90±8.86, P<0.001) as compared to control, standard

and test drugs. Standard drug and test drugs showed insignificant results after 10 days of treatment whereas; after 21 days we found improved results with standard drug (9.20±4.54, P<0.001), ibuprofen (16.30±4.37, P<0.01) and celecoxib (13.20±5.67, P<0.001) respectively (table # 4.1).

Effect on long term memory in water maze test

Long term memory of rats after 24 hour of training session was also assessed through Water maze test. In this test it was observed that CPZ administration produces significantly increased escape latency time (43.30±7.60, P<0.01) after 10 days as compared to control group and highly significant differences were found (82.60±14.99, P<0.001) after 21 days of CPZ treatment when compared with control, standard and test groups. Standard drug and test drugs showed nonsignificant results after 10 days of treatment whereas; after 21 days of treatment we found improved cognitive status with standard drug (12.50±4.08, P<0.01), ibuprofen (20.60±4.35, P<0.01) and celecoxib (17.50±5.54, P<0.01) respectively (table # 4.2).

Effect on passive avoidance test

Passive avoidance experiment is extensively used for the screening of drugs affecting learning and memory of animals. In this test majority of CPZ treated rats were passive and showed significant decreased escape latency time (51.30±14.85, P<0.01) after 10 days as compared to control group. Significant decrease was found (24.60±5.85, P<0.001) after 21 days of CPZ treatment as compared to control, standard and test groups. We found nonsignificant differences between the standard and test drugs after 10 days of treatment whereas; after 21 days we found significant improved escape latency time with standard drug (115.80±31.36, P<0.01), ibuprofen (90.0±19.44, P<0.05) and celecoxib (115.90±33.03, P<0.01) respectively as compared to control and CPZ group (table # 5).

DISCUSSION

In present study NSAIDs (Celecoxib and ibuprofen) were evaluated for the first time in order to prove whether NSAIDs could ameliorate PD associated cognitive impairment and motor sign and symptoms by inhibiting cytokines and prostaglandin up regulation. Ibuprofen and celecoxib are most commonly used NSAIDs to reduce inflammation and pain (Robert and Morrow, 2001). Ibuprofen non-selectively inhibits COX enzymes and prostanoids mediation where as celecoxib selectively inhibit COX-2 mediated prostaglandins in the brain (Small *et al*, 2008; Schlichtiger *et al*, 2010). COX 1 and COX 2 both have predominant localization in microglia (Choi *et al*, 2009) thus thought to be involved in neuroinflammatory diseases like Alzheimer (AD) and Parkinson (PD) (Lima *et al*, 2012).

In our study parkinsonism was induced by chlorpromazine administration for 21 days in all treated groups. Chlorpromazine is a neuroleptic drug and frequently used to develop parkinsons disease in an animal model (Shandu and Rana, 2013; Vafaee *et al*, 2015; Bais *et al*, 2015). CPZ produces motor deterioration by blocking dopamine D2 receptors in substantia nigra and decreased monoamine levels at nerve terminals (Parikh *et al*, 2003). In our study CPZ treated rats showed significant cataleptic behavior, impaired motor function and muscle coordination after 10 and 21 days treatment. Chlorpromazine significantly induced catalepsy in rats as evident by a significant increase in time spent on bar test as compared to control group. Treatment with NSAIDs (ibuprofen and celecoxib) groups significantly reduced latency period in catalepsy model and results are also comparable to levodopa/carbidopa (standard) group. These findings are consistent with previous studies (Swaitkiewicz *et al*, 2013), that indicated that NSAIDs decrease oxidative stress by inhibiting iNOS and ROS species and increase PPAR□. The protective effect of ibuprofen and celecoxib against chlorpromazine induced cataleptic model suggests that NSAIDs can be beneficial in Parkinson through inhibition of COX.

Weak muscular coordination and grip strength were observed in wire hanging test. These results are in accordance with previous researches which explain that CPZ produced hypolocomotion, passivity and muscular rigidity by blocking dopamine receptor and monoamines reduction at nerve terminals (Dexter *et al*, 1994; Bias *et al*, 2015; Naeem *et al*, 2015). Celecoxib and ibuprofen treated rats significantly improved their motor activities in open field test and showed better muscular coordination and grip strength in comparison with L-dopa/carbidopa treated rats after 21 days. Celecoxib and ibuprofen inhibit COX mediated microglial activation and decreases cytokines production like IL-1 β and TNFα within the brain (Kaizaki *et al*, 2013; Imbimbo *et al*, 2010). Furthermore, raised levels of monoamines, dopamine and glutathione were found with different NSAIDs treatment in parkinson experimental models (Ambhore *et al*, 2014; Swaitkiewicz*et al*, 2013) suggesting improved neurotransmission. High levels of dopamine in basal ganglia is responsible for hyper locomotion and muscular strength (Wise and Bozarth, 1987).

In present study, short term and long term both water maze activities with CPZ treated rats showed more time taken to locate the platform after 21 days of treatment. This observation is consistent with the recent researchers that explain that CPZ effectively increases lipid peroxidation, free radical formation as well as decreases glutathione in brain (Deavall *et al*, 2012, Sandhu and Rana, 2013). Decreased glutathione and super oxide dismutase levels in different brain areas impair H_2O_2 clearance in basal ganglia and produce oxidative stress by

forming toxic hydroxyl radicals (Naidu *et al*, 2002; Li *et al*, 2013). We observed improved memory status in water maze test with celecoxib and ibuprofen treatment after 21 days. This result is comparable with standard group and proves that celecoxib and ibuprofen by reducing oxidative stress in hippocampus and amygdala restore short term and long term memory. In animal PD models elevated levels of PGE2, TNFα and other cytokines were found which produced free radical in rats hippocampus and alter function of NMDA receptors and cognitive functions (Menza *et al*, 2010; Pepicelli *et al*, 2005). NSAIDs restore memory function in animals by inhibiting PGs production and oxidative stress (McKee *et al*, 2008; Combs *et al*, 2000).

The passive avoidance test showed that latency in CPZ treated rats was decreased. Our rats took less time to enter in punishment box (dark box) after 21 days of CPZ treatment that shows impaired memory and learning behavior. This finding is in accordance with previous research. Johansson *et al*, (2012) also reported that CPZ in experimental models induced free radical formation that produces damage to dopaminergic cells and decreased epinephrine and serotonin concentration which ultimately lead to amnesia and learning deficit (Johansson *et al*, 2012). However, administration of ibuprofen and celecoxib after 21 days significantly revert amnestic behavior of CPZ and showed better memory and learning performance in passive avoidance (table # 5). This could be because of the inhibition of COX pathway and inflammatory cytokines which reduces oxidative stress and ultimately restored dopamine levels.

CONCLUSION

Different studies were conducted for evaluating role of NSAIDs in improving memory and motor impairments in animal models. We observed a consistent and pharmacological beneficial result for controlling Parkinsonism in animal models by using celecoxib and ibuprofen. Since these drugs are easily available, clinically proven with less toxicity, it is recommended that these drugs may be used routinely for effective treatment of Parkinsonism. To prove it, further in-vitro studies and molecular level investigations will be useful for utilizing these drugs and their combinations for the treatment of clinical Parkinsonism**.**

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