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Inhibition of drug induced Parkinsonism by chronic supplementation of quercetin in haloperidol-treated wistars

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Abstract: Haloperidol is a neuroleptic medication that is used to treat a wide range of neuropsychiatric conditions. It has been shown to produce medicinal effects against hyperactivity, agitation and mania, as well as schizophrenia. Long-term usage of haloperidol raises the risk of acquiring a neurological condition like Parkinson's disease. Haloperidol causes drug-induced Parkinsonism (DIP) by blocking central dopamine receptors and causing extrapyramidal symptoms during long-term treatment. Quercetin has been shown to reduce the loss of striatal neurons, which may enhance motor capabilities and protect against agents that cause the production of reactive oxygen species (ROS). As a result, present study intended to evaluate the efficacy of quercetin on haloperidol-related motor abnormalities. To develop behavioral impairments, rats (n=24) randomly divided to control and haloperidol group for four weeks. The animals were split into four groups after four weeks: control, quercetin, haloperidol and haloperidol + quercetin. Animals were administered haloperidol i.p injections of 5 mg/kg and quercetin (100 mg/kg) orally for 21 days. The treatment of haloperidol-treated rats with quercetin was successful in reversing the haloperidol alterations. It decreased animal food intake and alleviated anxiogenic behavior. The chronic treatment of quercetin further reduced the movement abnormalities in animal model of drug induced pseudo-Parkinson

Keywords: Antioxidant, anxiolytic, drug induced parkinsonism (DIP), movement impairment.

INTRODUCTION

Haloperidol is a typical neuroleptic drug used to treat a variety of neuropsychiatric diseases. It has been reported to reduce hyperactivity and schizophrenia. The primary mode of action is dopamine inhibition; it works as an antagonist of postsynaptic dopamine D2 receptors in the mesolimbic pathway, reducing dopaminergic neurotransmission. (Janno *et al*., 2004). Neuroleptics have also been linked to neurodegeneration caused by oxidative stress. The most prevalent side effect of neuroleptics is cytotoxicity. Treatment with neuroleptics alters SOD/CAT activity via increasing lipid peroxidation and affecting the antioxidant defense system, according to animal studies. In mice, a single dosage of haloperidol resulted in increased oxidative stress, according to a research (Saeed *at al.,* 2017). Another study found that rats with vacuous chewing movements had higher levels of oxidative stress markers in the striatum, indicating that these animals had higher levels of free radical production and oxidative stress.

The prolonged use of haloperidol increases the risk of neurological illness such as Parkinson's disease. It is mainly characterized by autonomic dysfunction and psychiatric illness. Motor abnormalities, such as tremor, stiffness, bradykinesia and postural instability, are the most common symptoms (Postuma and Berg, 2016). The non-motor symptoms of PD often dependent on emotions. The main pathology is dopamine insufficiency in the nigrostriatal pathway, but the neurodegeneration in the ventral tegmental region (which stems from the mesocorticolimbic system) has also been investigated. The modulation of emotion and anxiety is closely linked to the participation of the mesocorticolimbic circuit (Thomas and Thomas, 2015).

Upon chronic administration, haloperidol exhibits extrapyramidal symptoms by inhibiting central dopamine receptors and may cause drug induced Parkinsonism (DIP) (Shin and Chung, 2012). Movement distortions are adverse effects of antipsychotics that stigmatize the daily living activities. DIP is the most common cause of dopaminergic receptors dysfunction and often misdiagnosed as PD due to similar clinical manifestations (Thanvi and Treadwell, 2009) and recognized as “pseudo Parkinson” which may reverse with L-3,4-dihyrdroxyphenylalnine (L-Dopa); a precursor of dopamine synthesis (Carlsson *et al*., 1957).

Quercetin is reported to attenuate the loss of striatal neurons which may improve motor functions (Zarai *et al*. 2013) and guards against the agents which leads to the development of ROS generation. It has various pharmacological effects enable its use in many pathological condition. Quercetin treatment reported to prevent the loss of dopamine and has also showed successful results against MPTP-induced PD-like syndromes (Lee *et al*., 2001). Therefore, the aim of present work is exhibited in this postulation to evaluate the effects of quercetin on haloperidol associated motor abnormalities and oxidative stress.

MATERIAL AND METHODS

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Twenty four male Albino Wistar rats weighing from 180 to 200gm were brought from DOW University, Karachi /(OJHA) and approved by Board of Advanced Studies and Research (BASR), University of Karachi with letter number 03346/Sc. They were acclimatized for three days under control environment including 22±2ºC temperature, 12 hour light-dark cycle and 30-35% humidity. All animals were housed individually and received normal standard diet. The behavioral deficits were induces by the injection of haloperidol at 5mg/kg, i.p. The animals were divided as control and haloperidol for four weeks (fig. 2). After the induction of behavioral deficits, animals were divided in to four groups: Control, quercetin, haloperidol and haloperidol + quercetin. For 28 days, animals were given quercetin (100mg/kg) according to their groups. Quercetin was purchased from Sigma and dissolved in water before administration.

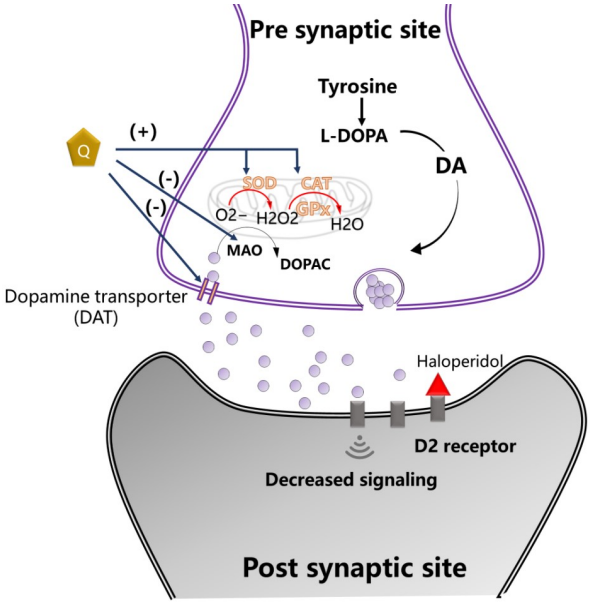


Fig. 1: The potential pharmacological effects of quercetin (Q) on haloperidol induced cytotoxicity. Quercetin increases the level of antioxidative enzymes (+) and reduced the activity of MAO-B (-). It also inhibit the dopamine reuptake transporter which ensure the availability of dopamine in synapse to perform physiological functions.

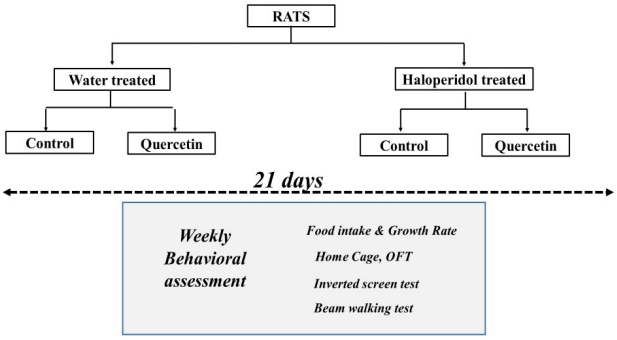


Fig. 2: Experimental protocol.

Behavioral assessment

Food intake and weight

To measure the food consumption, a known food quantity was allowed to individual cages and consumption was measured 24 hours of 1st day treatment and then weekly. The monitoring was done by weighing the left amount of food in individual cage.

To observe the influence of diet and treatment on body weight, each animal was placed in a basket on a weighing machine. The measurement was done on the first day of experimentation and then weekly.

Home cage test

To observe to activity of animals in familiar surroundings (fig. 2.2), square shaped (26x26x26cm) apparatus was used which was floored with saw dust. Each animal was allowed to sit in the center and ambulatory activity was monitored for 10 minutes and the counts of cage cross was monitored (Haleem *et al*., 2007).

Open field test (OFT)

The observation of activity outside the familiar environment is generally done by open field activity test (fig. 2.3) in order to explore the emotional state of animals (Hall, 1932). The novel apparatus used in this test was 42 cm high square shape. The walls of apparatus were opaque (76x76 cm). The floor was designed with 25 equal squares. At the time of test, each animal allowed to sit in center and counts of cage cross in next 5 minutes were observed to determine the anxiogenic/anxiolytic behavior.

Inverted screen

To test the neuromuscular strength, inverted screen test was used. The rats were placed on a horizontal grid attached 20cm above the surface (fig. 2.9). The rat was allowed to grab on the grid with all paws, the grid was then inverted to upside down (Kondziella, 1964). The maximum hanging time/latency to fall from grid (seconds) was recorded for 30 seconds.

Beam walk test

The beam walk test is used to evaluate the motor coordination of rats, especially of their hind limbs. The apparatus used for the present study was a narrow beam having a width of about 3 cm that was placed between the start platform and the home cage of the rats. The wooden beam was held above the floor with the help of the wooden supports (Goldstein and Davis, 1990). In order to perform the experiment, the rat was placed on one side of the beam and it was then allowed to walk on the wooden beam for 3 minutes. The latency to cross the beam had been monitored in the experiment.

Estimations of oxidative stress

MDA

Samples (0.2ml) were reacted with reagent (2ml). The samples were placed in 100ºC and then allowed to cool (4ºC). Centrifugation was done at 3500rpm over 10 minutes and absorbance was noted at 535nm. The MDA levels were presented as µM/g (Okawa, 1979).

SOD

Brain homogenate (0.3 ml) was added with 0.1 ml of N-Methylphenazonium ethosulphate and 1.2ml of buffer. The addition of 0.2 ml of NADH required to initiate the reaction which was inhibited by 1ml ethanoic acid after 60 seconds. The measurement of chromogen was recorded at 560nm. The units for SOD level were unit/mg protein (Kakkar *et al*., 1984).

Catalase

Each sample (0.1ml) was added to 0.5ml H_2O_2 separately, then incubated at 37ºC for 1.5 minutes. Dichromate was added to inhibit the reaction. The test tube were incubated at 100ºC for 15 minutes. The levels of H_2O_2 which were consumed, measured at 570nm in spectrophotometer. The activity of enzyme was expressed as mmol/g of tissue (Sinha *et al*, 1972).

Glutathione (GSH)

Brain homogenate (0.3ml) was added with 1 ml of TCA. The mixture was refrigerated overnight at 4 degrees Celsius. The solution was then centrifuged at 5000rpm (4ºC) for approximately 15 minutes. The collected supernatant (0.1ml) reacted with buffer (2ml) and DTNB (0.5ml) and vortex was used to shake till the yellow appearance. The absorbance was taken at 412nm. The concentration of was presented as nmol/gm of tissue (Ellman, 1959).

Glutathione peroxidase (GPx)

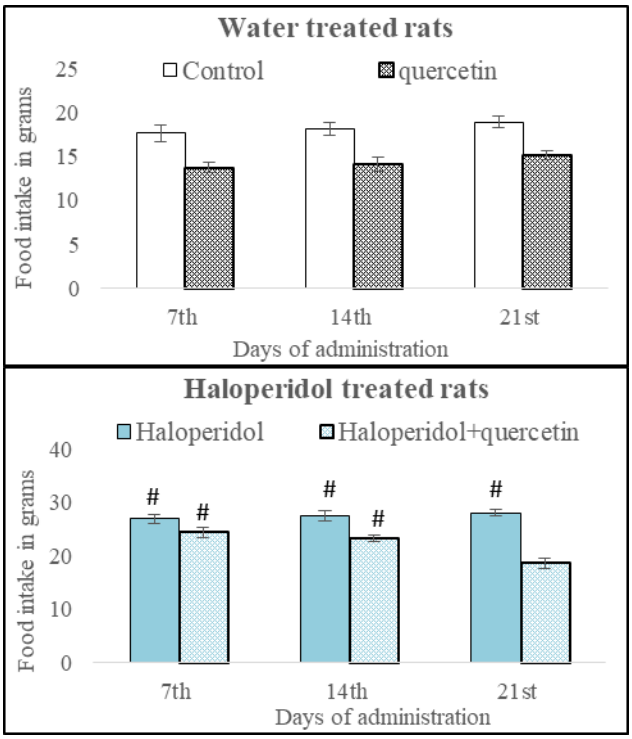
The brain homogenate (0.1ml) was added to 1.4 ml of buffer, NaN3 (0.1ml) was added, EDTA (0.1ml), glutathione reductase (0.05ml), GSH (0.05 ml), NADPH (0.01ml), H2O2 (0.01ml). The mixture was incubated at 25ºC. The absorbance was recorded at 340 nm. The molar extinction coefficient (6.22x103) was used to calculate GPx activity which was expressed as µmol/min/g of tissues (Mohandas *et al*., 1984).

STATISTICAL ANALYSIS

Results are present as mean ±SD. Variation between mean values were analyzed by three-way ANOVA of SPSS version 21. Newman-Kuels test was used to compare the mean of different groups, $p<0.05$ and $p<0.01$ were consider as significant.

RESULTS

Fig. 3 presented the results of food intake. Three-way ANOVA was used for data analysis and the effects of repeated administration ($F= 13.685$; $df= 2, 29$; $p<0.01$), haloperidol ($F=1527.6$; $df= 1, 29$; $p<0.01$), haloperidol +quercetin ($F= 464.82$; $df= 1, 29$; $p<0.01$) and interaction between all the factors ($F=43.954$; $df= 2, 29$; $p<0.01$) were significant. Post hoc analysis by Newman-Keuls test showed that administration of haloperidol increased food intake ($p<0.01$) of animals as compared to their water treated control animals. The hypophagic effects were seen in haloperidol treated rats but no significant values were seen.



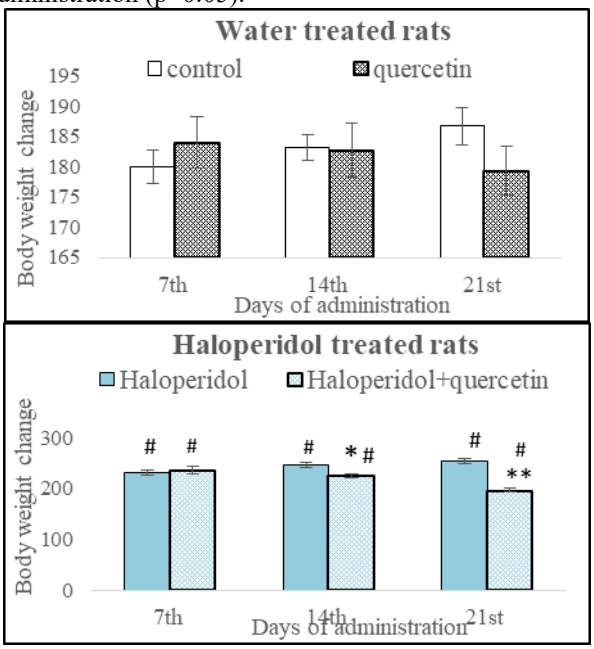
Values are presented as mean±SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as # $p<0.01$ from respective water treated group.

Fig. 3: Effects of quercetin on haloperidol treated rats on food intake.

Fig. 4 presented the results of body weight. Three-way ANOVA was used for data analysis and the effects of repeated administration ($F= 35.915$; $df= 2, 29$; $p<0.01$), haloperidol ($F=474.9$; $df= 1, 29$; $p<0.01$), haloperidol +quercetin ($F= 32.845$; $df= 1, 29$; $p<0.01$) and interaction between all the factors ($F=49.505$; $df=2, 29$; $p<0.01$) were significant. Post hoc analysis by Newman-Keuls test showed that administration of haloperidol increased body weight ($p<0.01$) of animals as compared to their water treated control animals. The doses of quercetin significantly reduced the body weight after 14th administration ($p<0.05$) in haloperidol treated rats than their positive control group.

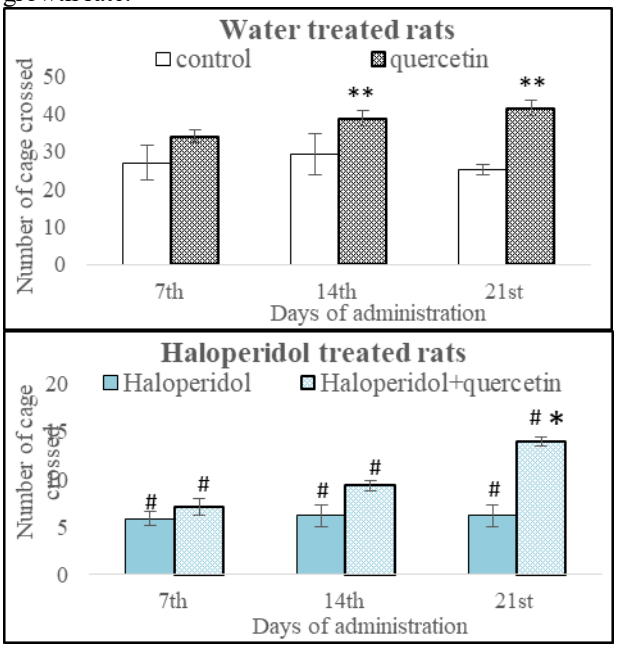
Fig. 5 presented the results of locomotor activity. Three-way ANOVA was used for data analysis and the effects of repeated administration ($F= 14.380$; $df= 2, 29$; $p<0.01$), haloperidol ($F=116.573$; $df= 1, 29$; $p<0.01$), haloperidol +quercetin ($F= 1242.073$; $df= 1, 29$; $p<0.01$) and

interaction between all the factors (F=30.139; df= 2, 29; p<0.01) were significant. Post hoc analysis by Newman-Keuls test showed that administration of quercetin increased energy expenditure (p<0.01) of normal animals as compared to their control group. However, the administration of haloperidol reduced significantly reduced the activity of rats when compared with normal rats (p<0.01) this reduced activity in haloperidol treated rats were reversed after the treatment of quercetin on 21st administration (p<0.05).



Values are presented as mean±SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as *p<0.05, **p<0.01 from similar control group, # p<0.01 from water treated group.

Fig. 4: Effects of quercetin on haloperidol treated rats on growth rate.

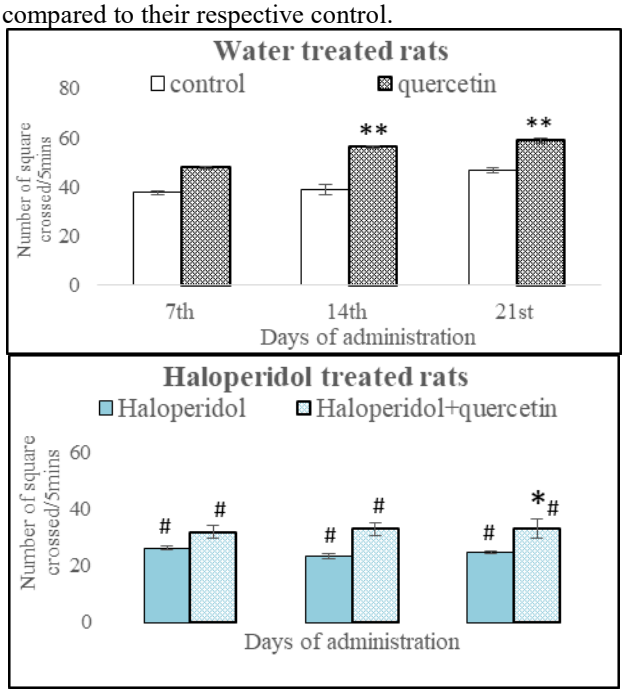


Values are presented as mean±SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as * p<0.05, **p<0.01 from similar control group, # p<0.01 from water treated group.

Fig. 5: Effects of quercetin on haloperidol treated rats on locomotor activity.

Fig. 6 presented the results of OFT. Three-way ANOVA was used for data analysis showed that effects of repeated administration (F= 34.02; df= 2, 29; p<0.01), haloperidol (F=987.423; df= 1, 29; p<0.01), haloperidol+quercetin (F= 310.99; df= 1, 29; p<0.01) and interaction between all the factors (F=165.914; df= 2, 29; p<0.01) were significant. Post hoc analysis showed that administration of quercetin increased square crossed (p< 0.01) of normal animals as compared to their control group after 14th administration. The effects of quercetin on 21st administration (p< 0.05) were shown to increase the squares as compared to haloperidol treated control rats.

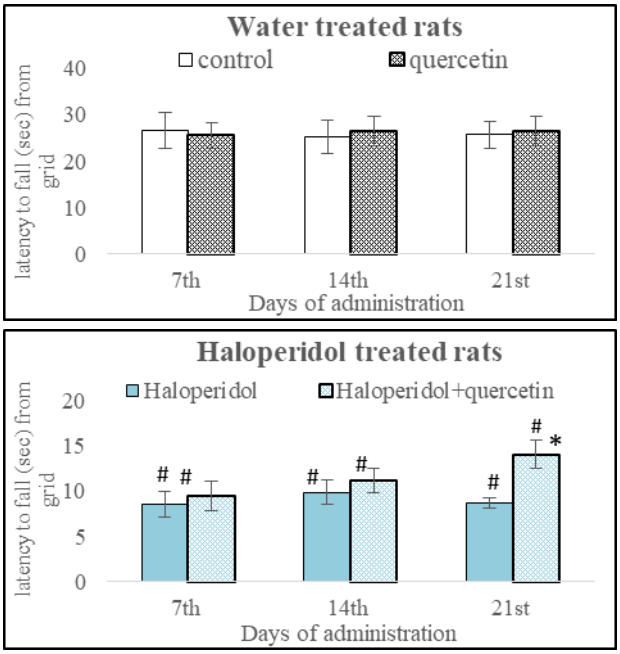
Fig. 7 presented the results of inverted screen test. Three-way ANOVA was used for data analysis and the effects of days (F=2.94; df=2, 29) was non-significant. The effects of haloperidol (F=6.331; df=1, 29; p<0.05), haloperidol+ quercetin (F=771.6; df=1, 29; p<0.01) and interaction between all the factors (F=8.842; df=2, 29; p<0.01) were significant. Post hoc analysis by Newman-Keuls test showed that administration of haloperidol reduced the activity of animals as compared to normal rats. The significant (p<0.01) reduced latency to fall was seen in haloperidol treated animals as compared to normal rats. The effects of quercetin on were shown to increase (p<0.05) the latency of haloperidol treated animals as compared to their respective control.



Values are presented as mean ± SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-

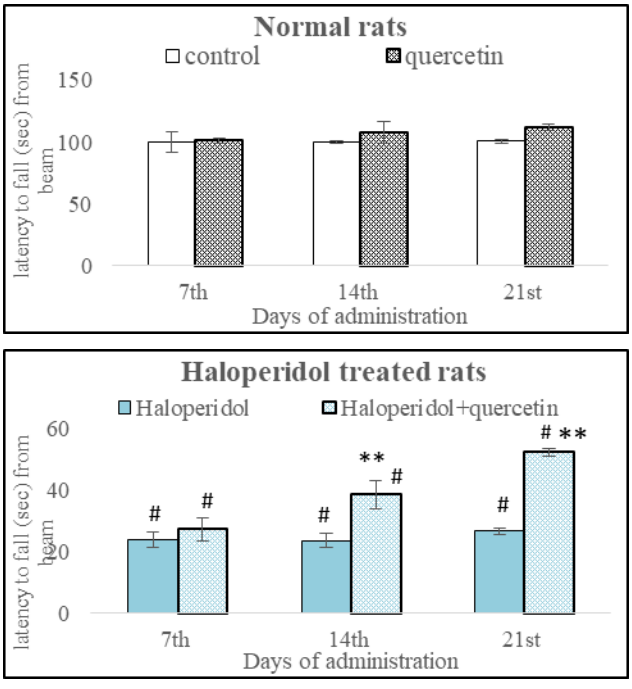
Kuels test are presented as * p<0.05, ** p<0.01 from similar control group, # p<0.01 from respective water treated group.

Fig. 6: Effects of quercetin on haloperidol treated rats on OFT.



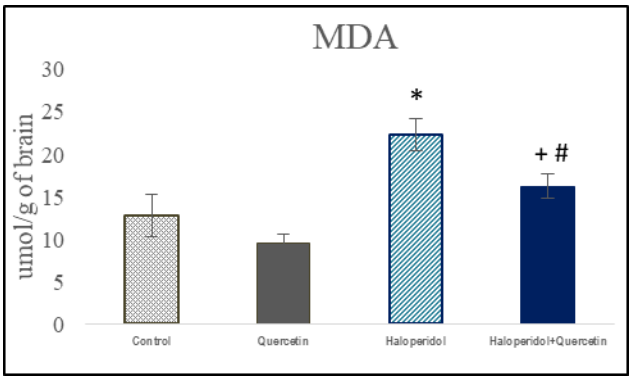
Values are presented as mean±SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as * p<0.05 from similar control group, # p<0.01 from respective water treated group.

Fig. 7: Effects of quercetin on haloperidol treated rats on inverted screen test.



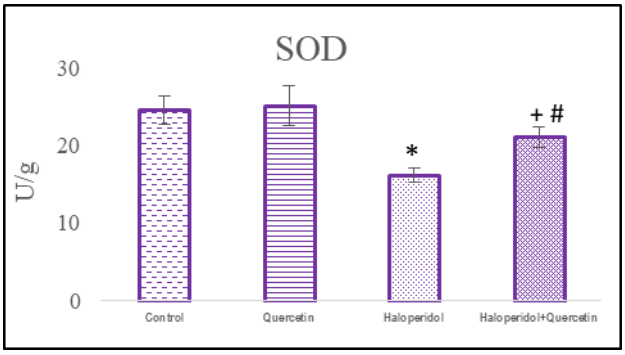
Values are presented as mean±SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as ** p<0.01 from control, # p<0.01 from respective water treated group.

Fig. 8: Effects of quercetin on haloperidol treated rats on beam walking test.



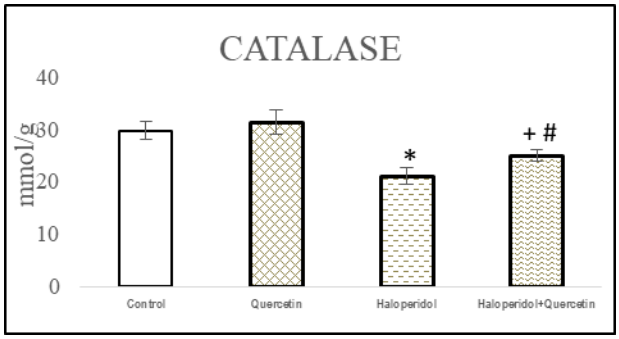
Values are presented as mean± SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as *p<0.05 from control, +p<0.05 from haloperidol, # p<0.01 from water treated quercetin control group.

Fig. 9: Effects of quercetin on MDA level of Haloperidol treated rats.



Values are presented as mean ±SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as *p<0.05 from control, +p<0.05 from haloperidol, # p<0.01 from water treated quercetin control group.

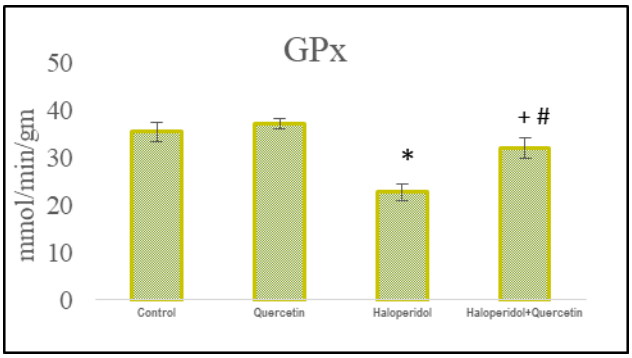
Fig. 10: Effects of quercetin on SOD level of Haloperidol treated rats.



Values are presented as mean ±SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as *p<0.05 from control, +p<0.05 from haloperidol, # p<0.01 from water treated quercetin control group.

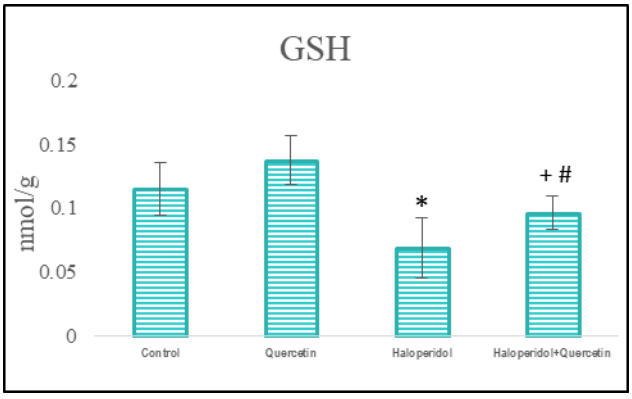
Fig. 11: Effects of quercetin on CAT level of Haloperidol treated rats.

Fig. 8 presented the results of beam walking test. Three-way ANOVA was used for data analysis and the effects of days (F=11.699; df=2, 29; p<0.01), haloperidol (F=104.67; df=1, 29; p<0.01), haloperidol+ quercetin (F=473.68; df=1, 29; p<0.01) and interaction between all the factors (F=47.89; df=2, 29; p<0.01) were significant. Post hoc analysis shown the effects of haloperidol, the significant reduced latency to fall form beam (p<0.01) when compared with normal rats. The administration of quercetin increased latency of animals as compared to their respective haloperidol treated control group after 14th (p<0.05) and 21st (p<0.01) administration. The effects of quercetin on 21st administration (p<0.05) were shown to increase the as compared to 1st administration.



Values are presented as mean±SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as *p<0.05 from control, +p<0.05 from haloperidol, # p<0.01 from water treated quercetin control group.

Fig. 12: Effects of quercetin on GPx level of Haloperidol treated rats.



Values are presented as mean±SD (n=6). Three-way ANOVA was used to analyze data. Significant differences by Newman-Kuels test are presented as *p<0.05 from control, +p<0.05 from haloperidol, # p<0.01 from water treated quercetin control group.

Fig. 13: Effects of quercetin on GSH level of Haloperidol treated rats.

Fig. 9 represented the effects of quercetin on oxidative stress. Data analyzed by One-way ANOVA showed that the effects of quercetin on MDA (F=74.8; df=3, 28; p<0.05) were significant. The post hoc test explained that the haloperidol significantly increased the oxidative stress (p<0.05) as compared to normal rats, however the long term quercetin administration suppressed the production of MDA (p<0.05) significantly as compared to haloperidol treated control rats.

Fig. 10-13 also shows the impact of quercetin on antioxidative enzymes. The effects of quercetin on SOD (F=44.1; df=3, 28; p<0.05), CAT (F=56.4; df=3, 28; p<0.05), GPx (F=101.7; df=3, 28; p<0.05) and GSH (F=17.8; df=3, 28; p<0.05) were significant, according to data evaluated using One-way ANOVA. In comparison to haloperidol-treated control rats, the post hoc test revealed that haloperidol decreased the level of antioxidant enzymes (p<0.05), whereas quercetin improved the level of antioxidant enzymes as shown in fig. 10-13, thus increased the antioxidant defense mechanism (p<0.05).

DISCUSSION

Antipsychotics are a type of dopamine antagonist that is used to treat severe mental illnesses like schizophrenia. Aside from these clinical consequences, some drugs can elicit extrapyramidal symptoms (EPS), such as Parkinson's disease, when dopaminergic D2 receptors are blocked and striatal dopamine activity is reduced (Muller *et al*., 2021). By reducing dopaminergic neurotransmission, haloperidol, the most common antipsychotic, can exhibit muscular strength (Vasconcelos *et al*., 2003). In preclinical studies, the experimental animals are used to treat by neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydroxypyridine (MPTP) and 6-OHDA and haloperidol for the development of PD models and better understanding of certain aspects of motor disorders (Zaidi *et al*., 2016). The findings of this study show that haloperidol doses raised food intake and body weight much more than their control groups. Increased food intake and body weight are linked to aberrant leptin levels and obesity is linked to major health problems (Weston-Green *et al*., 2008). On haloperidol-induced increased food consumption and changes in body weight, quercetin generated hypophagic (fig. 3) and weight-reducing effects (fig. 4). The mechanism behind quercetin's appetite management is assumed to be the regulation of leptin, which governs energy metabolism (Ostadmohammadi *et al*., 2019). Because haloperidol acts as a dopamine antagonist, suppressing dopaminergic

neurotransmission and altered movement stability indicates decreased locomotor activity in haloperidol-treated rats, the mechanism of antipsychotic-induced weight gain is unknown. It could be due to a stronger appetite and increased food intake due to abnormal leptin levels, reduced physical activity and altered movement stability (fig. 5). Since haloperidol acts as a dopamine antagonist, suppressing dopaminergic neurotransmission and altering movement stability, haloperidol-treated rats have lower locomotor activity. Antagonizing effects of haloperidol on D2 receptors resulted in decreased activity through lowering excitability (Zvezdochkina *et al*., 2004).Quercetin increases the stimulatory activity and suppresses the effects of haloperidol, as evidenced by the increased number of cage crossings and altered movement stability in the rats given quercetin. Anxiogenic behavior was observed in a behavioral test for assessing the psychological effects of haloperidol medication (fig. 6), as anxiety and depression are co-morbidities in patients with psychosis and haloperidol doses have been shown to reduce exploratory activity in animals (Haleem *et al*., 2007). Anxiogenic responses are linked to a lack of dopamine in the ventral tegmental region, which is linked to the mesocortical circuit (Halmi, 2019). Dopamine neurotransmission is thought to control motor activity and haloperidol dosages have been shown to disrupt this system and impair motor control. The inverted screen test was used to assess the neuromuscular strength of the animals and (fig. 7) demonstrates motor dysfunction followed by haloperidol therapy, indicating DIP symptoms since the animals receiving haloperidol treatment have less neuromuscular ability. The beam walking test is useful measure of coordination and balance using all fore limbs and detect motor deficits due to pharmacological manipulations (fig. 8) represent the motor deficits in rats treated with haloperidol doses decreases the muscle coordination and may reduce muscular strength, the results of present study is also supported by other studies in which mice models are used to assess the motor coordination (Saeed *et al*., 2017). The present study demonstrated that quercetin may be able to reverse the P.D. like symptoms if administered along with the drugs used for the treatment of P.D. The blockade of dopamine by the treatment of haloperidol may increase the dopamine turnover which lead to increase the production of hydrogen peroxide following degradation of dopamine by MAO-B, resulting in oxidative stress. Quercetin, as a plant polyphenol, has various pharmacological properties enable its use in many pathological conditions due to the presence of pro-oxidant properties, guards against the agents which leads to the development of ROS generation. It is reported to inhibit the MAO-B activity and enhance protective mechanism against excessive oxidative stress (Kabra *et al*., 2020).

CONCLUSION

The current study indicated that the prolonged use of neuroleptics is linked to movement disorders because they disrupt the dopaminergic system and decrease motor coordination. The effects of haloperidol in this study lowered the activity and resulted in motor-function impairment. Neuroleptics have also been linked to increase in food consumption, anxiogenic behavior and loss of motor coordination.The treatment of quercetin in haloperidol treated rats successfully reverses the alteration of the doses of haloperidol. It reduces food intake of animals and alleviate the anxiogenic behavior. The chronic treatment of quercetin further reduced the movement abnormalities in animal model of drug induced pseudo-Parkinson.

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