CHAPTER IV
RESULTS

1. Neuroprotective Effect of Conventional Quercetin Administration (Oral Administration) Against Parkinson's Like Symptoms Induced by 6-OHDA.

The current study showed that oral administration failed to show the significant changes on stereotype behaviors including grooming, licking and rearing as shown in table 1 and figure 5-7. The cognitive enhancing effect of quercetin was evaluated by using Morris water maze test as shown in table 2-3 and figure 8-9. Table 2 and figure 8 showed that vehicle produced no significant change on escape latency both before and after the lesion induced by 6-OHDA. Administration of quercetin at dose of 300 mg/kg BW significantly decreased escape latency at 7 days of treatment (p-value<.01; compared to vehicle and vehicle). Unfortunately, the prolonged treatment further to 14 days failed to show the significant changes of this parameter at all dosage range of this study although the reduction trend of escape latency was still observed. In addition, both L-dopa and vitamin C treated groups also did not show the significant change on escape latency.

It was found that the rats which subjected to vehicle administration and 6-OHDA injection showed markedly increased in escape latency time at 7 days after the lesion which indicated the impairment of spatial memory (p-value<.01; compared to control, compared to vehicle and compared to vehicle+NSS). This enhanced escape latency time was still be observed (p-value<.01; compared to control, p-value<.001 compared to vehicle and p-value<.05 compared to vehicle+NSS) as shown in table 2 and figure 8. Both L-dopa and vitamin C which served as the positive control in this study significantly reversed the enhanced escape latency induced by 6-OHDA at 7 days after the lesion induction and this significance was still observed until the end of experiment (p-value<.001 all; compared to vehicle+6-OHDA). At 7 days after lesion, the rats which subjected to quercetin pretreatment at doses of 100, 200 and 300 mg/kg BW at a period of 2 weeks before and continually treated until the day of assessment showed the significant decreased escape latency time (p-value<.05, .01 and .001

respectively; compared to vehicle+6-OHDA). When the treatment prolonged further to 14 days after the lesion induction, the significant changes were still observed (p-value<.001 all; compared to vehicle+6-OHDA).

The effect of quercetin on retention time was also investigated. Figure 9 showed that before lesion L-dopa significantly increased retention time at 7 days after treatment (p-value<.05; compared to vehicle) but this significance disappeared after 14 days of treatment. No significant increased in retention time was observed after the treatment of vitamin C and low dose of quercetin. Oral administration of quercetin at doses of 200 and 300 mg/kg BW produced significant increase retention time at 7 days after lesion (p-value<.05 all; compared to vehicle treated group). The prolonged treatment further to 14 days failed to show significant changes as shown in table 3 and figure 9.

It was found that 6-OHDA significantly decreased the retention time at 14 days of treatment (p-value<.01; compared to vehicle+NSS). Both vitamin C and L-dopa could attenuate the decreased retention time induced by 6-OHDA (p-value<.05 all; compared to vehicle+6-OHDA). Rats which previously treated with quercetin at dose of 300 mg/kg BW at a period of 2 weeks before the lesion induction and continually treated until the day of memory assessment could attenuate the decreased retention time since 7 days after lesion (p-value<.05; compared to vehicle+6-OHDA). When the treatments of quercetin at various doses were prolonged to 14 days after the lesion induction, all quercetin treated groups could produce the significant attenuation effect on the reduction of retention time (p-value<.05, .05 and .01 respectively; compared to vehicle+6-OHDA).

Evaluation of motor change following 6-OHDA administration was assessed by using elevated body swing test. The results showed that 6-OHDA significantly increased the percentage of left biased swing both at 7 and 14 days after the lesion induction which indicated the abnormal movement in rats as shown in table 4 and figure 10. L-dopa significantly attenuated the left swing induced by 6-OHDA at 7 and 14 days after the lesion induction while the significant change induced by vitamin C was observed at 14 days after the lesion induction (p-value<.05 all; compared to vehicle+6-OHDA). High dose of quercetin could attenuate the left bias induced by

6-OHDA at 7 days after the lesion (p-value<.05 all; compared to vehicle+6-OHDA) and this significance was still observed at 14 days after lesion (p-value<.01; compared to vehicle+6-OHDA). At 14 days after the lesion induction, rats subjected to quercetin treatment both at 100 and 200 mg/kg BW also produced significant attenuation on this parameter (p-value<.05 all; compared to vehicle+6-OHDA).

In addition, a rotational behavior was also evaluated. Table 5 and figure 11 showed that both L-dopa and vitamin C could significantly decrease the rotational behavior at 14 days after lesion. At 7 days after the lesion induction rats subjected to quercetin treatment at dose of 300 mg/kg significantly decreased rotational behavior (p-value<.05; compared to vehicle+6-OHDA). When the treatment was prolonged to 14 days after the lesion induction, the significant change of this parameter was observed after treatment with quercetin at doses of 200 and 300 mg/kg BW (p-value<.05 all; compared to vehicle+6-OHDA).

2. Neuroprotective Effect of Transdermal Zein Based Quercetin Nanofiber Patch Against Parkinson's like Symptoms Induced by 6-OHDA.

In order to enhance the delivery system and to avoid the rapid fluctuation of the substance level in the plasma which also influenced on the distribution of substance in the target tissue, the administration of quercetin loaded zein based nanofiber patch wad administered via the transdermal route. It was also found the before making the lesion, the rats which received quercetin loaded zein based nanofiber patch at concentration of 5, 10 and 15% showed no significant changes of stereotype behaviors including grooming, licking and rearing as shown in table 6 and figure 12-14. After lesion, the similar pattern of changes was still observed.

The effect of quercetin loaded zein based nanofiber patch on spatial memory was also investigated. The current data showed that quercetin loaded nanofiber patch at concentration of 15% showed the significant decrease escape latency time (p-value<.05; compared to zein+6-OHDA) at 14 days of treatment before the induction of lesion. After the administration of 6-OHDA in to substantia nigra, the escape latency time of rat subjected to zein based nanofiber patch plus 6-OHDA decreased significantly at 14 days after treatment (p-value<.05; compared to control).

Surprisingly, the quercetin loaded zein based nanofiber patch at concentration of 5, 10 and 15% showed the significant decrease in escape latency time (p-value<.05 all; compared to zein+6-OHDA) as shown in table 7 and figure 15. However, it was found that both zein based nanofiber and quercetin loaded zein based nanofiber patch did not produce the significant change on retention time before producing the lesion. However, after the lesion induction, quercetin loaded zein based nanofiber patch significantly increased retention time at 14 days post-lesion (p-value<.05; compared to zein+6-OHDA) while no significant change was observed in other treatment groups as shown in table 8 and figure 16.

The rats which received zein based nanofiber match and received the 6-OHDA administration significantly increased percentage of left biased swing both at 7 and 14 days post-lesion as shown in table 9 and figure 17. These changes were reversed by the quercetin at concentration 15% loaded zein based nanofiber (p-value<.05 all; compared to zein+6-OHDA). In addition the quercetin loaded nanofiber patch at the mentioned concentration also decreased the net rotation assessing via rotational behavior test as shown in table 10 and figure 18.

3. The Possible Underlying Mechanism of the Neuroprotective Effect of Quercetin.

Since quercetin could enhance the spatial memory in animal model of Parkinson's disease, the alterations of acetylcholinesterase (AChE) in hippocampus and striatum were also determined. The data obtained from this study showed that rats subjected to vehicle treatment and 6-OHDA significantly increased AChE in both mentioned area as shown in table 19 and figure 38-39. The administration of quercetin at dose 300 mg/kg BW significantly suppressed the activities of AChE in both area mentioned above (p-value<.05 all; compared to zein+6-OHDA). The effect of quercetin loaded zein based nanofiber on this parameter was also investigated. Table 28 and figure 59-60 showed that quercetin at concentration of 15% loaded zein based nanofiber could inhibit AChE activities in both hippocampus and striatum.

Based on the previous information that oxidative stress plays the crucial role on the pathophysiological of various conditions including Parkinson's disease, the effect of quercetin on oxidative marker was also investigated as shown in table 15 and figure

30-31. The rats which received vehicle plus 6-OHDA significantly increased the level of malondialdehyde (MDA) in both striatum (p-value<.01, .001 and .01; compared to control, vehicle and vehicle+NSS respectively) and hippocampus (p-value<.05, .01 and .01; compared to control, vehicle and vehicle+NSS respectively). Both L-dopa and vitamin C significantly attenuated the elevation of MDA in striatum (p-value<.001 compared to vehicle+6-OHDA) but no significant change was observed in hippocampus. Quercetin at doses of 100 and 200 mg/kg BW significantly decreased the elevation of MDA induced by 6-OHDA only in striatum (p-value<.001 all; compared to vehicle+6-OHDA). However, the high dose of quercetin could produce a significant reduction of MDA level in both striatum and hippocampus (p-value<.001 all; compared to vehicle+6-OHDA).

Table 16 and figure 32-33 showed that 6-OHDA decreased the activity of superoxide dismutase (SOD) in striatum (p-value<.01 all; compared to control, vehicle and vehicle+NSS respectively) but no significant change was observed in hippocampus. Both L-dopa and vitamin C could attenuated the decreased SOD both in striatum and in hippocampus (p-value<.01 all; compared to vehicle+6-OHDA). Oral administration of quercetin at doses of 100 and 200 mg/kg BW significantly attenuated the reduction of SOD induced by 6-OHDA only in striatum (p-value<.01 all; compared to vehicle+6-OHDA) while the high dose of quercetin could attenuate the reduction of SOD both in striatum (p-value<.01; compared to vehicle+6-OHDA) and in hippocampus (p-value<.05; compared to vehicle+6-OHDA).

It was found that glutathione peroxidase (GPx) activities in both striatum and hippocampus did not show significant changes after 6-OHDA lesion. Both L-dopa and vitamin C could enhance the activity of GPx in both area mentioned earlier (p-value<.05 all; compared to vehicle+6-OHDA). The oral administration of quercetin at dose 300 mg/kg BW also enhanced GPx activity in both area (p-value<.01, .05 respectively; compared to vehicle+6-OHDA) as shown in table 17 and figure 34-35.

The pattern of change of catalase (CAT) also showed the same manner. Table 18 and figure 36-37 showed that 6-OHDA failed to show significant changes on CAT in both striatum and hippocampus. Vitamin C and quercetin at doses of 100 and 200 mg/kg BW significantly enhanced CAT activity in striatum (p-value<.05 all;

compared to vehicle+6-OHDA) while L-dopa and quercetin at dose of 300 mg/kg BW produced significant elevation of CAT in both areas (p-value<.05 all; compared to vehicle+6-OHDA).

In addition to the alteration of oxidative markers, the neuron density in various brain areas was also determined. Table 11 and figure 19-23 demonstrated the reduction of neuron density in CA1, CA2, CA3 and dentate gyrus (p-value<.001, .001, .001 and .01 respectively; compared to vehicle+NSS). L-dopa could mitigate the reduction of neuron density induced by 6-OHDA in CA1, CA2 and dentate gyrus (p-value<.05, .01 and .05 respectively; compared to vehicle+NSS) while vitamin C could produce significant changes only in CA1 and CA2 (p-value<.05; compared to vehicle+6-OHDA). In addition, it was also demonstrated that quercetin at dose of 300 mg/kg BW could mitigate the reduction of neuron density in right substantia nigra (table 12 and figure 24-25) and right striatum (table 13 and figure 26-27) (p-value<.01 and .05 respectively; compared to vehicle+6-OHDA) while no significant change was observed after exposing to other treatments. The density of dopaminergic neuron in substantia nigra was also evaluated. Table 14 and figure 28-29 also demonstrated that 6-OHDA decreased the density of dopaminergic neuron in right substantia nigra (p-value<.001; compared vehicle+NSS). L-dopa and quercetin at dose of 300 mg/kg BW could mitigate the decreased dopaminergic neuron density in right substantia nigra (p-value<.05 and.01 respectively; compared to vehicle+6-OHDA).

The effect of quercetin loaded zein based nanofiber on oxidative markers was also investigated. Table 24 and figure 51-52 clearly demonstrated that rats which subjected to zein base nonofiber and 6-OHDA significantly increased the MDA level in both striatum and hippocampus (p-value<.05, .01 respectively; compared to control). Quercetin loaded zein based nanofiber at concentration of 10 and 15% could attenuate the elevation of MDA in striatum (p-value<.05, .01 respectively; compared to zein). However, only quercetin at concentration of 15% could mitigate an elevation of MDA in hippocampus (p-value<.01; compared to zein).

Table 25 and figure 53-54 showed that rats subjected to zein based nanofiber plus 6-OHDA decreased SOD activity both in striatum and hippocampus (p-value<.05 all; compared to control). It was found that quercetin 15% loaded nanofiber could

enhance SOD and GPx activities both in striatum (p-value<.05 and .01 respectively; compared to zein+6-OHDA) and in hippocampus (p-value<.05 all; compared to zein+6-OHDA) as shown in table 25-26 and figure 53-56. However, table 27 and figure 57-58 showed that quercetin at concentration of 15% loaded nanofiber could enhance CAT activity only in striatum (p-value<.05; compared to zein+6-OHDA).

The effect of quercetin loaded zein based nanofiber on the neuron density was also determined. Table 20 and figure 40-44 clearly revealed that zein based nanofiber plus 6-OHDA could decrease the neuron density in all area of hippocampus (p-value<.001 all; compared to control). Quercetin loaded nanofiber at concentration of 10% could mitigate the reduction of neuron density only in CA1 (p-value<.05; compared to zein+6-OHDA) while quercetin loaded nanofiber at concentration of 15% produced significant changes in CA1 (p-value<.01; compared to zein+6-OHDA), CA2 (p-value<.01; compared to zein+6-OHDA), CA3 (p-value<.001; compared to zein+6-OHDA) and dentate gyrus (p-value<.05; compared to zein+6-OHDA). In addition, 6-OHDA also decreased the neuron density in right substantia nigra and striatum (p-value<.001 all; compared to control) as shown in table 21-22 and figure 45-48. These phenomena were mitigated by quercetin 15% loaded nanofiber (p-value<.05 all; compared to zein+6-OHDA). Moreover, quercetin 15% loaded nanofiber was also able to attenuate the decreased dopaminergic neuron in right substantia nigra (p-value<.01; compared to zein+6-OHDA) as shown in table 23 and figure 49-50.

4. Comparison of the Effect of Conventional and Transdermal Quercetin Administration.

Cognitive enhancing effect of oral quercetin administration in PD model was determined by assessing escape latency and retention time. It was found that the significant changes were observed in escape latency at 7 days of treatment and this effect was still existed until 2 weeks after 6-OHDA injection. The results of retention time were shown in the same pattern with escape latency. In transdermal route, the significant decrease in escape latency was observed after treatment quercetin

nanofiber for 14 days and only a significant was found after lesion for 2 weeks in rats subjected to quercetin nanofiber patch.

The significant of motor changes were observed in elevated body swing test and rotational behavior at day 7 and 14 after 6-OHDA injection. In transdermal route, the results of left biased swing showed in the same manner, the significant was observed after 6-OHDA injection for both 7 days and 14 days but the improvement of rotational behavior was found only after lesion for two week.

The results of neuron density showed that oral quercetin administration could attenuate neurodegeneration in all subregions of hippocampus, substantia nigra and striatum as same as the neurodegeneration of dopaminergic neuron stained by using tyrosine hydroxylase immunohistochemistry. In transdermal route, the improvement of neuron density was also observed in those three areas mentioned earlier.

The alteration of MDA and activity of scavenging enzymes were also determined and the results suggested that oral quercetin administration could decrease the MDA level, but increase the activity of SOD, GPx and CAT in striatum and hippocampus. In transdermal route, quercetin nanofiber could also decrease MDA level but increase SOD and GPx. The significant increased of CAT was observed only in striatum. In addition, quercetin administration via oral route could inhibit the activity of AChE in striatum and hippocampus and quercetin nanofiber could produce the same results.

In general, quercetin administration both oral and transdermal exert the neuroprotective effect against PD like symptom induced by 6-OHDA at the same manner but the most effective dose of quercetin conventional administration was 300 mg/kg BW, whereas quercetin concentration at 15% from zein-based polymer biodegradable polymer loaded with quercetin nanofiber was the most effective dose for transdermal administration. In order to compare the effect these two routes, quercetin nanofiber at 15% concentration was calculated to the unit of mg/kg from the area of nanofiber patch that given to the animal each day. It was found that quercetin at 15% concentration was equal to 3 mg/kg/day which is lower than oral dose 100 times. This is suggesting that transdermal route appears to be a novel route for drug delivery and could provide the beneficial effect at the same magnitude of oral route but has less toxic that might occur due to high intake amount.

Table 1 The effect of oral quercetin administration on stereotype behavior.

Group (Treatment)	Time point	Number (5 min)		
		Grooming	Rearing	Licking
Control	Single	3.250 ± 1.149	23.875 ± 8.441	0.375 ± 0.133
Vehicle	dose	2.571 ± 0.571	25.143 ± 3.203	0.286 ± 0.184
Vehicle + NSS		2.875 ± 0.743	23.000 ± 3.179	0.375 ± 0.263
Vehicle + 6-OHDA		2.889 ± 0.423	23.000 ± 2.444	0.444 ± 0.338
QC100 + 6-OHDA		3.333 ± 0.333	20.444 ± 2.709	0.444 ± 0.242
QC200 + 6-OHDA		2.889 ± 0.261	24.333 ± 2.034	0.556 ± 0.242
QC300 + 6-OHDA		2.778 ± 0.222	21.778 ± 1.998	0.444 ± 0.176
L-dopa + 6-OHDA		2.889 ± 0.484	22.111 ± 2.611	0.778 ± 0.278
Vitamin C + 6-OHDA		3.778 ± 0.324	19.889 ± 2.208	1.000 ± 0.373
Control	Day 7	2.750 ± 0.972	16.625 ± 5.878	0.500 ± 0.177
Vehicle		3.286 ± 0.474	19.571 ± 3.415	1.429 ± 0.612
Vehicle + NSS		3.125 ± 0.718	15.125 ± 2.722	0.375 ± 0.263
Vehicle + 6-OHDA		3.444 ± 0.530	16.444 ± 2.346	0.778 ± 0.278
QC100 + 6-OHDA		3.667 ± 0.816	19.556 ± 4.083	0.778 ± 0.547
QC200 + 6-OHDA		4.000 ± 0.527	17.111 ± 3.339	0.889 ± 0.539
QC300 + 6-OHDA		3.222 ± 0.547	18.667 ± 3.536	0.889 ± 0.423
L-dopa + 6-OHDA		3.556 ± 0.648	22.444 ± 3.548	0.889 ± 0.455
Vitamin C + 6-OHDA		4.444 ± 0.648	18.444 ± 3.193	1.000 ± 0.408
Control	Day14	3.750 ± 1.326	19.750 ± 6.983	0.500 ± 0.177
Vehicle		2.429 ± 0.429	20.429 ± 3.497	0.429 ± 0.202
Vehicle + NSS		2.500 ± 0.423	18.500 ± 2.706	0.250 ± 0.164
Vehicle + 6-OHDA		2.778 ± 0.364	20.111 ± 3.747	0.556 ± 0.242
QC100 + 6-OHDA		3.667 ± 0.471	22.556 ± 3.606	0.222 ± 0.222
QC200 + 6-OHDA		3.222 ± 0.364	16.889 ± 2.330	0.333 ± 0.167
QC300 + 6-OHDA		3.333 ± 0.601	19.889 ± 2.010	0.222 ± 0.147
L-dopa + 6-OHDA		3.444 ± 0.338	21.222 ± 3.752	0.556 ± 0.242
Vitamin C + 6-OHDA		3.444 ± 0.835	14.556 ± 3.338	0.556 ± 0.294

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. They were determined stereotype behavior by using number of grooming, rearing and licking as indices. Data were presented as mean ± S.E.M. (n=8 per group).

Table 1 The effect of oral quercetin administration on stereotype behavior. (Cont.)

Group (Treatment)	Time point	Number (5 min)		
		Grooming	Rearing	Licking
Control	Day 7 post-lesion	2.750 ± 0.972	11.500 ± 4.066	0.625 ± 0.221
Vehicle		2.429 ± 0.481	12.286 ± 1.107	0.429 ± 0.297
Vehicle + NSS		2.000 ± 0.535	11.625 ± 1.224	0.375 ± 0.263
Vehicle + 6-OHDA		2.000 ± 0.500	12.375 ± 1.772	0.250 ± 0.250
QC100 + 6-OHDA		3.125 ± 0.479	8.875 ± 1.432	0.250 ± 0.250
QC200 + 6-OHDA		2.750 ± 0.366	9.375 ± 2.026	0.250 ± 0.164
QC300 + 6-OHDA		3.125 ± 0.295	8.625 ± 2.187	0.250 ± 0.164
L-dopa + 6-OHDA		3.125 ± 0.479	12.750 ± 1.373	0.250 ± 0.250
Vitamin C + 6-OHDA		3.250 ± 0.526	8.875 ± 0.833	0.875 ± 0.479
Control	Day14 post-lesion	2.875 ± 1.016	16.125 ± 5.701	0.250 ± 0.088
Vehicle		3.000 ± 0.617	15.143 ± 3.622	0.429 ± 0.297
Vehicle + NSS		2.250 ± 0.590	12.375 ± 0.999	0.125 ± 0.125
Vehicle + 6-OHDA		2.250 ± 0.491	14.750 ± 2.763	0.000 ± 0.000
QC100 + 6-OHDA		3.500 ± 0.732	13.250 ± 2.085	0.375 ± 0.263
QC200 + 6-OHDA		3.125 ± 0.398	15.500 ± 3.684	0.500 ± 0.378
QC300 + 6-OHDA		3.250 ± 0.412	11.875 ± 2.594	0.250 ± 0.164
L-dopa + 6-OHDA		3.750 ± 0.726	11.625 ± 2.507	0.500 ± 0.500
Vitamin C + 6-OHDA		3.500 ± 0.327	10.000 ± 1.512	0.625 ± 0.324

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. They were determined stereotype behavior by using number of grooming, rearing and licking as indices. Data were presented as mean ± S.E.M. (n=8 per group).

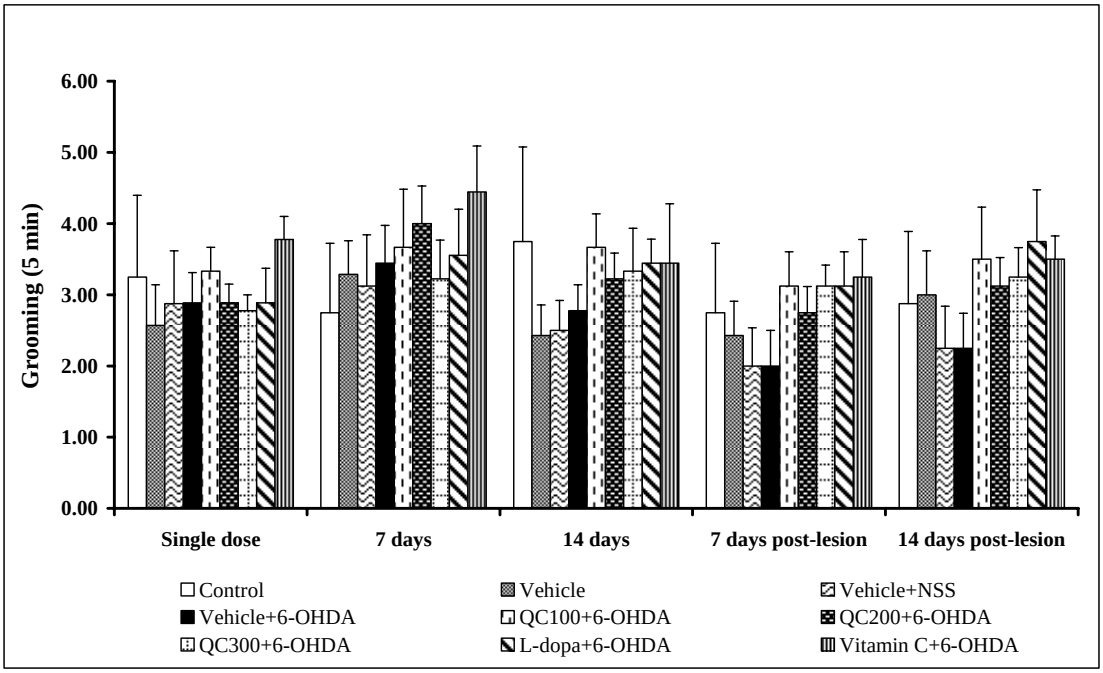


Figure 5 The effect of oral quercetin administration on grooming. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=8 per group).

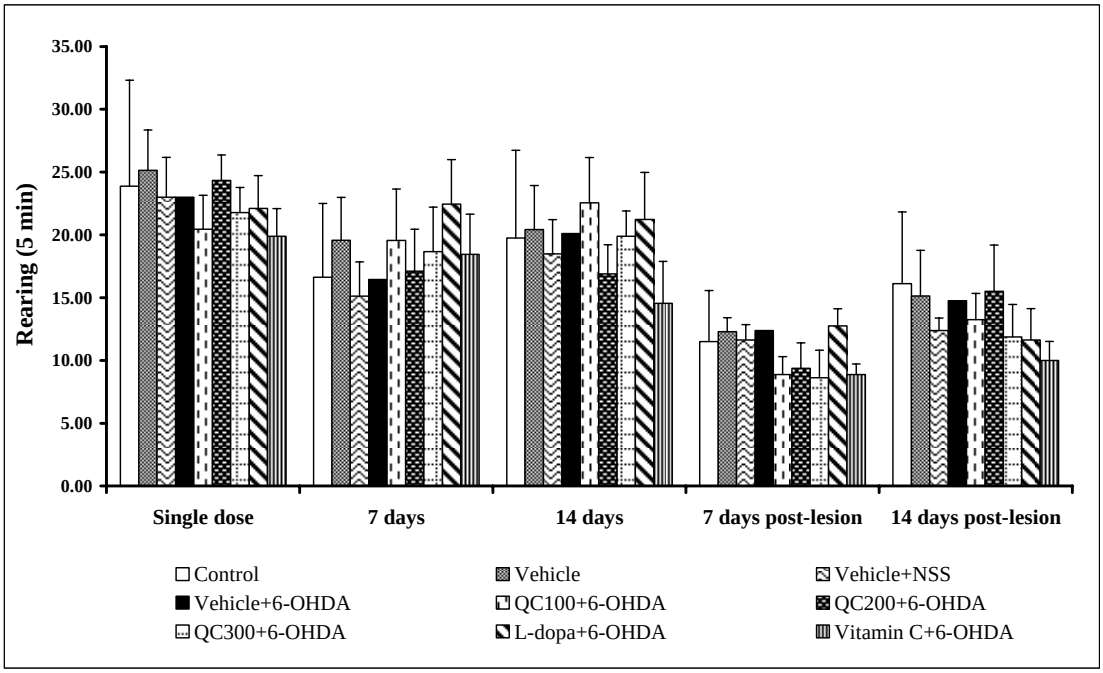


Figure 6 The effect of oral quercetin administration on rearing. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=8 per group).

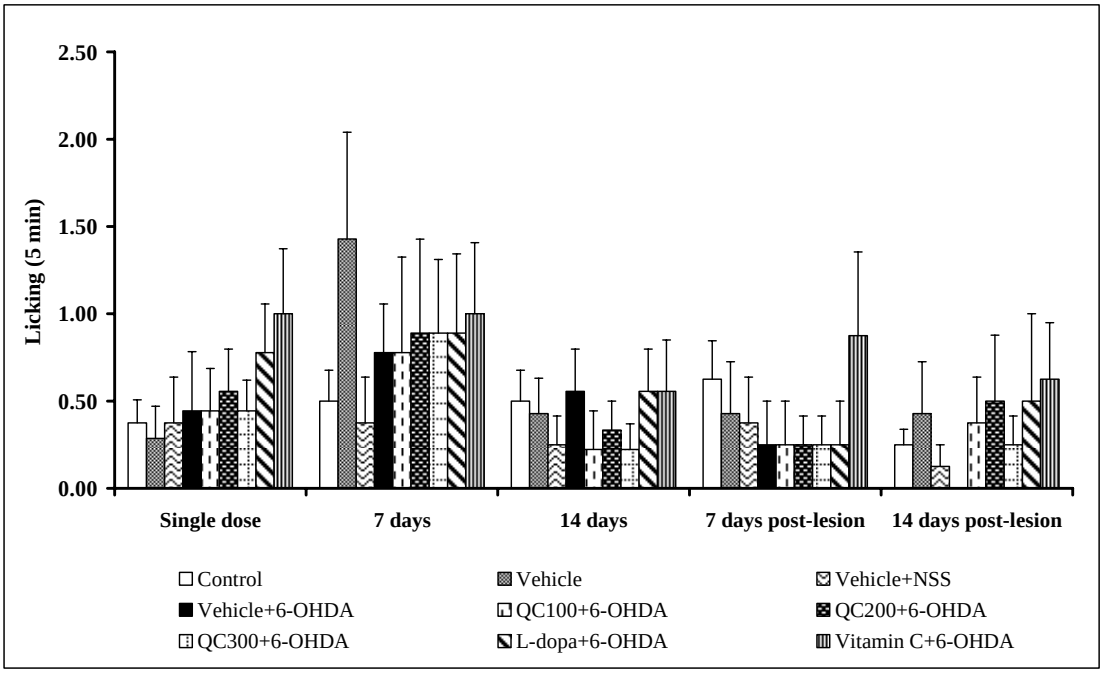


Figure 7 The effect of oral quercetin administration on licking. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=8 per group).

Table 2 The effect of oral quercetin administration on escape latency in Morris water maze test.

Group (Treatment)	Escape latency (second)		
	Before 6-OHDA injection		
	Single dose	Day 7	Day 14
Control	3.813 ± 0.877	3.438 ± 0.324	3.500 ± 0.333
Vehicle	4.821 ± 0.809	4.714 ± 0.252	4.250 ± 0.568
Vehicle + NSS	4.813 ± 0.586	4.844 ± 0.630	3.313 ± 0.544
Vehicle + 6-OHDA	4.722 ± 0.496	4.917 ± 1.051	3.306 ± 0.227
QC100 + 6-OHDA	4.028 ± 0.561	3.917 ± 0.514	3.167 ± 0.393
QC200 + 6-OHDA	3.972 ± 0.564	3.667 ± 0.417	3.361 ± 0.686
QC300 + 6-OHDA	3.278 ± 0.392	2.528 ± 0.202 aa, bb, ##	2.722 ± 0.287 a
L-dopa + 6-OHDA	4.000 ± 0.479	3.722 ± 0.376	3.528 ± 0.420
Vitamin C + 6-OHDA	4.056 ± 0.605	3.528 ± 0.394	3.278 ± 0.470

Group (Treatment)	After 6-OHDA injection	
	Day 7 post-lesion	Day 14 post-lesion
Control	2.813 ± 0.235	3.250 ± 0.418
Vehicle	3.714 ± 0.586	2.929 ± 0.607
Vehicle + NSS	3.688 ± 0.555	3.844 ± 0.988
Vehicle + 6-OHDA	5.781 ± 0.696 **, aa, bb	5.625 ± 0.391 **, aaa, b
QC100 + 6-OHDA	3.938 ± 0.639 #	2.688 ± 0.281 ###
QC200 + 6-OHDA	3.250 ± 0.218 ##	2.813 ± 0.182 ###
QC300 + 6-OHDA	2.656 ± 0.204 ###	2.719 ± 0.201 ###
L-dopa + 6-OHDA	2.719 ± 0.343 ###	2.875 ± 0.285 ###
Vitamin C + 6-OHDA	3.656 ± 0.689 ###	3.156 ± 0.467 ###

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. They were determined spatial memory by using Morris water maze and recorded escape latency as index. Data were presented as mean ± S.E.M. (n=8 per group).

**	p-value <0.01 compared with control
a	p-value <0.05 compared with vehicle
aa	p-value <0.01 compared with vehicle
aaa	p-value <0.001 compared with vehicle
b	p-value <0.05 compared with vehicle + NSS
bb	p-value <0.01 compared with vehicle + NSS

p-value <0.05 compared with vehicle + 6-OHDA

p-value <0.01 compared with vehicle + 6-OHDA

p-value <0.001 compared with vehicle + 6-OHDA

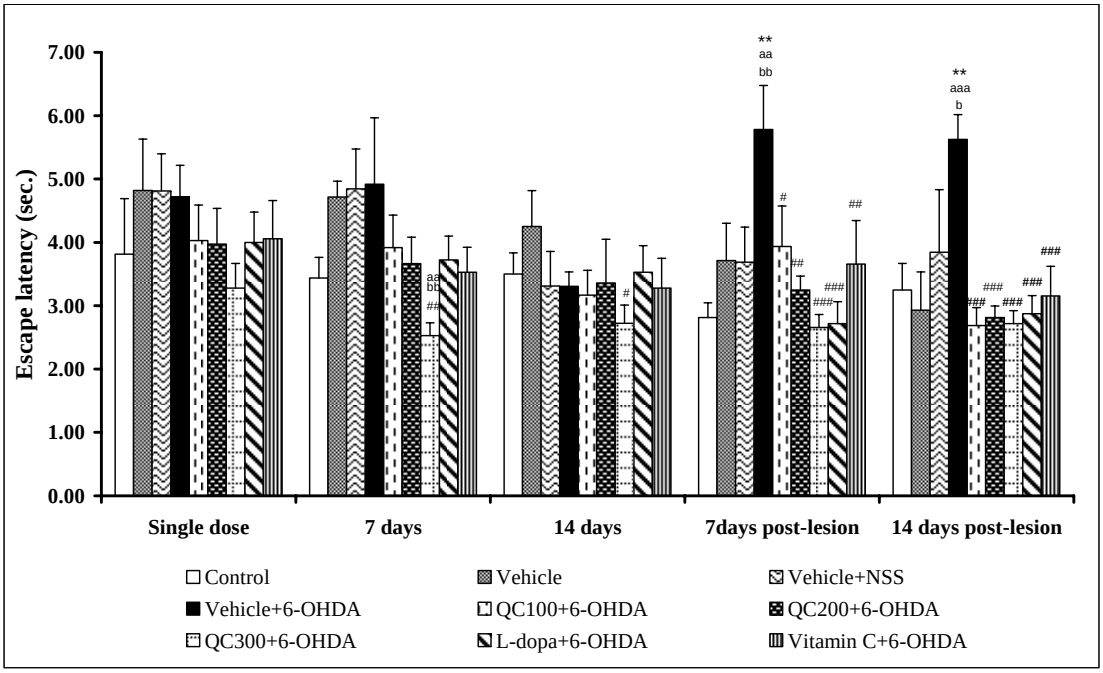


Figure 8 The effect of oral quercetin administration on escape latency in Morris water maze test. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=8 per group).

** p-value <0.01 compared with control

aa p-value <0.01 compared with vehicle

aaa p-value <0.001 compared with vehicle

b p-value <0.05 compared with vehicle + NSS

bb p-value <0.01 compared with vehicle + NSS

p-value <0.05 compared with vehicle + 6-OHDA

p-value <0.01 compared with vehicle + 6-OHDA

p-value <0.001 compared with vehicle + 6-OHDA

Table 3 The effect of oral quercetin administration on retention time in Morris water maze test.

Group (Treatment)	Retention time (second)		
	Before 6-OHDA injection		
	Single dose	Day 7	Day 14
Control	16.781 ± 0.876	16.344 ± 1.227	16.969 ± 1.576
Vehicle	16.036 ± 1.179	14.536 ± 0.812	17.250 ± 0.895
Vehicle + NSS	16.125 ± 1.709	15.938 ± 1.565	17.219 ± 0.856
Vehicle + 6-OHDA	16.806 ± 0.862	15.528 ± 1.524	14.944 ± 1.446
QC100 + 6-OHDA	19.194 ± 0.660	16.278 ± 0.706	18.000 ± 1.754
QC200 + 6-OHDA	18.056 ± 1.244	16.667 ± 2.515 [a]	17.750 ± 1.029
QC300 + 6-OHDA	19.028 ± 1.281	18.889 ± 1.255 [a]	18.861 ± 0.631[#]
L-dopa + 6-OHDA	18.472 ± 1.221	19.194 ± 1.232 [a]	16.083 ± 0.502
Vitamin C + 6-OHDA	16.694 ± 0.601	19.583 ± 1.149 [#]	18.361 ± 1.793

Group (Treatment)	After 6-OHDA injection	
	Day 7 post-lesion	Day 14 post-lesion
Control	17.875 ± 1.599	16.125 ± 1.463
Vehicle	16.643 ± 1.939	16.214 ± 0.925
Vehicle + NSS	17.625 ± 1.316	16.063 ± 0.904
Vehicle + 6-OHDA	13.844 ± 1.481 [*]	11.125 ± 1.061 [**, aa, bb]
QC100 + 6-OHDA	16.906 ± 1.626	14.438 ± 1.073 [#]
QC200 + 6-OHDA	16.906 ± 1.046	15.563 ± 1.425 [#]
QC300 + 6-OHDA	18.813 ± 1.175 [#]	15.563 ± 0.854 [##]
L-dopa + 6-OHDA	14.938 ± 1.314	16.375 ± 0.774 [#]
Vitamin C + 6-OHDA	15.094 ± 0.525	14.844 ± 1.062 [#]

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. They were determined spatial memory by using Morris water maze and recorded retention time as index. Data were presented as mean ± S.E.M. (n=8 per group).

*	p-value <0.05 compared with control
**	p-value <0.01 compared with control
a	p-value <0.05 compared with vehicle
aa	p-value <0.05 compared with vehicle
bb	p-value <0.01 compared with vehicle + NSS

p-value <0.05 compared with vehicle + 6-OHDA

p-value <0.01 compared with vehicle + 6-OHDA

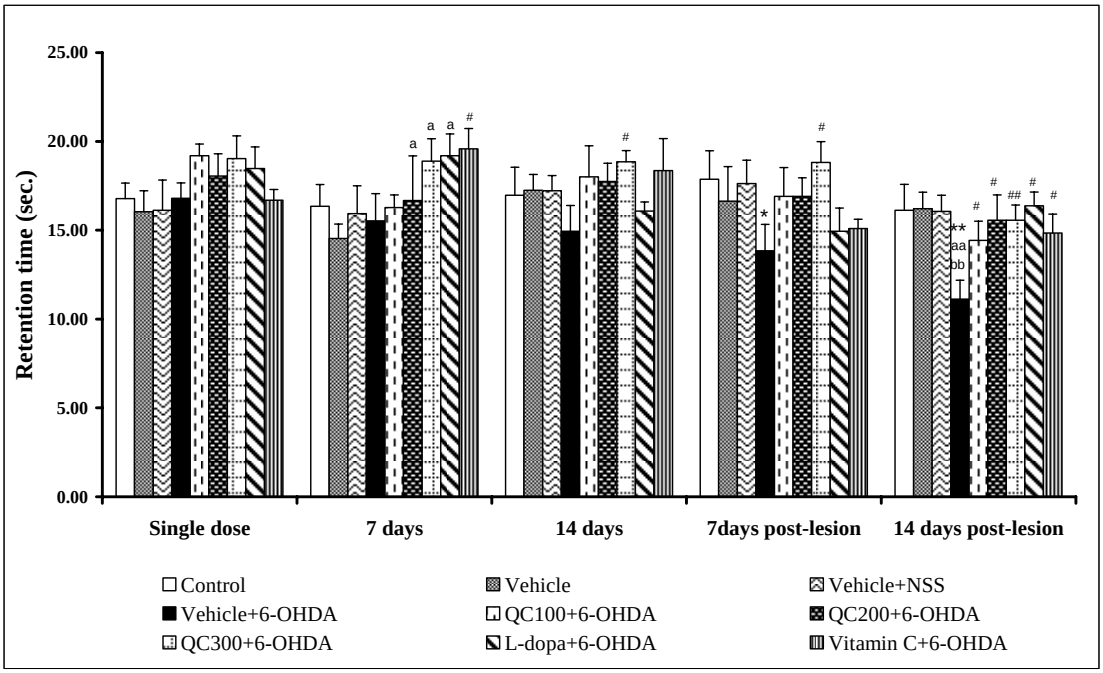


Figure 9 The effect of oral quercetin administration on retention time in Morris water maze test. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were represented as mean ± S.E.M. (n=8 per group).

* p-value <0.05 compared with control

** p-value <0.01 compared with control

a p-value <0.05 compared with vehicle

aa p-value <0.05 compared with vehicle

bb p-value <0.01 compared with vehicle + NSS

p-value <0.05 compared with vehicle + 6-OHDA

p-value <0.01 compared with vehicle + 6-OHDA

Table 4 The effect of oral quercetin administration on elevated body swing test after 6-OHDA injection.

Group (Treatment)	% Left biased swing (1 min)	
	Day 7 post-lesion	Day 14 post-lesion
Control	49.969 ± 4.487	51.077 ± 5.264
Vehicle	48.169 ± 2.458	53.727 ± 2.462
Vehicle + NSS	49.257 ± 3.509	49.193 ± 2.889
Vehicle + 6-OHDA	66.306 ± 5.030 *, a, b	65.597 ± 3.565 *, a, b
QC100 + 6-OHDA	57.250 ± 5.315	54.346 ± 3.971 #
QC200 + 6-OHDA	57.831 ± 4.393	53.916 ± 2.483 #
QC300 + 6-OHDA	52.725 ± 2.657 #	47.710 ± 4.887 ##
L-dopa + 6-OHDA	52.521 ± 2.632 #	53.061 ± 3.420 #
Vitamin C + 6-OHDA	55.193 ± 4.684	54.222 ± 5.139 #

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. They were determined motor change by using elevated body swing test and recorded the percentage of left biased swing in a minute as index. Data were presented as mean ± S.E.M. (n=8 per group).

* p-value <0.05 compared with control

a p-value <0.05 compared with vehicle

b p-value <0.05 compared with vehicle + NSS

\# p-value <0.05 compared with vehicle + 6-OHDA

\## p-value <0.01 compared with vehicle + 6-OHDA

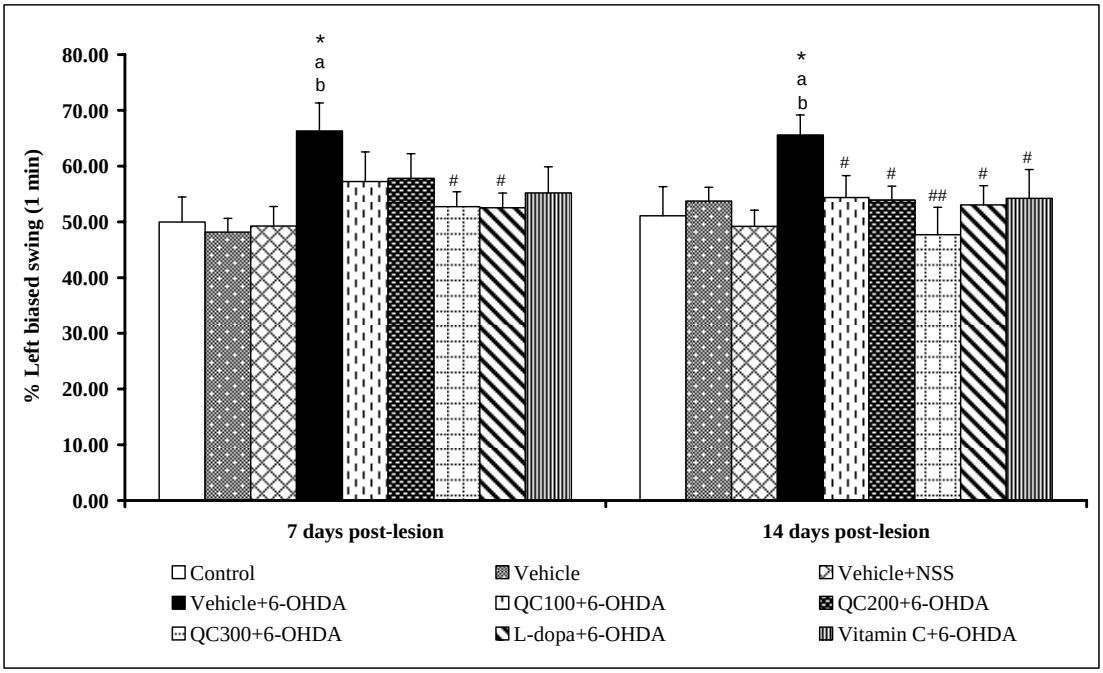


Figure 10 The effect of oral quercetin administration on elevated body swing test after 6-OHDA injection. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

a p-value <0.05 compared with vehicle

b p-value <0.05 compared with vehicle + NSS

\# p-value <0.05 compared with vehicle + 6-OHDA

\## p-value <0.01 compared with vehicle + 6-OHDA

Table 5 The effect of oral quercetin administration on rotational behavior after 6-OHDA injection.

Group (Treatment)	Total net rotation (45 min)	
	Day 7 post-lesion	Day 14 post-lesion
Vehicle + 6-OHDA	116.250 ± 10.528	120.625 ± 10.664
QC100 + 6-OHDA	80.625 ± 6.936	84.125 ± 11.686
QC200 + 6-OHDA	80.500 ± 15.383	79.125 ± 19.659 #
QC300 + 6-OHDA	75.750 ± 10.206 #	73.250 ± 7.930 #
L-dopa + 6-OHDA	80.625 ± 17.343	74.250 ± 15.142 #
Vitamin C + 6-OHDA	91.500 ± 12.476	75.250 ± 12.705 #

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. They were determined motor changes by using rotational behavior and recorded the total net rotation as index. Data were presented as mean ± S.E.M. (n=8 per group).

p-value <0.5 compared with vehicle + 6-OHDA

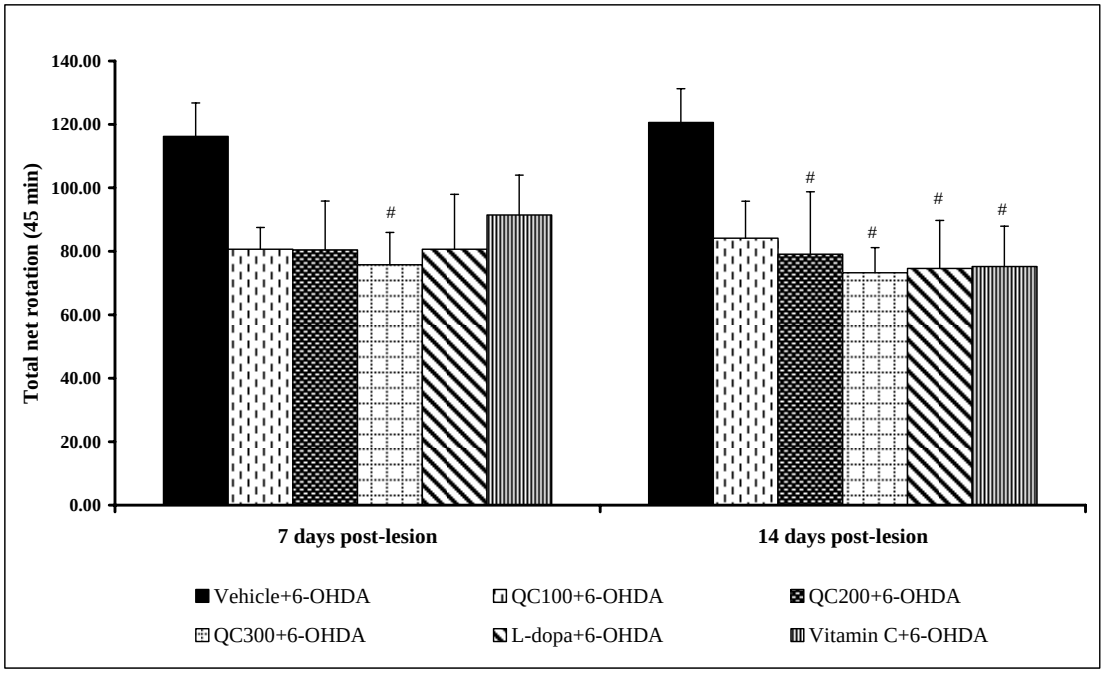


Figure 11 The effect of oral quercetin administration on rotational behavior after 6-OHDA injection. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=8 per group).

\# p-value <0.5 compared with vehicle + 6-OHDA

Table 6 The effect of transdermal quercetin administration on stereotype behavior.

Group (Treatment)	Time point	Stereotype behavior (number / 5 min)		
		Grooming	Rearing	Licking
Control	Day 1	4.125 ± 0.611	18.000 ± 2.053	1.875 ± 0.441
Zein + 6-OHDA		4.500 ± 0.756	19.500 ± 2.322	2.500 ± 0.655
QC5% + 6-OHDA		5.300 ± 0.790	14.800 ± 2.323	2.900 ± 0.605
QC10% + 6-OHDA		4.800 ± 0.814	14.800 ± 1.971	2.900 ± 0.586
QC15% + 6-OHDA		4.500 ± 0.619	20.300 ± 1.820	2.400 ± 0.400
Control	Day 7	2.750 ± 0.590	16.625 ± 3.267	1.250 ± 0.412
Zein + 6-OHDA		2.750 ± 0.412	15.625 ± 1.767	1.625 ± 0.625
QC5% + 6-OHDA		3.800 ± 0.573	13.500 ± 1.400	2.500 ± 0.373
QC10% + 6-OHDA		3.700 ± 0.448	13.800 ± 1.172	2.300 ± 0.367
QC15% + 6-OHDA		3.200 ± 0.573	13.800 ± 1.526	1.600 ± 0.499
Control	Day14	3.750 ± 0.590	15.000 ± 1.268	1.500 ± 0.535
Zein + 6-OHDA		3.250 ± 0.620	15.375 ± 2.329	1.375 ± 0.324
QC5% + 6-OHDA		3.500 ± 0.749	9.100 ± 1.656	1.900 ± 0.690
QC10% + 6-OHDA		2.700 ± 0.473	12.500 ± 1.447	1.700 ± 0.367
QC15% + 6-OHDA		2.600 ± 0.427	11.100 ± 1.378	18.00 ± 0.593
Control	Day 7 post-lesion	2.750 ± 0.412	11.500 ± 1.946	0.625 ± 0.375
Zein + 6-OHDA		2.625 ± 0.375	13.500 ± 2.557	0.500 ± 0.378
QC5% + 6-OHDA		1.900 ± 0.407	10.600 ± 1.222	0.900 ± 0.348
QC10% + 6-OHDA		2.000 ± 0.289	10.444 ± 1.069	0.444 ± 0.176
QC15% + 6-OHDA		2.222 ± 0.364	10.889 ± 1.285	0.333 ± 0.167
Control	Day14 post-lesion	2.875 ± 0.833	14.500 ± 0.732	0.750 ± 0.313
Zein + 6-OHDA		2.125 ± 0.479	10.500 ± 2.315	1.250 ± 0.366
QC5% + 6-OHDA		2.400 ± 0.427	10.900 ± 1.531	1.100 ± 0.314
QC10% + 6-OHDA		2.111 ± 0.351	12.000 ± 2.211	1.111 ± 0.351
QC15% + 6-OHDA		2.778 ± 0.364	11.111 ± 1.925	1.444 ± 0.444

Rats were treated with transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. They were determined stereotype behavior by using grooming, rearing and licking as the indices. Data were presented as mean ± S.E.M. (n=8 per group).

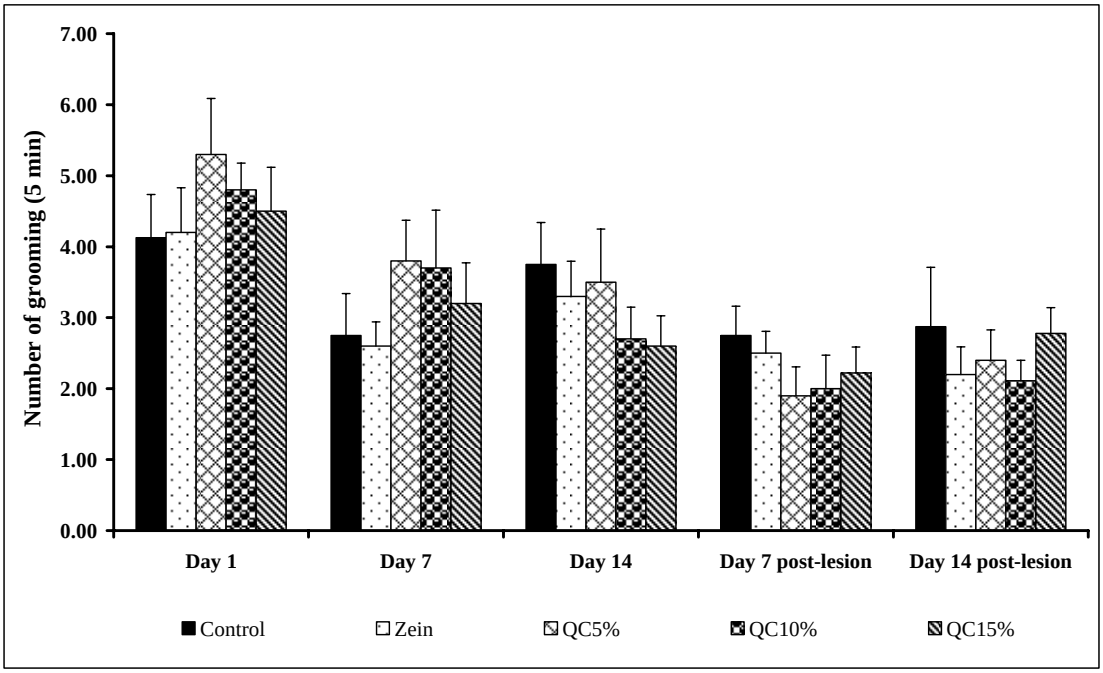


Figure 12 The effect of transdermal quercetin administration on grooming. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=8 per group).

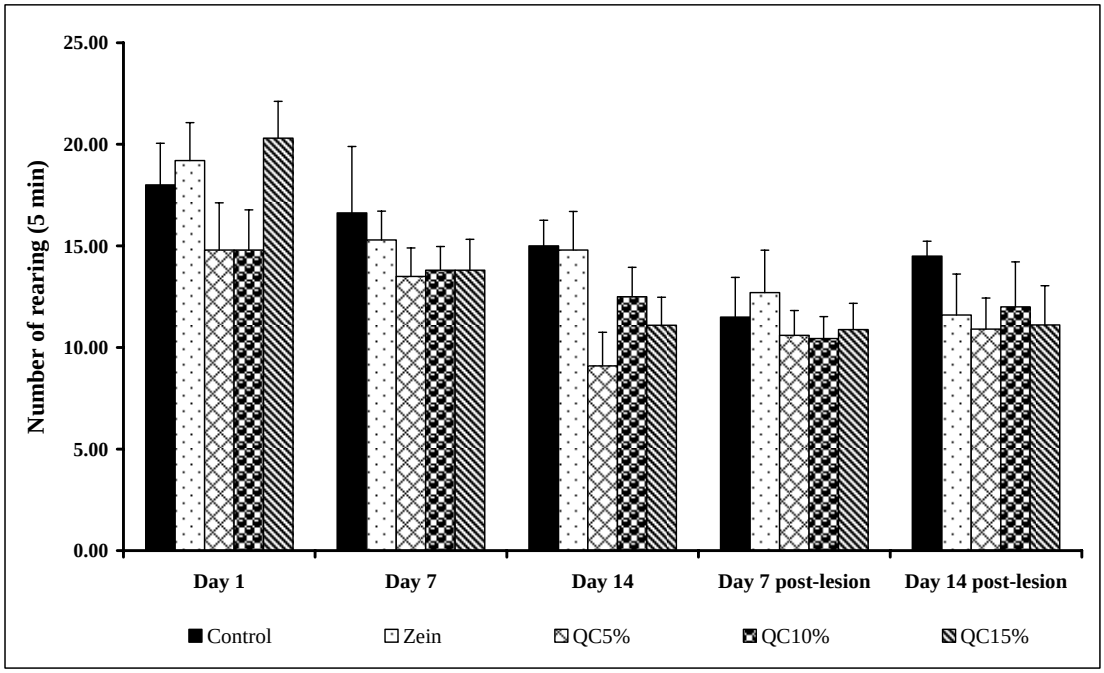


Figure 13 The effect of transdermal quercetin administration on rearing. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were represented as mean ± S.E.M. (n=8 per group)

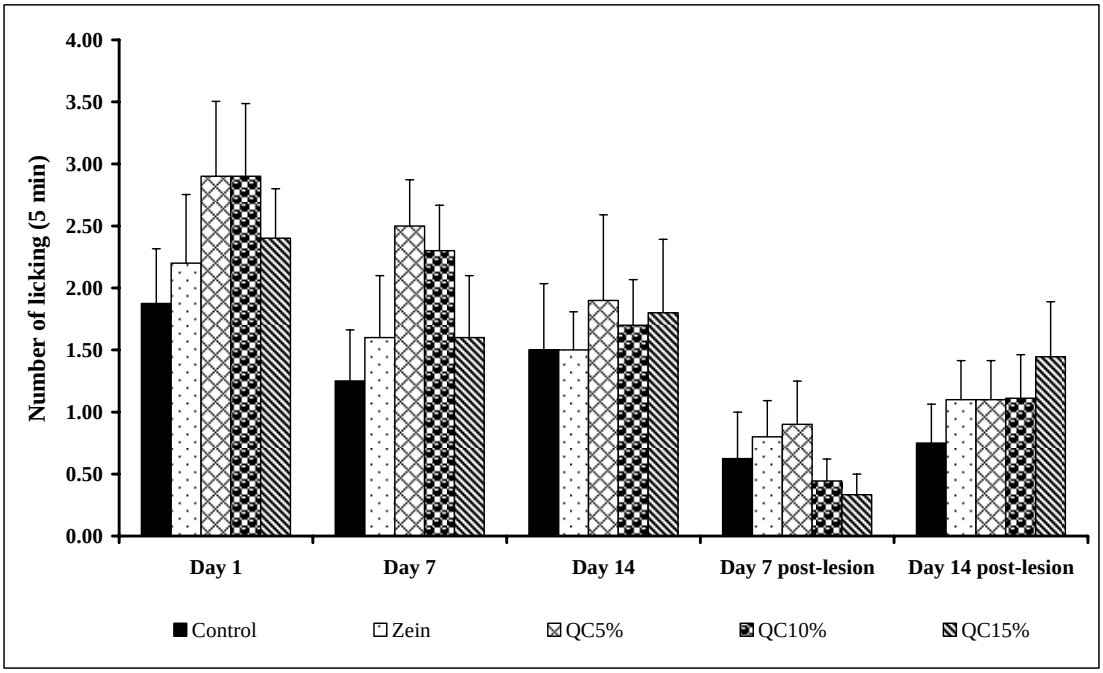


Figure 14 The effect of transdermal quercetin administration on licking. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=8 per group)

Table 7 The effect of transdermal quercetin administration on escape latency in Morris water maze test.

Group (Treatment)	Time point	Escape latency (second)
Control	Day 1	3.813 ± 0.930
Zein + 6-OHDA		4.281 ± 1.304
QC5% + 6-OHDA		4.350 ± 1.554
QC10% + 6-OHDA		3.575 ± 0.826
QC15% + 6-OHDA		3.500 ± 1.188
Control	Day 7	3.438 ± 0.343
Zein + 6-OHDA		4.031 ± 0.606
QC5% + 6-OHDA		4.350 ± 0.475
QC10% + 6-OHDA		4.350 ± 0.790
QC15% + 6-OHDA		3.450 ± 0.533
Control	Day 14	3.063 ± 0.282
Zein + 6-OHDA		3.594 ± 0.327
QC5% + 6-OHDA		3.075 ± 0.386
QC10% + 6-OHDA		2.925 ± 0.197
QC15% + 6-OHDA		2.625 ± 0.180 #
Control	Day 7 post-lesion	3.125 ± 0.303
Zein + 6-OHDA		5.906 ± 2.136
QC5% + 6-OHDA		3.100 ± 0.646 #
QC10% + 6-OHDA		2.944 ± 0.379 #
QC15% + 6-OHDA		2.556 ± 0.386 #
Control	Day 14 post-lesion	3.250 ± 0.443
Zein + 6-OHDA		5.656 ± 1.371 *
QC5% + 6-OHDA		3.225 ± 0.463 #
QC10% + 6-OHDA		3.222 ± 0.413 #
QC15% + 6-OHDA		2.861 ± 0.267 #

Rats were treated with transdermal zein based quercetin nanofiber patch at a period of 14 days before and after 6-OHDA injection. They were determined spatial memory and escape latency was recorded as the index. Data were presented as mean ± S.E.M. (n=8 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with zein + 6-OHDA

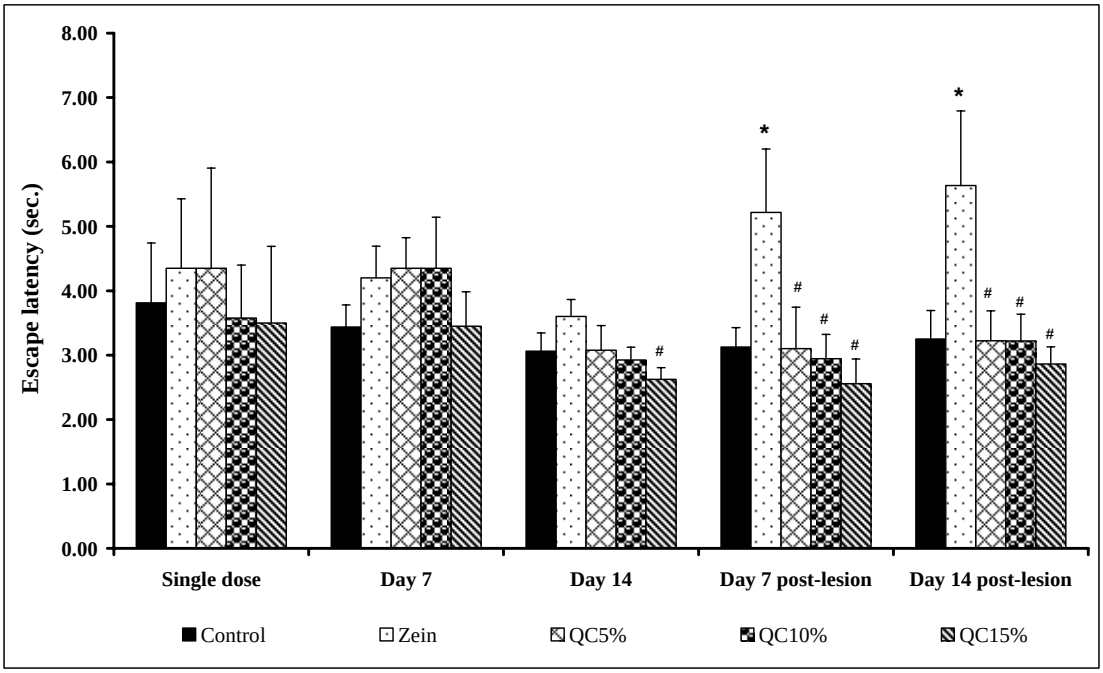


Figure 15 The effect of transdermal quercetin administration on escape latency in Morris water maze test. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=8 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with zein + 6-OHDA

Table 8 The effect of transdermal quercetin administration on retention time in Morris water maze test.

Group (Treatment)	Time point	Retention time (second)
Control	Day 1	16.781 ± 0.929
Zein + 6-OHDA		15.500 ± 1.023
QC5% + 6-OHDA		17.050 ± 0.580
QC10% + 6-OHDA		17.775 ± 1.176
QC15% + 6-OHDA		17.425 ± 0.512
Control	Day 7	18.094 ± 0.903
Zein + 6-OHDA		18.313 ± 1.492
QC5% + 6-OHDA		20.325 ± 0.673
QC10% + 6-OHDA		19.925 ± 1.254
QC15% + 6-OHDA		21.200 ± 1.294
Control	Day 14	21.656 ± 1.526
Zein + 6-OHDA		22.438 ± 2.311
QC5% + 6-OHDA		22.575 ± 1.094
QC10% + 6-OHDA		20.725 ± 1.363
QC15% + 6-OHDA		22.250 ± 1.114
Control	Day 7 post-lesion	24.156 ± 1.926
Zein + 6-OHDA		19.688 ± 0.889
QC5% + 6-OHDA		21.550 ± 1.749
QC10% + 6-OHDA		20.222 ± 1.775
QC15% + 6-OHDA		23.694 ± 1.525
Control	Day 14 post-lesion	21.563 ± 1.780
Zein + 6-OHDA		19.813 ± 1.376
QC5% + 6-OHDA		21.300 ± 1.505
QC10% + 6-OHDA		21.639 ± 1.298
QC15% + 6-OHDA		25.306 ± 2.087 #

Rats were treated with transdermal zein based quercetin nanofiber patch at a period of 14 days before and after 6-OHDA injection. They were determined spatial memory and retention time was recorded as the index. Data were presented as mean ± S.E.M. (n=8 per group).

\# p-value <0.05 compared with zein + 6-OHDA

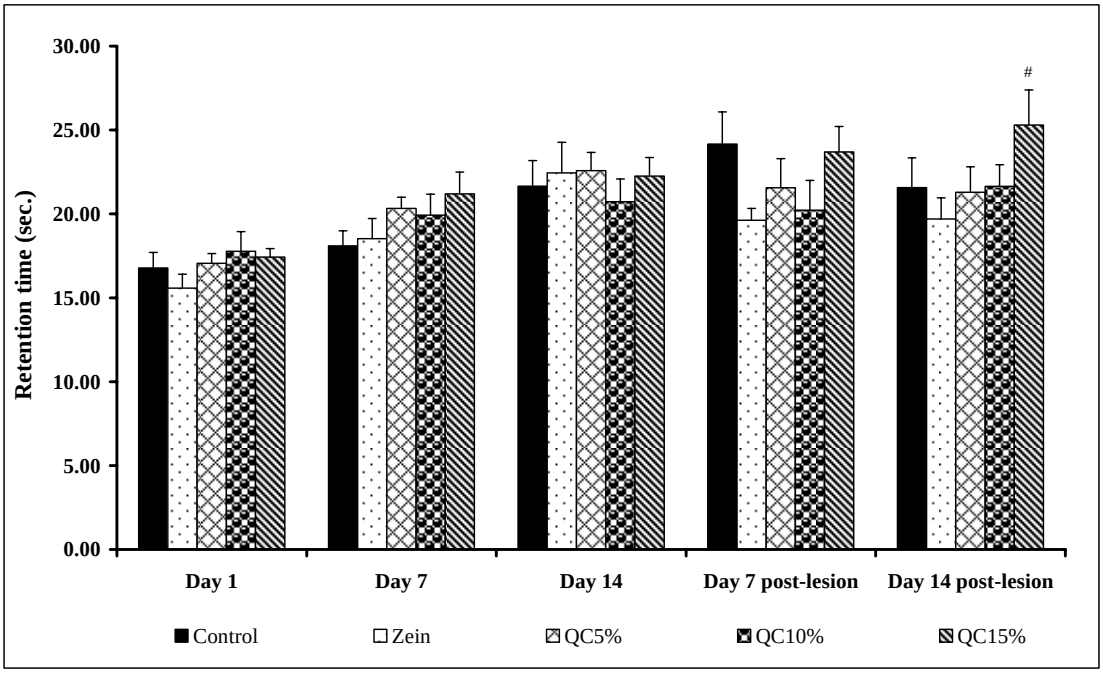


Figure 16 The effect of transdermal quercetin administration on retention time in Morris water maze test. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were represented as mean ± S.E.M. (n=8 per group).

\# p-value <0.05 compared with zein + 6-OHDA

Table 9 The effect of transdermal quercetin administration on elevated body swing test after 6-OHDA injection.

Group (Treatment)	Time point	% of left biased swing
Control	Day 7 post-lesion	49.969 ± 4.487
Zein + 6-OHDA		78.148 ± 4.703 ***
QC5% + 6-OHDA		71.998 ± 4.405
QC10% + 6-OHDA		70.234 ± 6.445
QC15% + 6-OHDA		58.129 ± 6.794 #
Control	Day 14 post-lesion	51.077 ± 5.264
Zein + 6-OHDA		71.342 ± 3.865 *
QC5% + 6-OHDA		61.546 ± 5.156
QC10% + 6-OHDA		56.201 ± 7.129
QC15% + 6-OHDA		51.219 ± 5.495 #

Rats were treated with transdermal zein based quercetin nanofiber patch at a period of 14 days before and after 6-OHDA injection. They were determined motor changes and the percentage of left biased swing was recorded as the index. Data were presented as mean ± S.E.M. (n=8 per group).

*** p-value <0.001 compared with control

p-value <0.05 compared with zein + 6-OHDA

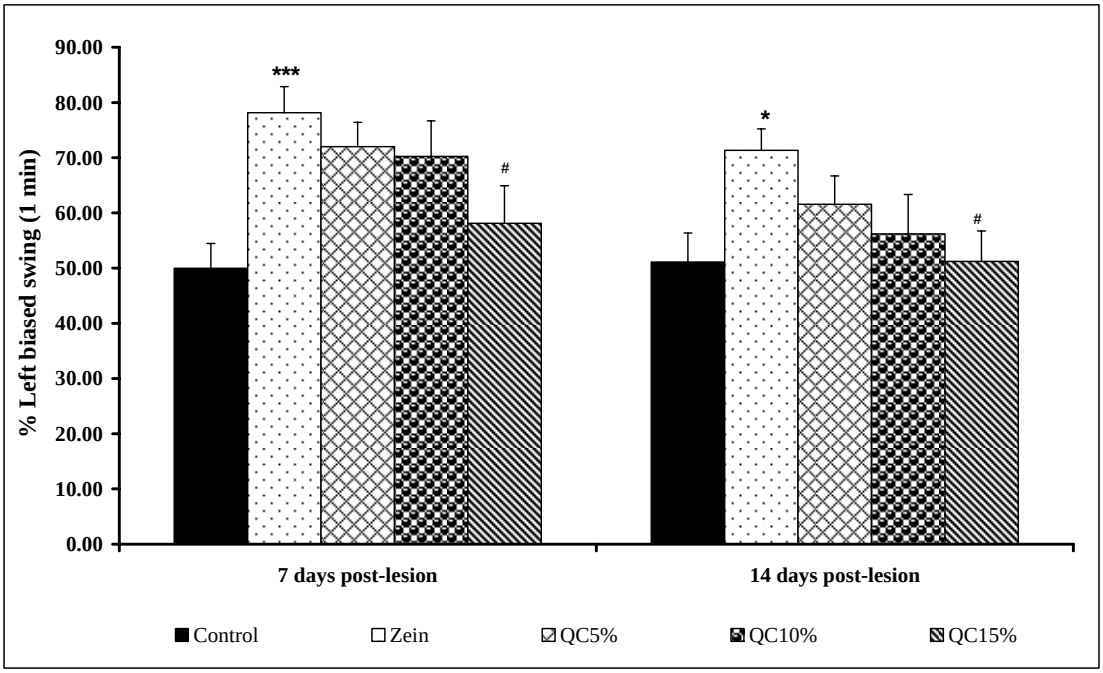


Figure 17 The effect of transdermal quercetin administration on elevated body swing test after 6-OHDA injection. Rats were received transdermal zein based quercetin nanofiber patch 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=8 per group).

*** p-value <0.001 compared with control

p-value <0.05 compared with zein + 6-OHDA

Table 10 The effect of transdermal quercetin administration on rotational behavior after 6-OHDA injection.

Group (Treatment)	Time point	Total net rotation (45 min)
Zein + 6-OHDA	7 days post-lesion	109.600 ± 13.507
QC5% + 6-OHDA		100.400 ± 10.637
QC10% + 6-OHDA		99.556 ± 15.208
QC15% + 6-OHDA		97.444 ± 13.848
Zein + 6-OHDA	14 day post-lesion	110.700 ± 13.939
QC5% + 6-OHDA		107.637 ± 6.214
QC10% + 6-OHDA		103.000 ± 10.259
QC15% + 6-OHDA		88.444 ± 15.565 #

Rats were treated with transdermal zein based quercetin nanofiber patch at a period of 14 days before and after 6-OHDA injection. They were determined motor changes and total net rotation was recorded as the index. Data were presented as mean ± S.E.M. (n=8 per group).

p-value <0.05 compared with zein + 6-OHDA

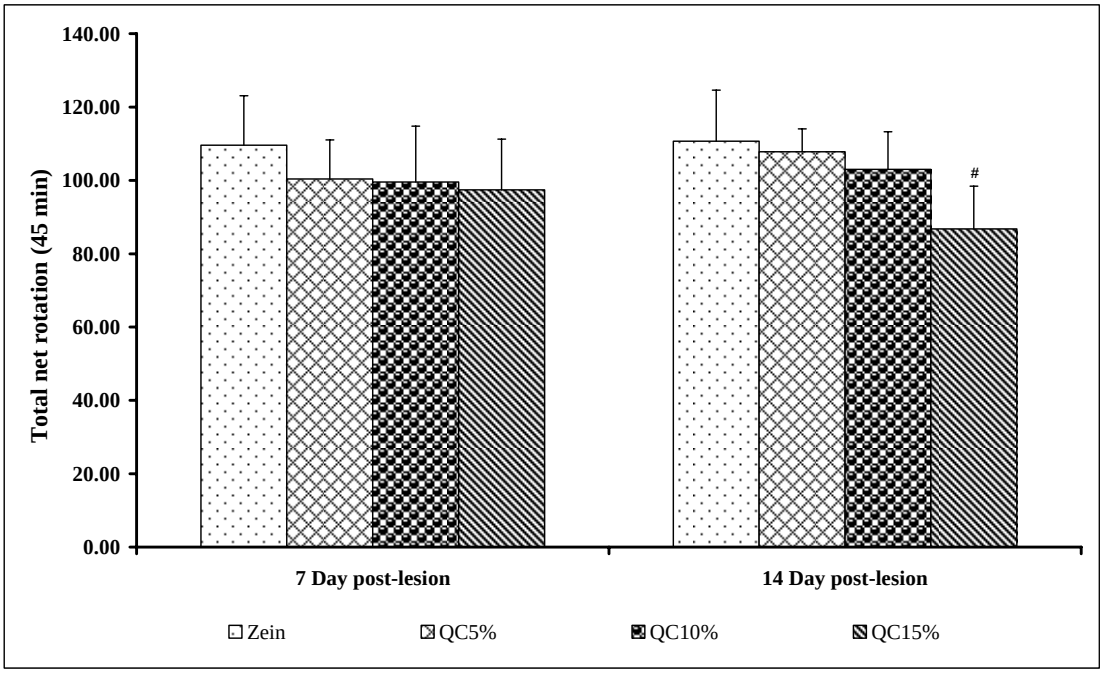


Figure 18 The effect of transdermal quercetin administration on rotational behavior after 6-OHDA injection. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were represented as mean ± S.E.M. (n=8 per group).

\# p-value <0.05 compared with zein + 6-OHDA

Table 11 The effect of oral quercetin administration on the density of survival neuron in right hippocampus.

Group (Treatment)	CA1 (cells/225μm^2)	CA2 (cells/225μm^2)	CA3 (cells/225μm^2)	Dentate gyrus (cells/225μm^2)
Control	82.200 ± 1.054	71.225 ± 1.120	69.650 ± 3.110	151.050 ± 4.074
Vehicle	80.950 ± 1.184	70.800 ± 1.153	65.225 ± 1.016	148.775 ± 1.948
Vehicle + NSS	80.500 ± 0.797	69.925 ± 0.740	64.850 ± 2.283	148.150 ± 1.428
Vehicle + 6-OHDA	63.425 ± 1.197 ***, aaa, bbb	60.050 ± 1.329 ***, aaa, bbb	55.725 ± 0.885 ***, aaa, bbb	138.600 ± 2.465 **, a, b
QC100 + 6-OHDA	67.850 ± 1.554 #	65.050 ± 1.44 #	59.575 ± 0.885	146.225 ± 3.161
QC200 + 6-OHDA	70.875 ± 1.358 ###	67.450 ± 1.178 ###	59.925 ± 1.366	148.175 ± 3.107 #
QC300 + 6-OHDA	71.225 ± 2.181 ###	67.700 ± 2.252 ###	61.925 ± 2.316 #	149.350 ± 4.479 #
L-dopa + 6-OHDA	67.175 ± 1.938 #	66.625 ± 1.900 ##	58.025 ± 1.358	149.600 ± 4.930 #
Vitamin C + 6-OHDA	67.825 ± 1.134 #	65.450 ± 1.852 #	56.425 ± 1.097	147.125 ± 2.059

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed and their brains were removed to determine the density of survival neuron in right hippocampus. Data were presented as mean ± S.E.M. (n=5 per group).

**	p-value <0.01 compared with control
***	p-value <0.001 compared with control
a	p-value <0.05 compared with vehicle
aa	p-value <0.01 compared with vehicle
aaa	p-value <0.001 compared with vehicle
b	p-value <0.05 compared with vehicle + NSS
bb	p-value <0.01 compared with vehicle + NSS
bbb	p-value <0.001 compared with vehicle + NSS
#	p-value <0.05 compared with vehicle + 6-OHDA
##	p-value <0.01 compared with vehicle + 6-OHDA

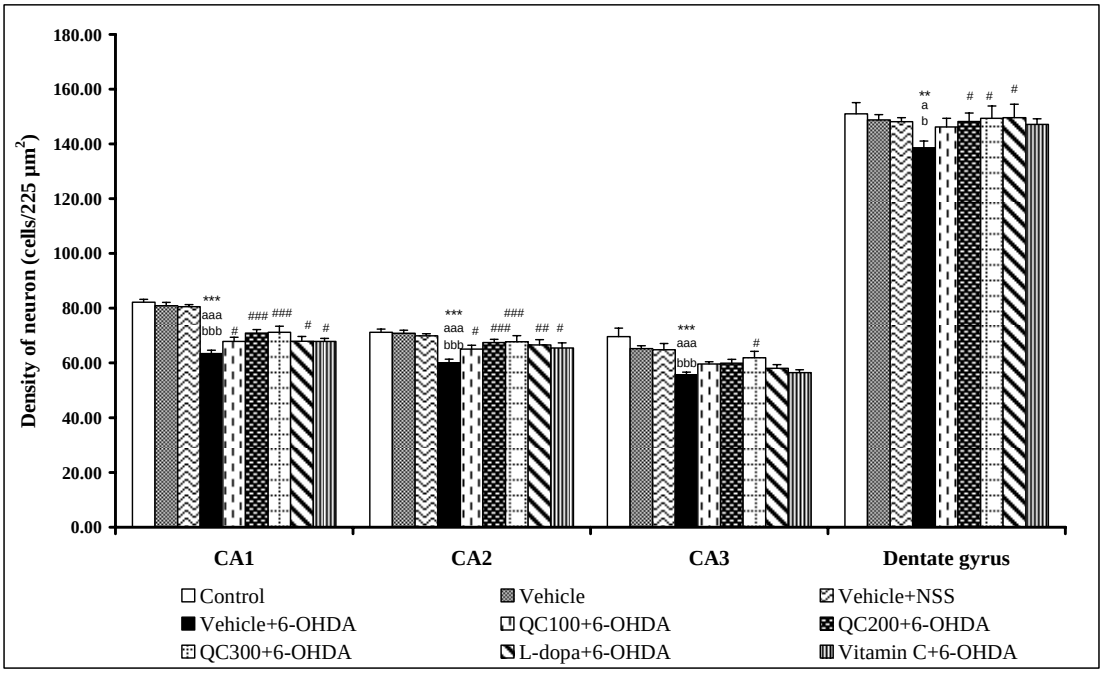
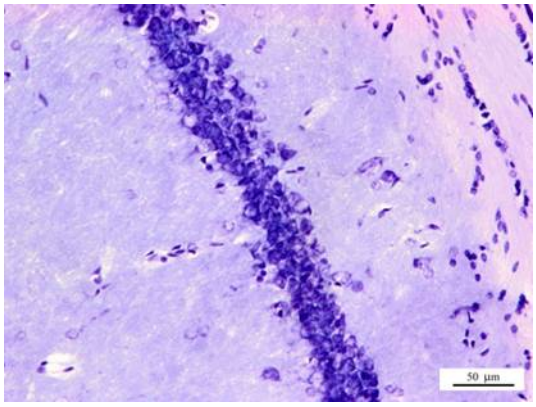


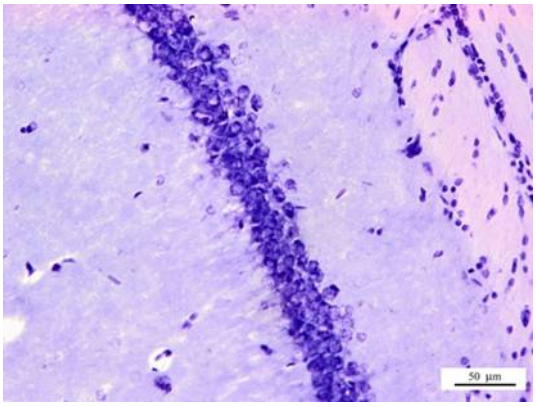
Figure 19 The effect of oral quercetin administration on the density of survival neuron in right hippocampus. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

**	p-value <0.01 compared with control
***	p-value <0.001 compared with control
a	p-value <0.05 compared with vehicle
aa	p-value <0.01 compared with vehicle
aaa	p-value <0.001 compared with vehicle
b	p-value <0.05 compared with vehicle + NSS
bb	p-value <0.01 compared with vehicle + NSS
bbb	p-value <0.001 compared with vehicle + NSS
#	p-value <0.05 compared with vehicle + 6-OHDA
##	p-value <0.01 compared with vehicle + 6-OHDA

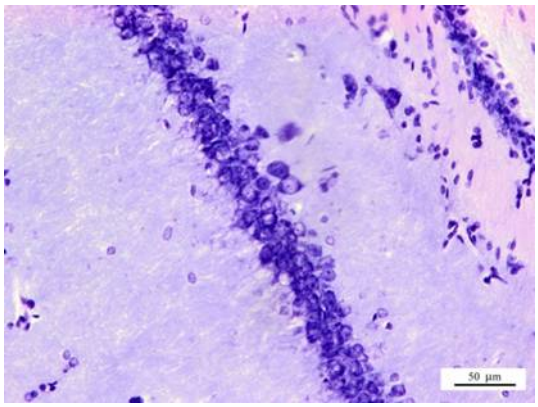
Control



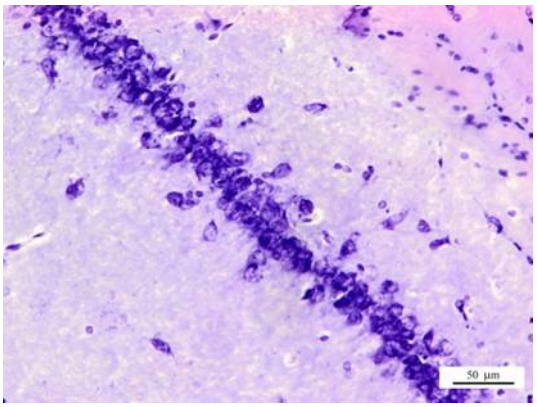
Vehicle



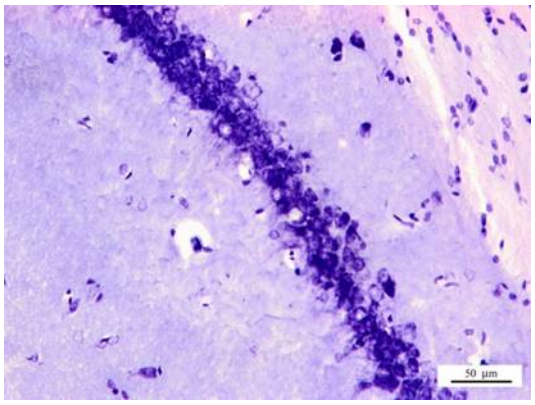
Vehicle + NSS



Vehicle + 6-OHDA



QC100 + 6-OHDA



QC200 + 6-OHDA

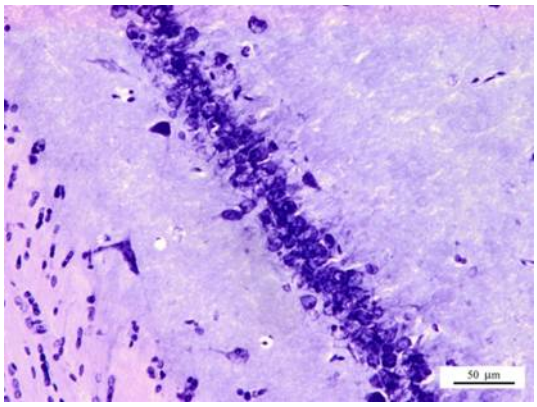
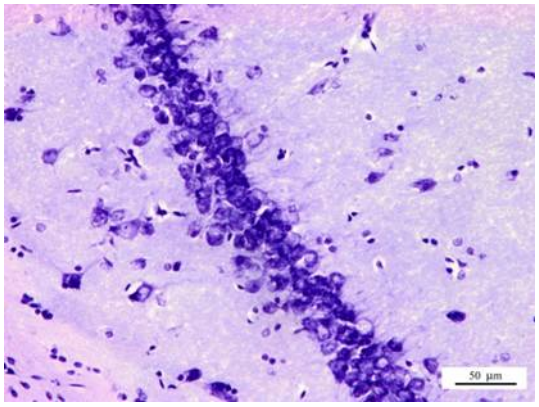
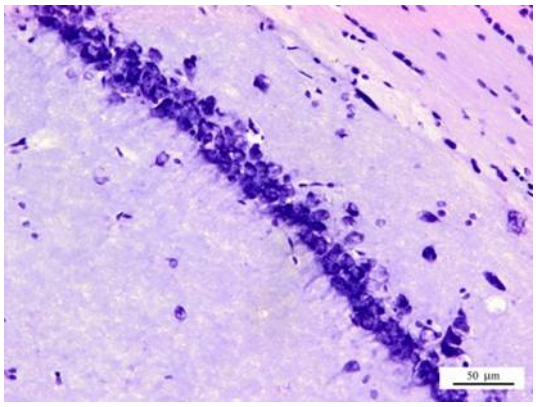


Figure 20 Photographs of coronal section of right hippocampus (CA1) stained with cresyl violet at 40X magnification.

QC300 + 6-OHDA



L-dopa + 6-OHDA



Vitamin C + 6-OHDA

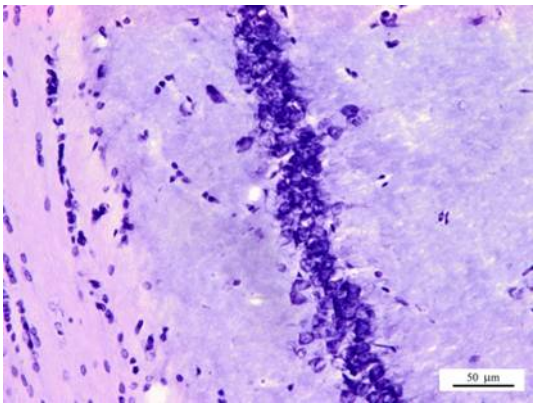
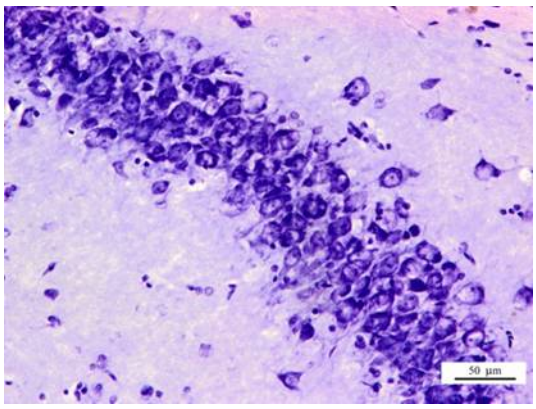
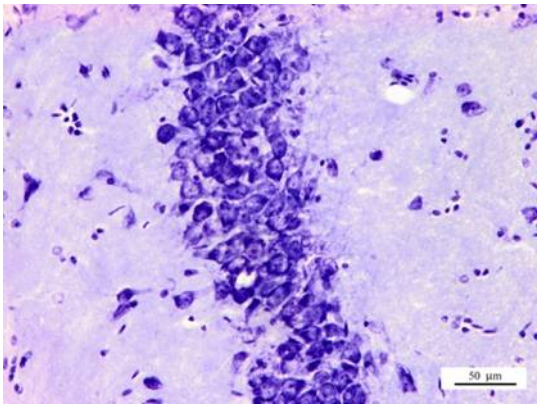


Figure 20 Photographs of coronal section of right hippocampus (CA1) stained with cresyl violet at 40X magnification. (Cont.)

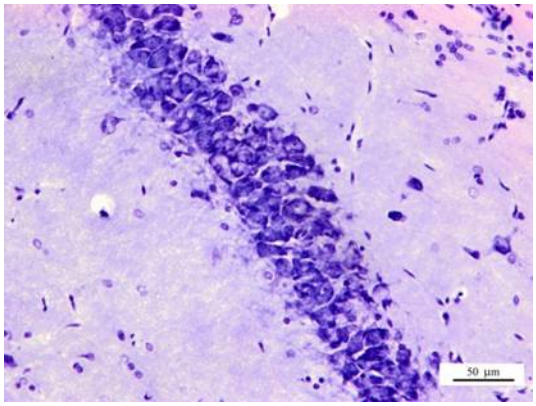
Control



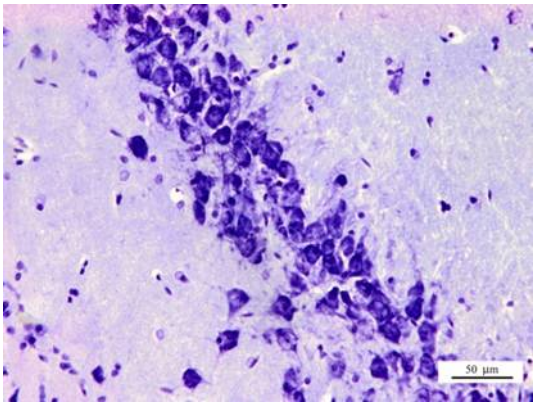
Vehicle



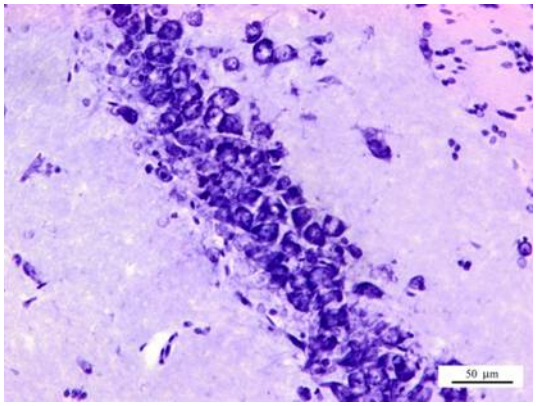
Vehicle + NSS



Vehicle + 6-OHDA



QC100 + 6-OHDA



QC200 + 6-OHDA

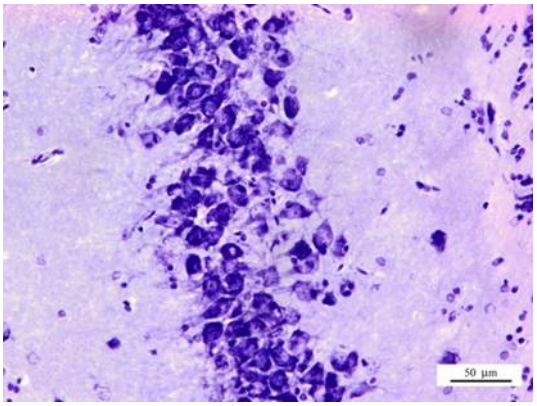
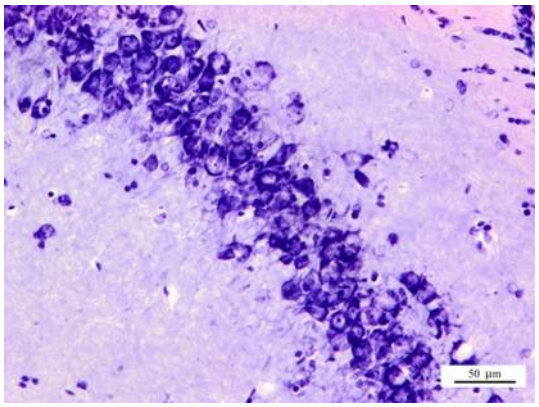
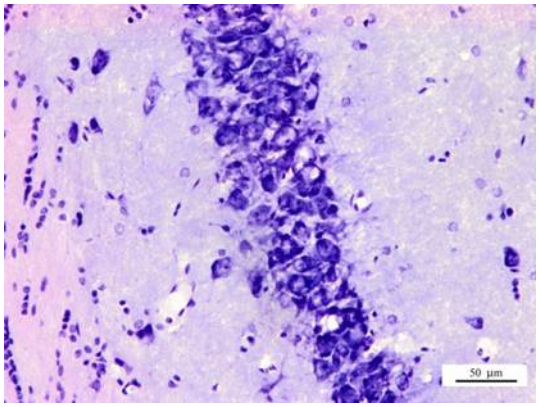


Figure 21 Photographs of coronal section of right hippocampus (CA2) stained with cresyl violet at 40X magnification.

QC300 + 6-OHDA



L-dopa + 6-OHDA



Vitamin C +6-OHDA

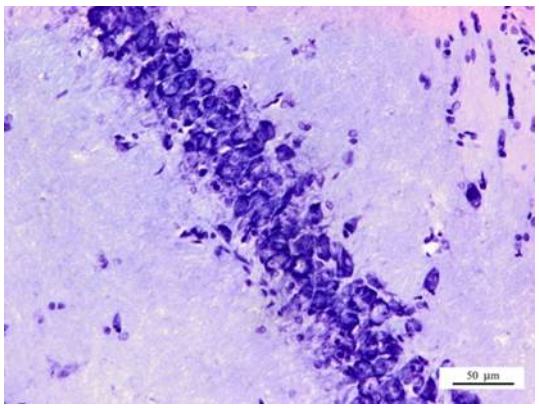
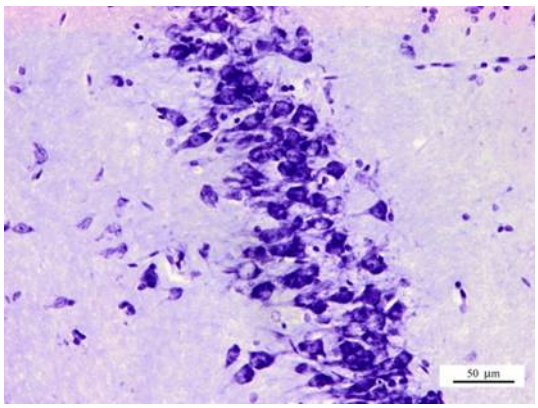
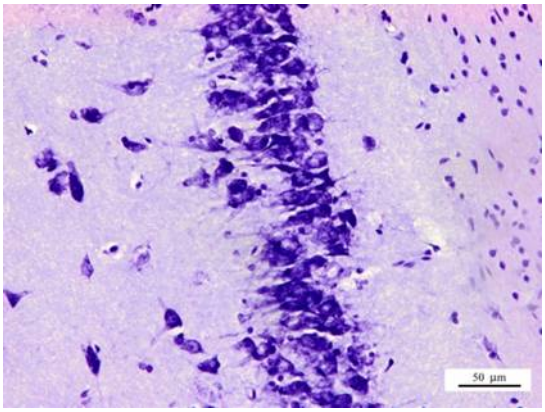


Figure 21 Photographs of coronal section of right hippocampus (CA2) stained with cresyl violet at 40X magnification. (Cont.)

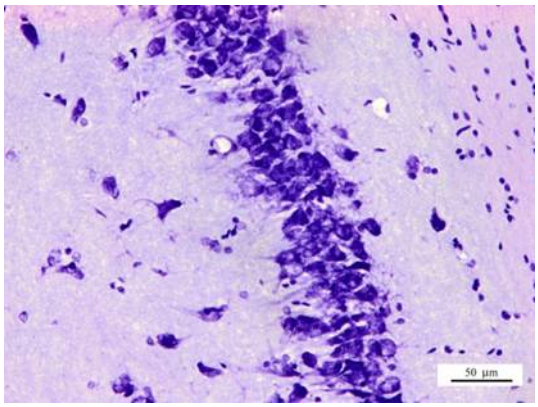
Control



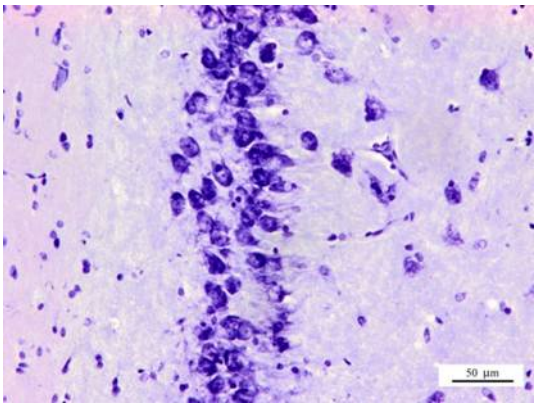
Vehicle



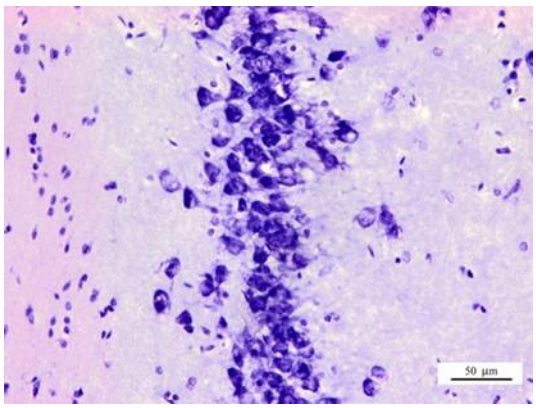
Vehicle + NSS



Vehicle + 6-OHDA



QC100 + 6-OHDA



QC200 + 6-OHDA

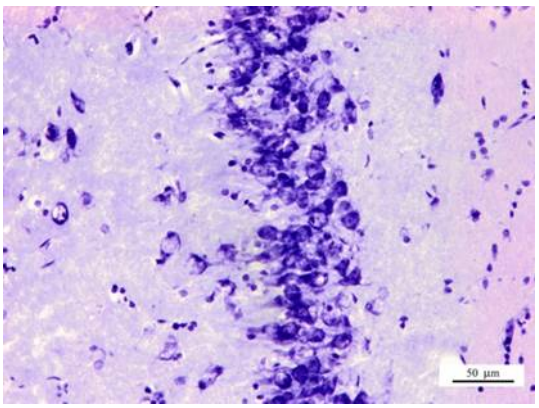
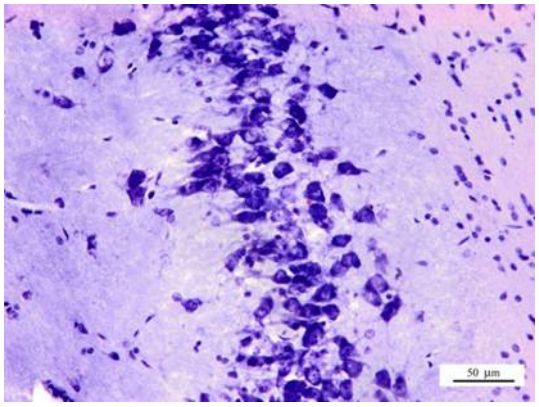
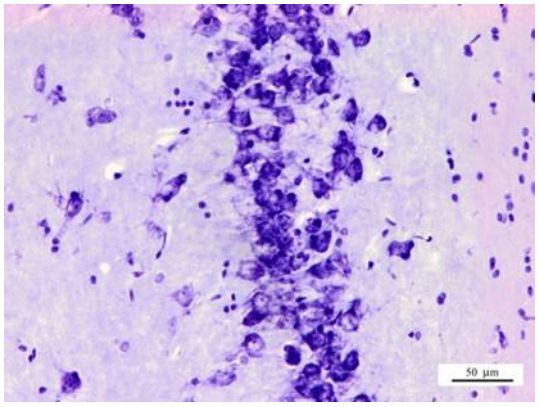


Figure 22 Photographs of coronal section of right hippocampus (CA3) stained with cresyl violet at 40X magnification.

QC300 + 6-OHDA



L-dopa + 6-OHDA



Vitamin C + 6-OHDA

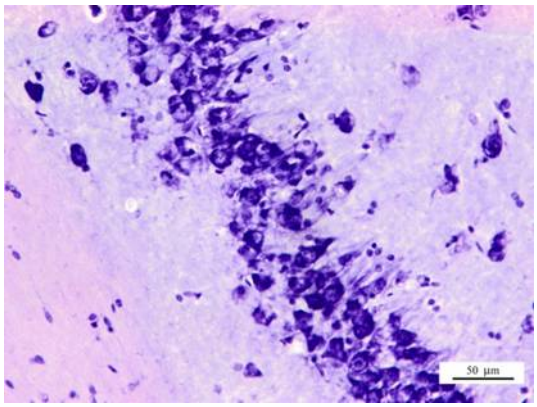
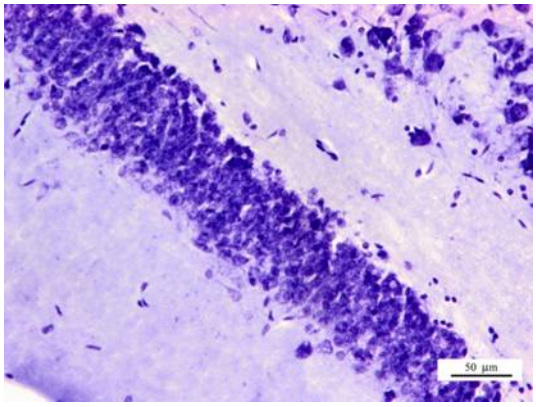
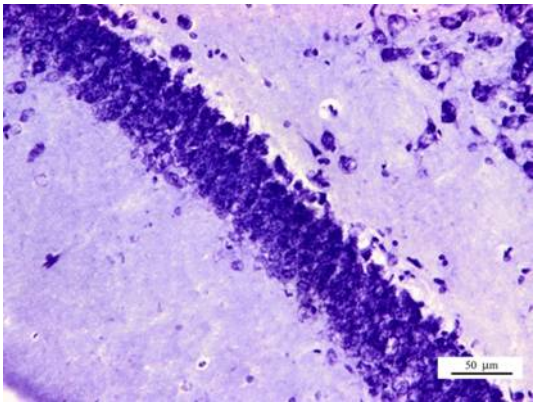


Figure 22 Photographs of coronal section of right hippocampus (CA3) stained with cresyl violet at 40X magnification. (Cont.)

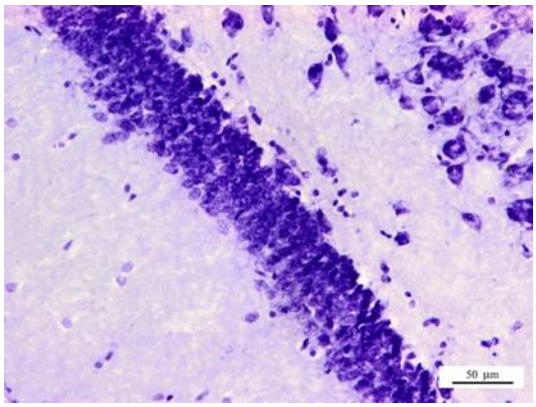
Control



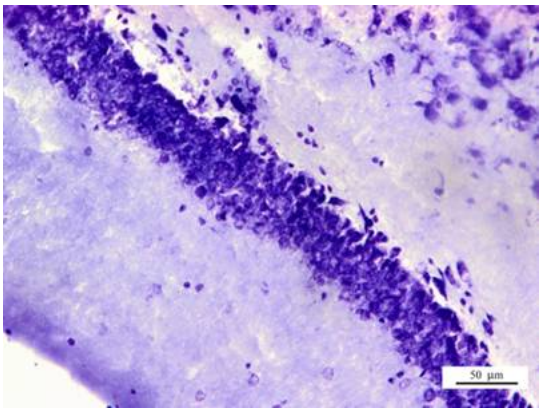
Vehicle



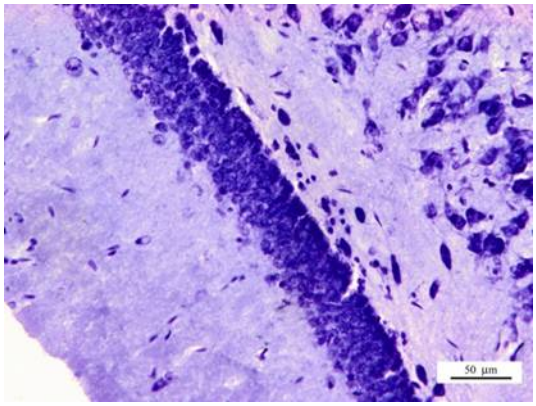
Vehicle + NSS



Vehicle + 6-OHDA



QC100 + 6-OHDA



QC200 + 6-OHDA

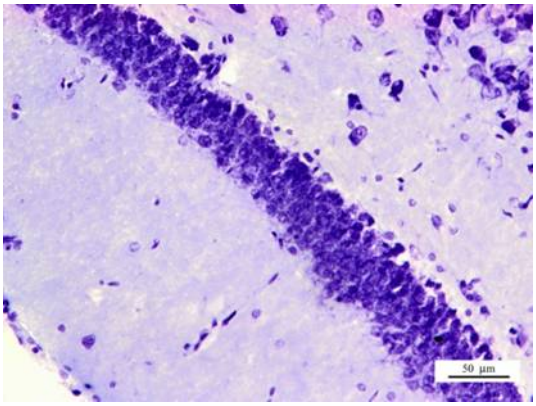
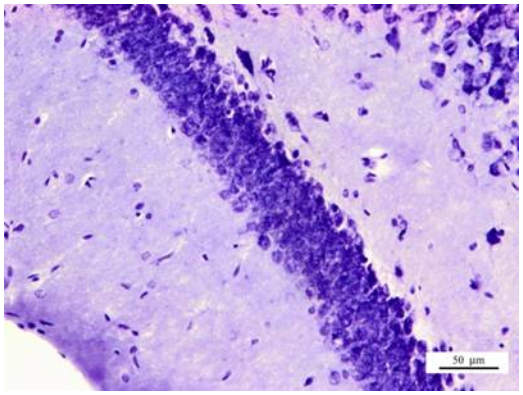
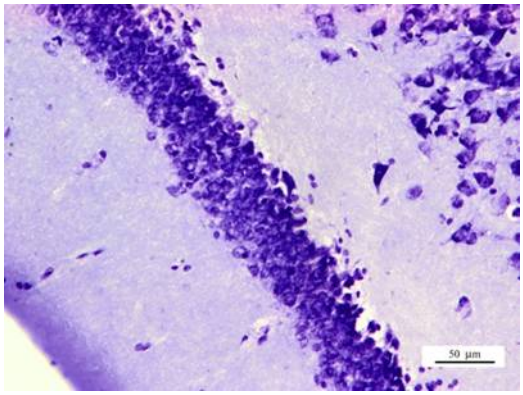


Figure 23 Photographs of coronal section of right hippocampus (dentate gyrus) stained with cresyl violet at 40X magnification.

QC300 + 6-OHDA



L-dopa + 6-OHDA



Vitamin C + 6-OHDA

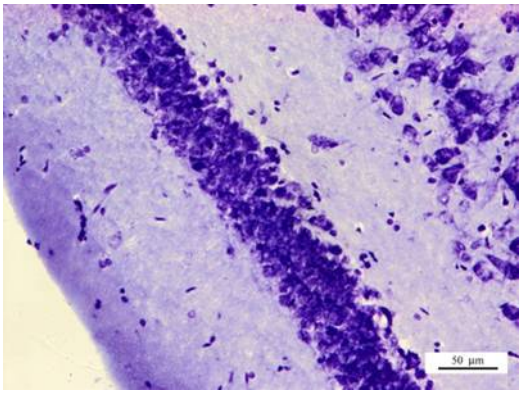


Figure 23 Photographs of coronal section of right hippocampus (dentate gyrus) stained with cresyl violet at 40X magnification. (Cont.)

Table 12 The effect of oral quercetin administration on the density of survival neuron in right substantia nigra.

Group (Treatment)	Density of neuron (cells/225μm^2)
Control	74.050 ± 2.043
Vehicle	70.025 ± 1.035
Vehicle + NSS	71.350 ± 1.388
Vehicle + 6-OHDA	56.625 ± 1.170 ***, aaa, bbb
QC100 + 6-OHDA	58.675 ± 1.009
QC200 + 6-OHDA	59.000 ± 1.281
QC300 + 6-OHDA	62.975 ± 1.720 ##
L-dopa + 6-OHDA	59.675 ± 1.503
Vitamin C + 6-OHDA	59.150 ± 1.542

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed and their brains were removed to determine the density of survival neuron in right substantia nigra. Data were presented as mean ± S.E.M. (n=5 per group).

*** p-value <0.001 compared with control

aaa p-value <0.001 compared with vehicle

bbb p-value <0.001 compared with vehicle + NSS

p-value <0.01 compared with vehicle + 6-OHDA

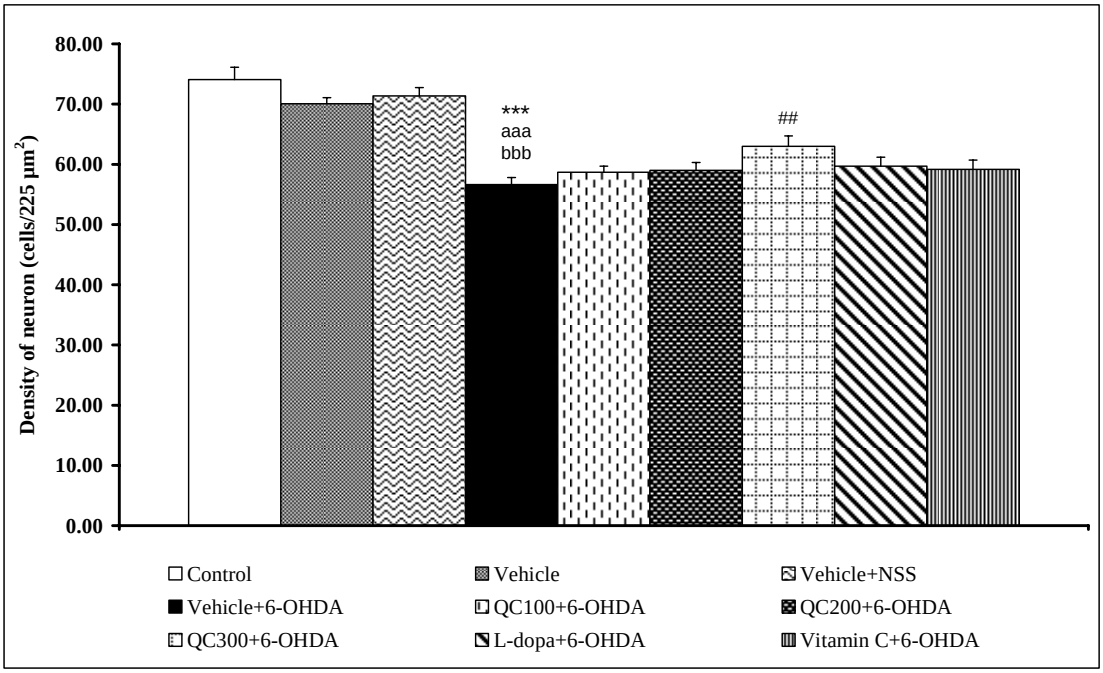


Figure 24 The effect of oral quercetin administration on the density of survival neuron in right substantia nigra. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

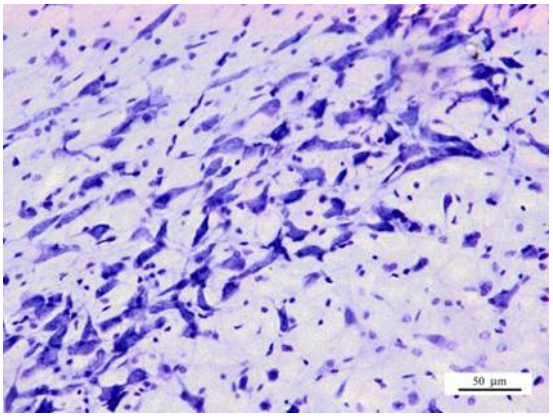
*** p-value <0.001 compared with control

aaa p-value <0.001 compared with vehicle

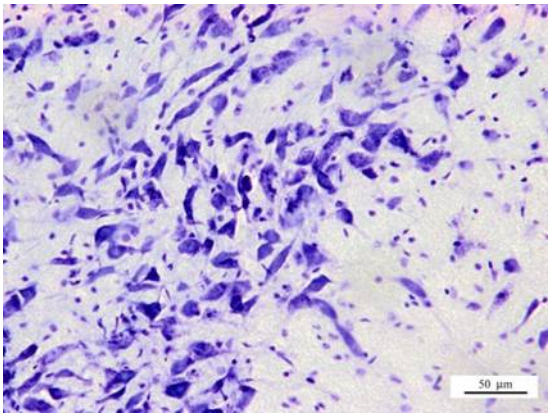
bbb p-value <0.001 compared with vehicle + NSS

p-value <0.01 compared with vehicle + 6-OHDA

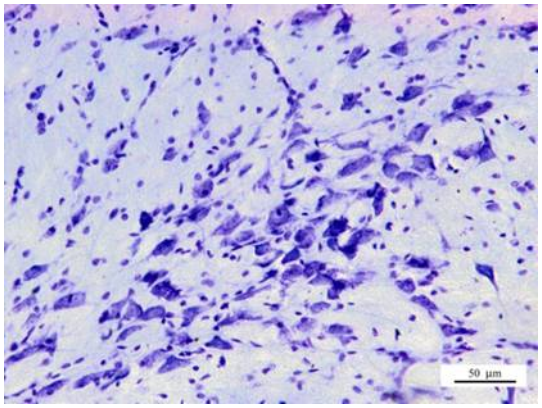
Control



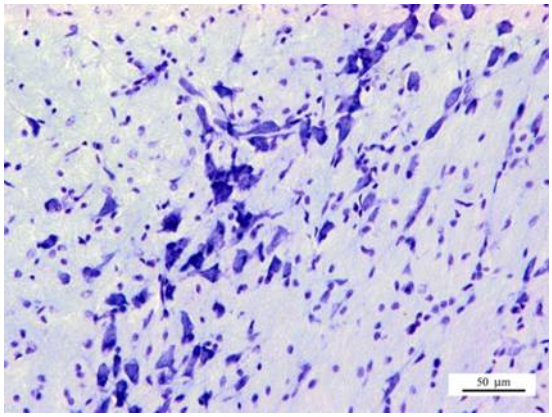
Vehicle



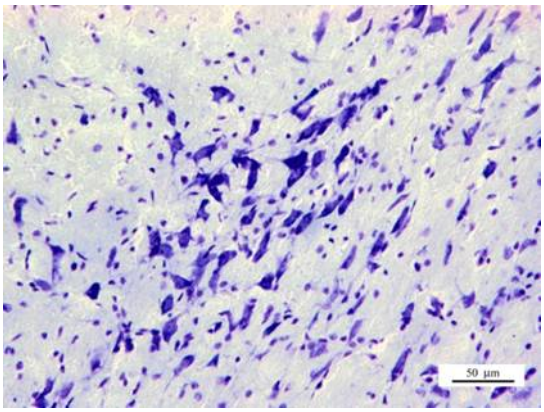
Vehicle + NSS



Vehicle + 6-OHDA



QC100 + 6-OHDA



QC200 + 6-OHDA

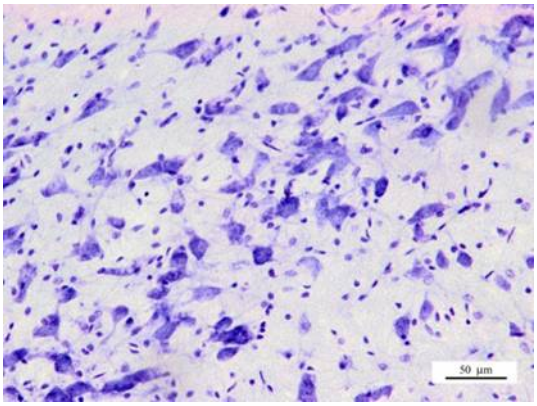
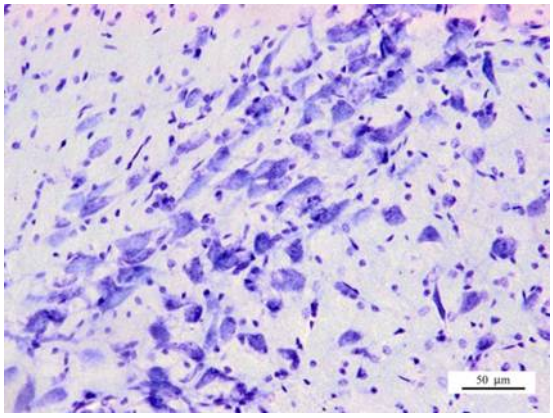
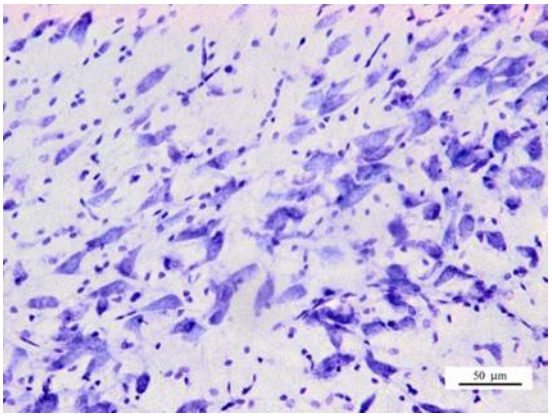


Figure 25 Photographs of coronal section of right substantia nigra stained with cresyl violet at 40X magnification.

QC300 + 6-OHDA



L-dopa + 6-OHDA



Vitamin C + 6-OHDA

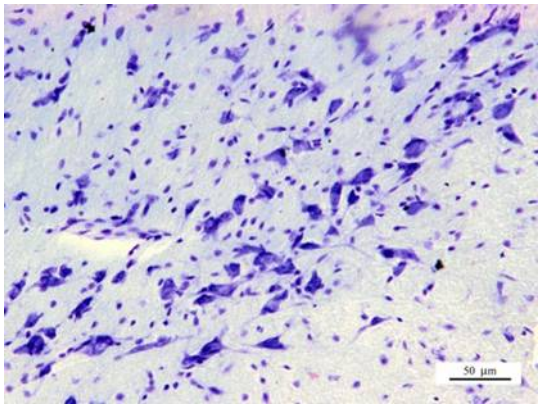


Figure 25 Photographs of coronal section of right substantia nigra stained with cresyl violet at 40X magnification. (Cont.)

Table 13 The effect of oral quercetin administration on the density of survival neuron in right striatum.

Group (Treatment)	Density of neuron (cells/225μm^2)
Control	152.450 ± 4.259
Vehicle	148.750 ± 3.453
Vehicle + NSS	147.500 ± 3.164
Vehicle + 6-OHDA	108.050 ± 2.096 ***, aaa, bbb
QC100 + 6-OHDA	110.425 ± 2.371
QC200 + 6-OHDA	112.300 ± 2.976
QC300 + 6-OHDA	118.275 ± 2.389 #
L-dopa + 6-OHDA	115.750 ± 2.669
Vitamin C + 6-OHDA	113.000 ± 3.074

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed and their brains were removed to determine the density of survival neuron in right striatum. Data were presented as mean ± S.E.M. (n=5).

*** p-value <0.001 compared with control

aaa p-value <0.001 compared with vehicle

bbb p-value <0.001 compared with vehicle + NSS

p-value <0.01 compared with vehicle + 6-OHDA

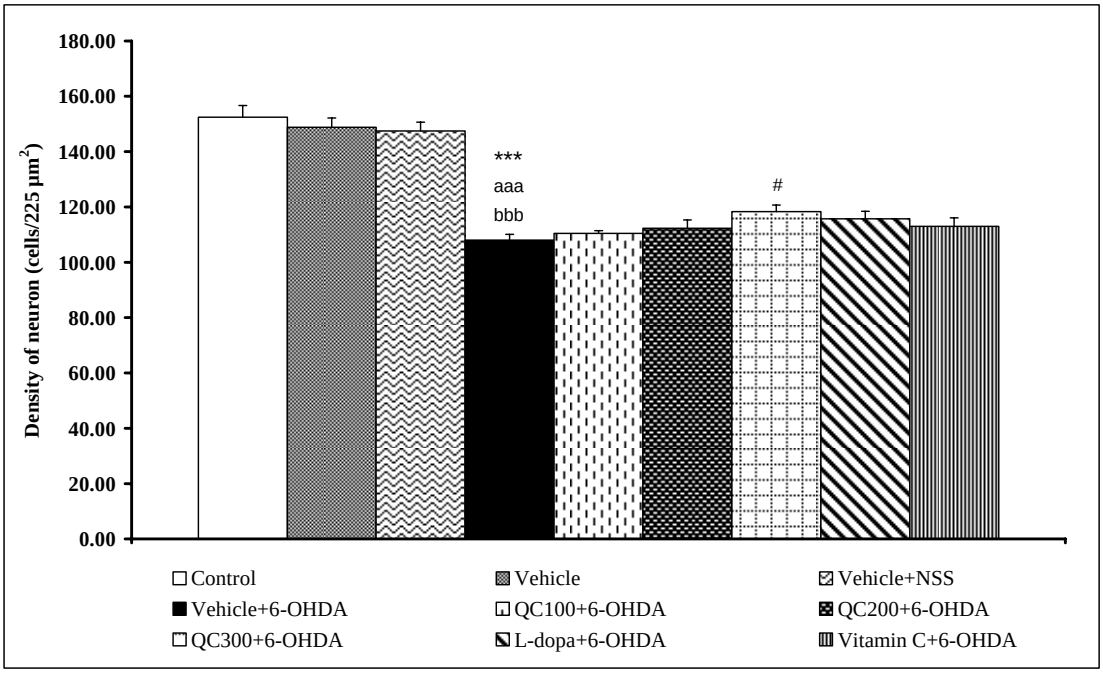


Figure 26 The effect of oral quercetin administration on the density of survival neuron in right striatum. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

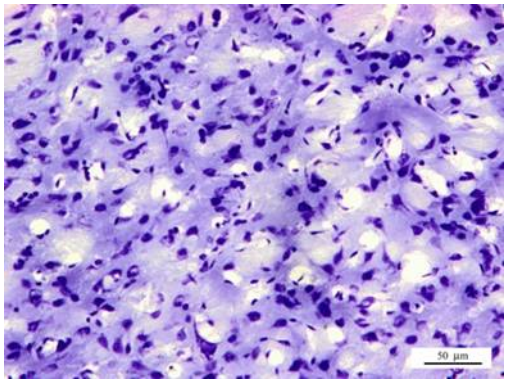
*** p-value <0.001 compared with control

aaa p-value <0.001 compared with vehicle

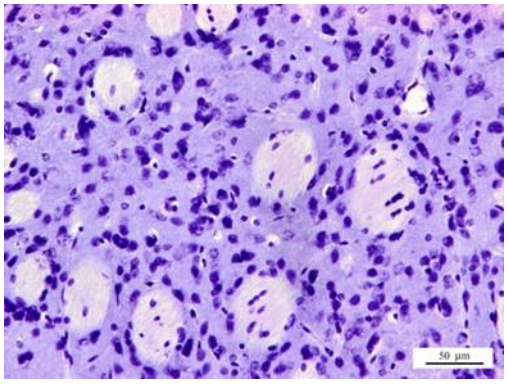
bbb p-value <0.001 compared with vehicle + NSS

p-value <0.01 compared with vehicle + 6-OHDA

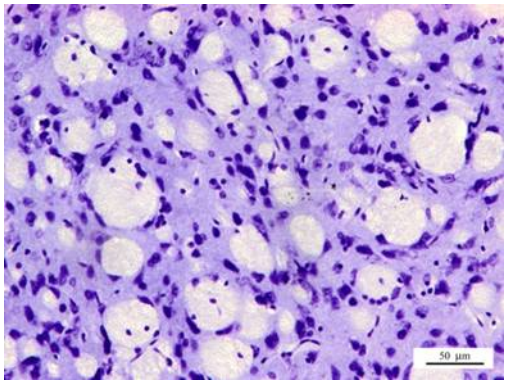
Control



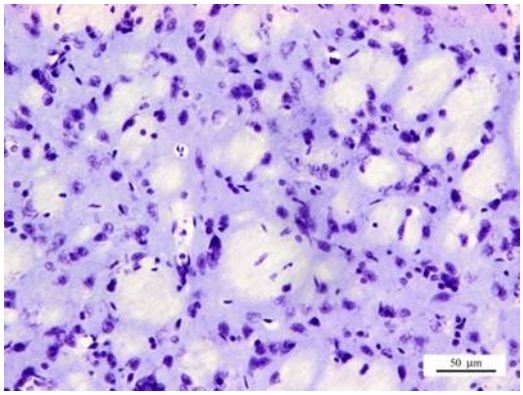
Vehicle



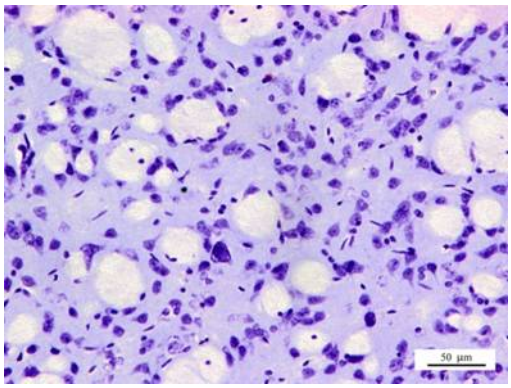
Vehicle + NSS



Vehicle + 6-OHDA



QC100 + 6-OHDA



QC200 + 6-OHDA

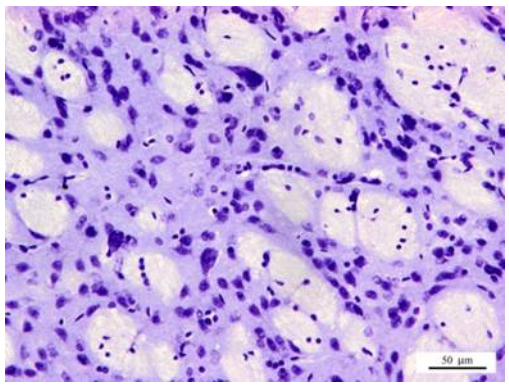
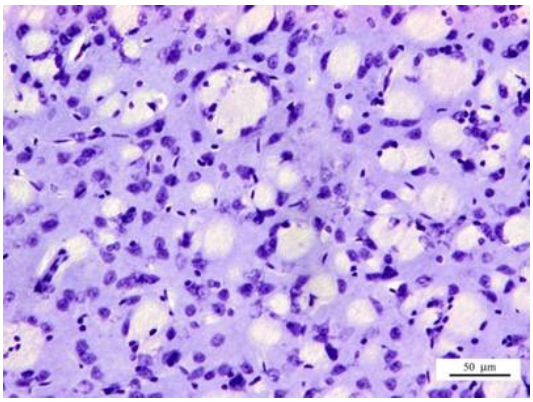
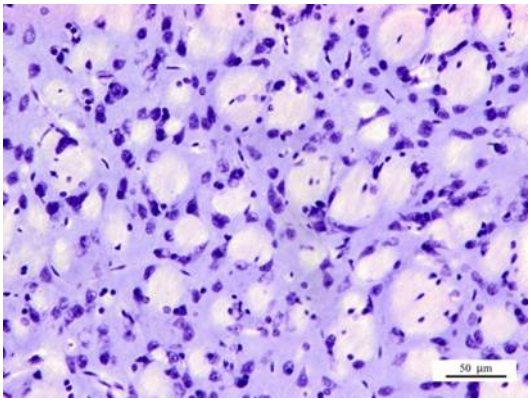


Figure 27 Photographs of coronal section of right striatum stained with cresyl violet at 40X magnification.

QC300 + 6-OHDA



L-dopa + 6-OHDA



Vitamin C + 6-OHDA

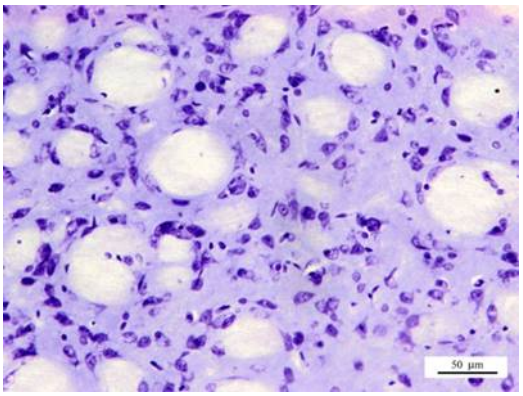


Figure 27 Photographs of coronal section of right striatum stained with cresyl violet at 40X magnification. (Cont.)

Table 14 The effect of oral quercetin administration on the density of tyrosine hydroxylase positive neuron in right substantia nigra.

Group (Treatment)	Density of neuron (cells/225μm^2)
Control	42.650 ± 1.347
Vehicle	41.300 ± 1.348
Vehicle + NSS	40.475 ± 1.196
Vehicle + 6-OHDA	13.750 ± 0.338 ***, aaa, bbb
QC100 + 6-OHDA	14.900 ± 0.582
QC200 + 6-OHDA	14.775 ± 0.482
QC300 + 6-OHDA	15.650 ± 0.414 ##
L-dopa + 6-OHDA	15.175 ± 0.308 #
Vitamin C + 6-OHDA	14.500 ± 0.690

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed and their brains were removed in order to determine the density of tyrosine hydroxylase positive neuron in right substantia nigra. Data were presented as mean ± S.E.M. (n=5).

***	p-value <0.001 compared with control
aaa	p-value <0.001 compared with vehicle
bbb	p-value <0.001 compared with vehicle + NSS
#	p-value <0.05 compared with vehicle + 6-OHDA
##	p-value <0.01 compared with vehicle + 6-OHDA

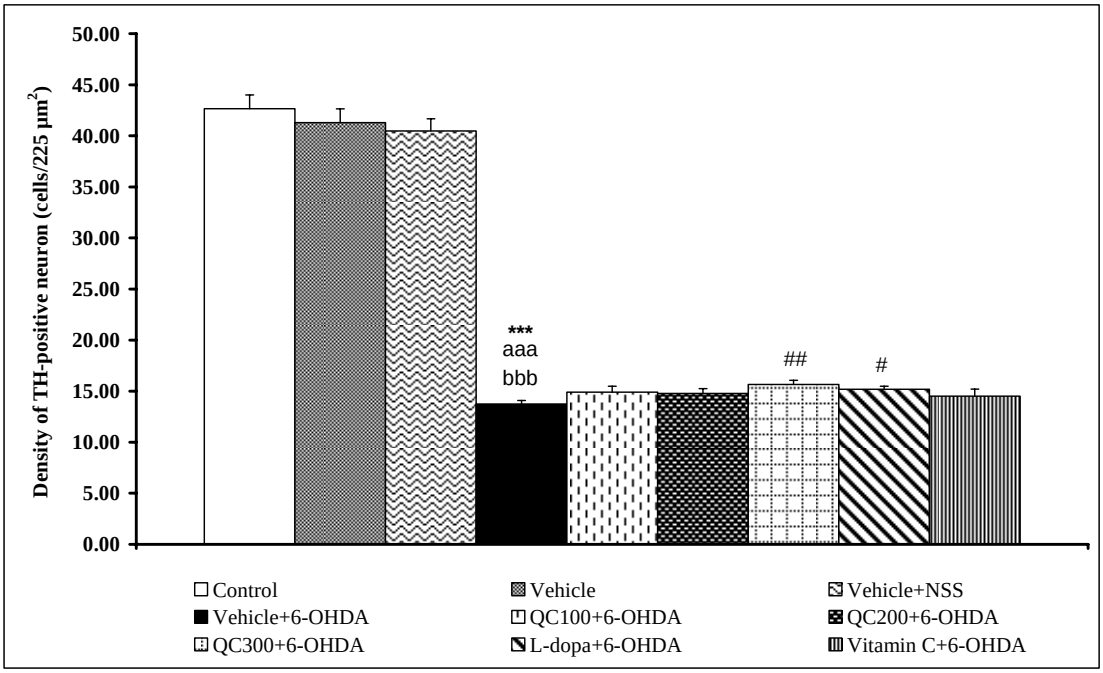


Figure 28 The effect of oral quercetin administration on the density of tyrosine hydroxylase positive neuron in right substantia nigra. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

*** p-value <0.001 compared with control

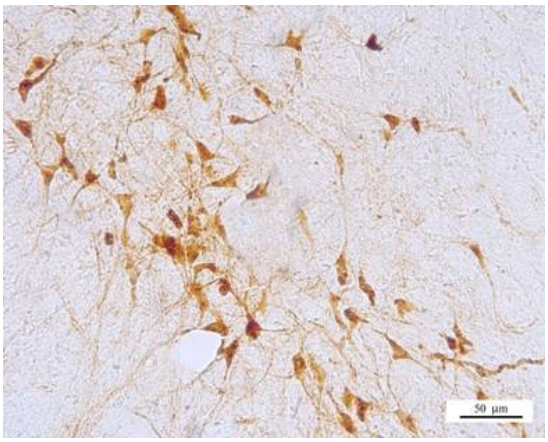
aaa p-value <0.001 compared with vehicle

bbb p-value <0.001 compared with vehicle + NSS

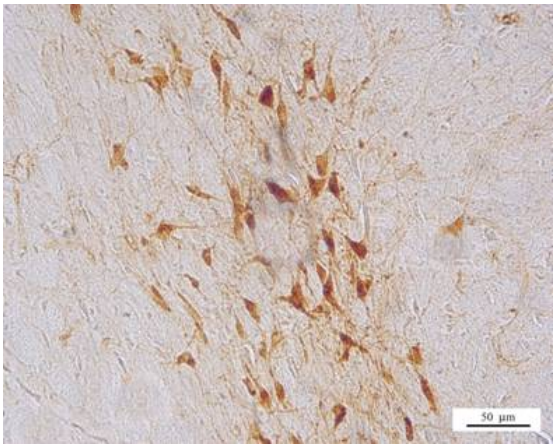
p-value <0.05 compared with vehicle + 6-OHDA

p-value <0.01 compared with vehicle + 6-OHDA

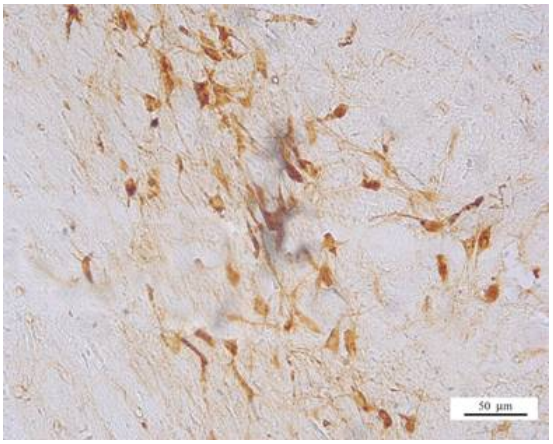
Control



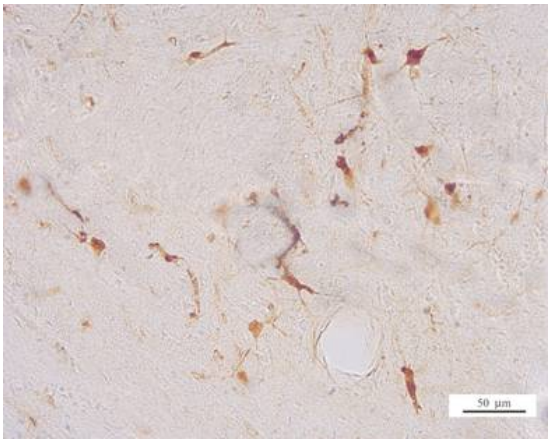
Vehicle



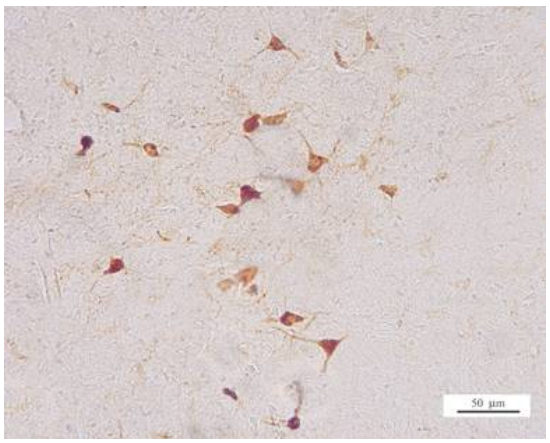
Vehicle + NSS



Vehicle + 6-OHDA



QC100 + 6-OHDA



QC200 + 6-OHDA

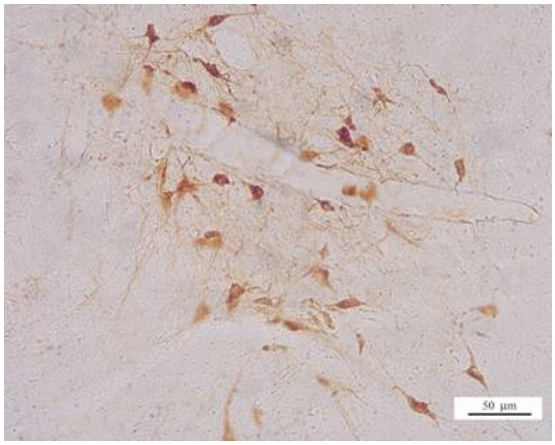
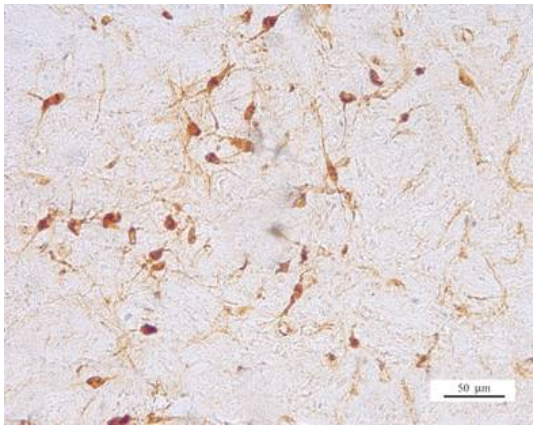
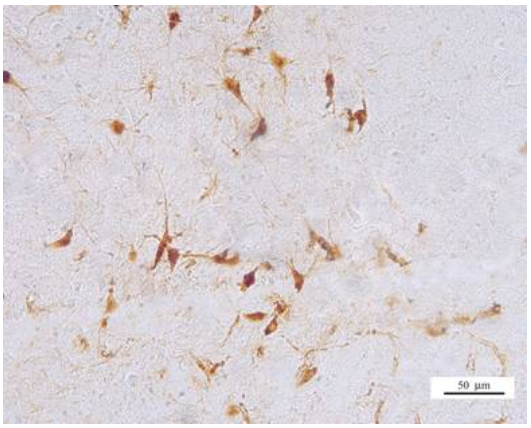


Figure 29 Photographs of coronal section of right substantia nigra stained with monoclonal antibody against tyrosine hydroxylase (TH) at 40X magnification.

QC300 + 6-OHDA



L-dopa + 6-OHDA



Vitamin C + 6-OHDA

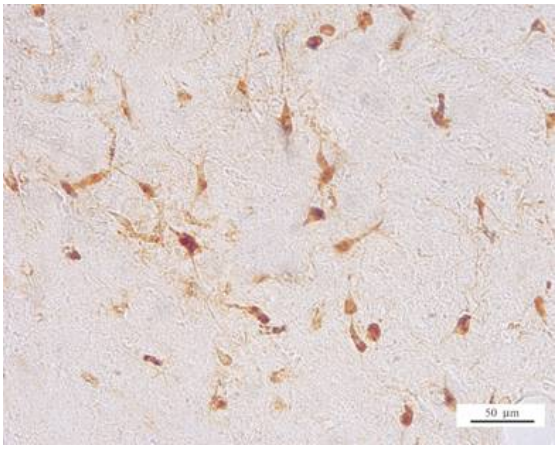


Figure 29 Photographs of coronal section of right substantia nigra stained with monoclonal antibody against tyrosine hydroxylase (TH) at 40X magnification. (Cont.)

Table 15 The effect of oral quercetin administration on the level of MDA in right striatum and hippocampus.

Group (Treatment)	MDA (nmole/ mg protein)	
	Striatum	Hippocampus
Control	1.363 ± 0.078	1.428 ± 0.064
Vehicle	1.234 ± 0.030	1.329 ± 0.054
Vehicle + NSS	1.311 ± 0.178	1.318 ± 0.087
Vehicle + 6-OHDA	1.831 ± 0.127 **, aaa, bb	1.931 ± 0.067 *, aa, bb
QC100 + 6-OHDA	1.224 ± 0.092 ###	1.971 ± 0.210
QC200 + 6-OHDA	1.404 ± 0.178 ##	2.062 ± 0.306
QC300 + 6-OHDA	1.018 ± 0.075 ###	1.429 ± 0.091 #
L-dopa + 6-OHDA	1.221 ± 0.087 ###	1.849 ± 0.136
Vitamin C + 6-OHDA	1.163 ± 0.045 ###	1.560 ± 0.119

Rats were orally administered quercetin at a period of 14 days before and after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the MDA level. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

** p-value <0.01 compared with control

aa p-value <0.01 compared with vehicle

aaa p-value <0.001 compared with vehicle

bb p-value <0.01 compared with vehicle + NSS

\# p-value <0.05 compared with vehicle + 6-OHDA

\## p-value <0.01 compared with vehicle + 6-OHDA

\### p-value <0.001 compared with vehicle + 6-OHDA

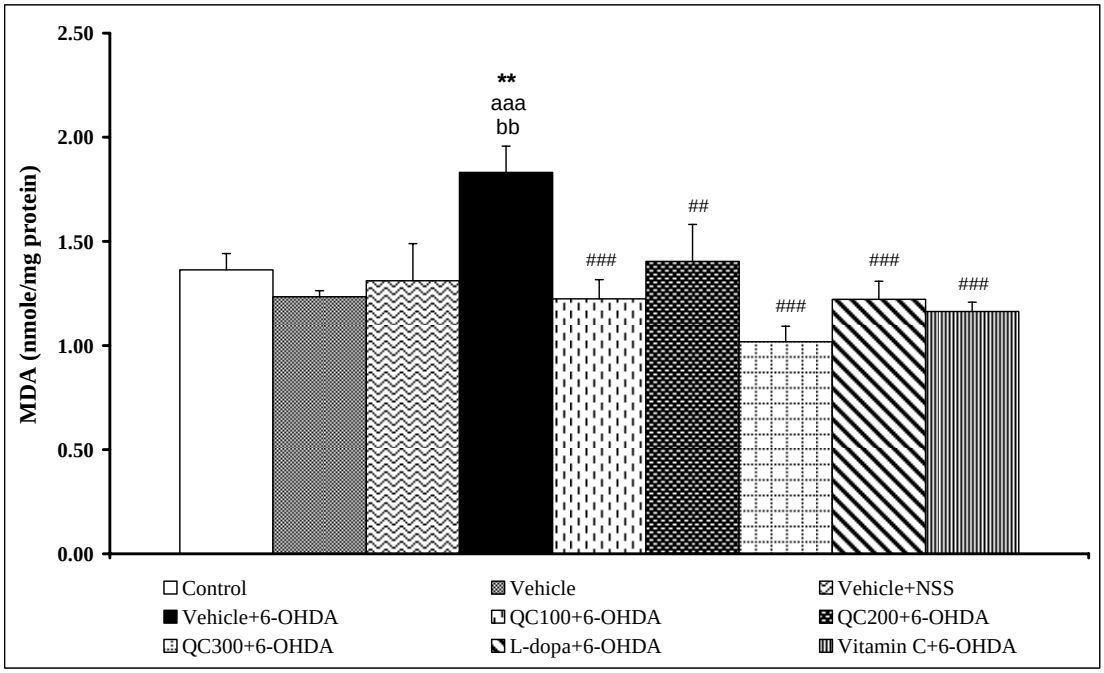


Figure 30 The effect of oral quercetin administration on the level of malondialdehyde (MDA) in right striatum. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

** p-value <0.01 compared with control

aaa p-value <0.001 compared with vehicle

bb p-value <0.01 compared with vehicle + NSS

p-value <0.01 compared with vehicle + 6-OHDA

p-value <0.001 compared with vehicle + 6-OHDA

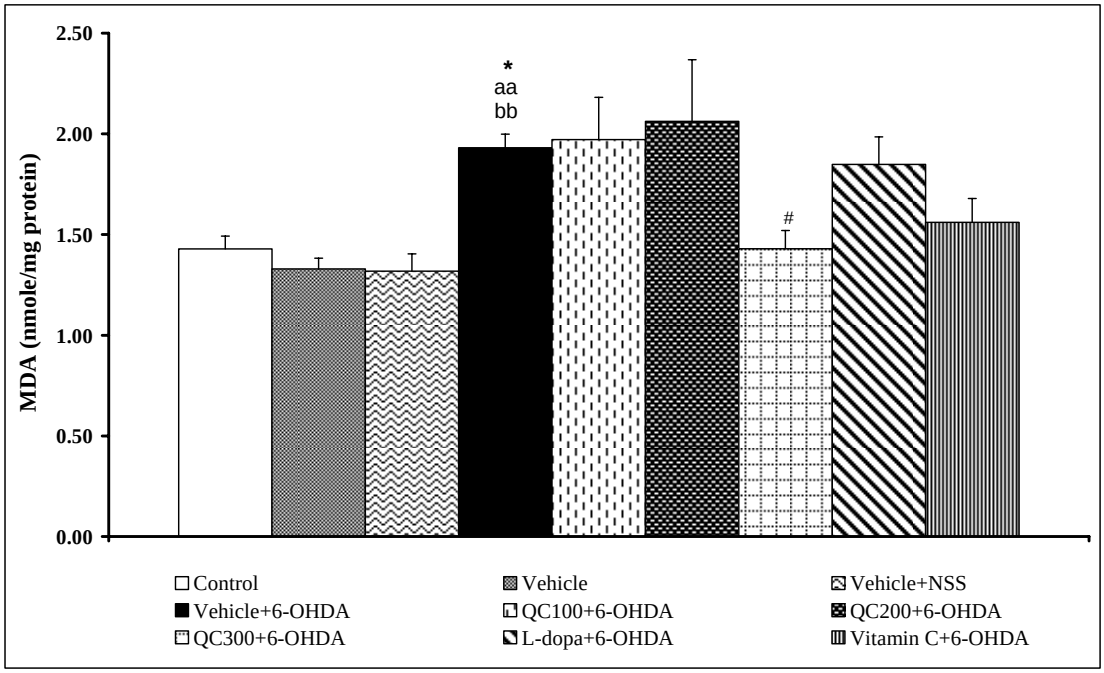


Figure 31 The effect of oral quercetin administration on the level of malondialdehyde (MDA) in right hippocampus. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

aa p-value <0.01 compared with vehicle

bb p-value <0.01 compared with vehicle + NSS

\# p-value <0.05 compared with vehicle + 6-OHDA

Table 16 The effect of oral quercetin administration on the activity of SOD (superoxide dismutase) in right striatum and hippocampus.

Group (Treatment)	SOD (units/ mg protein)	
	Striatum	Hippocampus
Control	8.853 ± 0.661	8.838 ± 2.644
Vehicle	8.397 ± 0.532	8.422 ± 2.178
Vehicle + NSS	8.363 ± 1.793	7.867 ± 2.504
Vehicle + 6-OHDA	4.698 ± 1.336 **, aa, bb	7.704 ± 1.319
QC100 + 6-OHDA	9.670 ± 0.710 ##	10.871 ± 0.485
QC200 + 6-OHDA	9.764 ± 0.533 ##	10.462 ± 1.145
QC300 + 6-OHDA	11.669 ± 0.934 **, aaa, bbb, ##	14.812 ± 2.326 #
L-dopa + 6-OHDA	12.734 ± 0.735 **, aaa, bbb, ##	16.661 ± 1.495 ##
Vitamin C + 6-OHDA	13.070 ± 1.567 **, aaa, bbb, ##	15.374 ± 2.501 ##

Rats were orally administered quercetin at a period of 14 days before and after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the activity of SOD. Data were presented as mean ± S.E.M. (n=5 per group).

**	p-value <0.01 compared with control
aa	p-value <0.01 compared with vehicle
aaa	p-value <0.001 compared with vehicle
bb	p-value <0.01 compared with vehicle + NSS
bbb	p-value <0.001 compared with vehicle + NSS
#	p-value <0.05 compared with vehicle + 6-OHDA
##	p-value <0.01 compared with vehicle + 6-OHDA
###	p-value <0.001 compared with vehicle + 6-OHDA

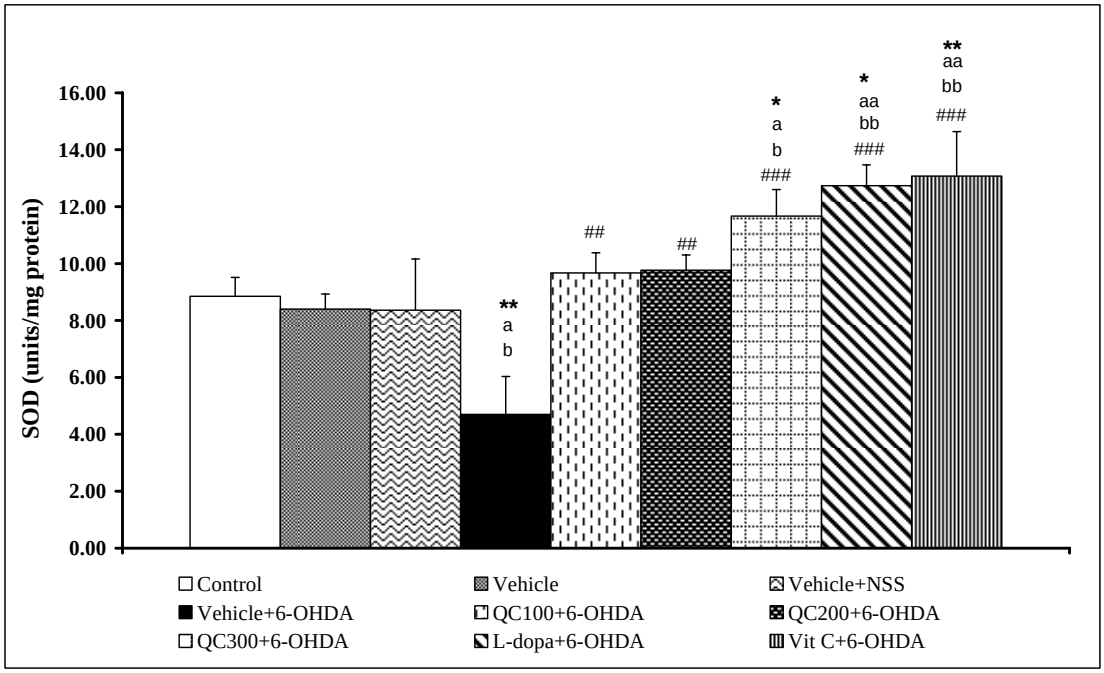


Figure 32 The effect of oral quercetin administration on the activity of superoxide dismutase (SOD) in right striatum. Rats were received quercetin at a period 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

**	p-value <0.01 compared with control
aa	p-value <0.01 compared with vehicle
aaa	p-value <0.001 compared with vehicle
b	p-value <0.05 compared with vehicle + NSS
bbb	p-value <0.001 compared with vehicle + NSS
###	p-value <0.001 compared with vehicle + 6-OHDA

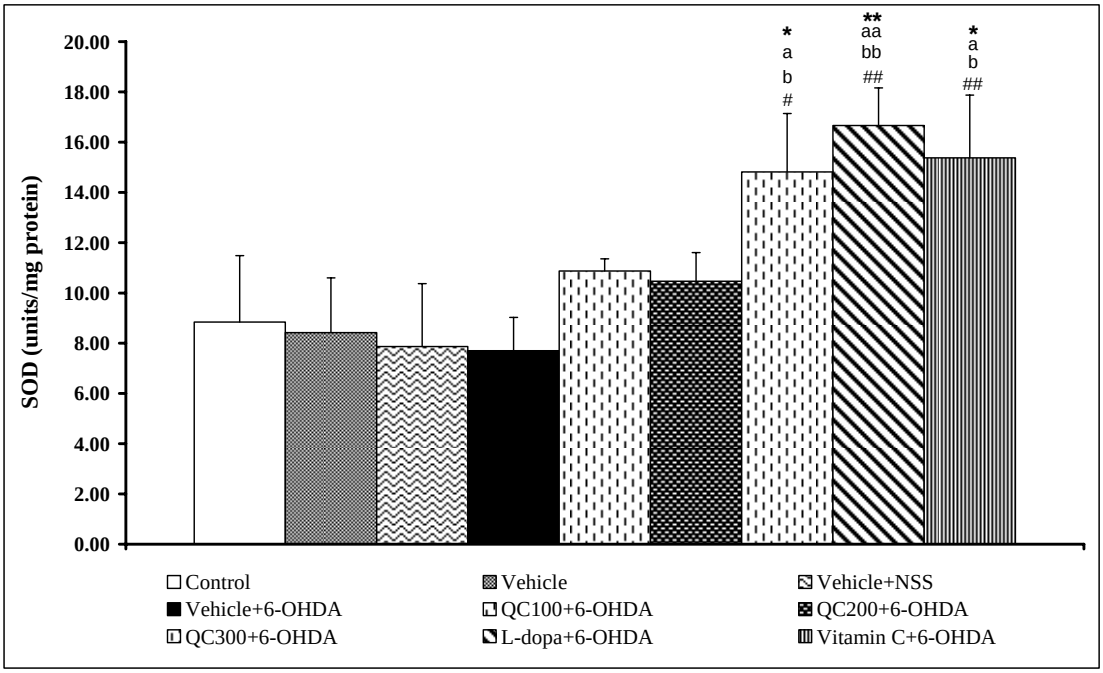


Figure 33 The effect of oral quercetin administration on the activity of superoxide dismutase (SOD) in right hippocampus. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

\# p-value <0.05 compared with vehicle + 6-OHDA

\## p-value <0.01 compared with vehicle + 6-OHDA

Table 17 The effect of oral quercetin administration on the activity of GPx (glutathione peroxidase) in right striatum and hippocampus.

Group (Treatment)	GPx (units/ mg protein)	
	Striatum	Hippocampus
Control	1.407 ± 0.059	2.133 ± 0.291
Vehicle	1.258 ± 0.112	2.040 ± 0.188
Vehicle + NSS	1.248 ± 0.133	2.285 ± 0.230
Vehicle + 6-OHDA	1.450 ± 0.159	1.512 ± 0.084 $^{*, a, bb}$
QC100 + 6-OHDA	1.599 ± 0.053 $^{a, b}$	2.076 ± 0.082 $^{\#}$
QC200 + 6-OHDA	1.626 ± 0.126 $^{a, b}$	2.042 ± 0.141 $^{\#}$
QC300 + 6-OHDA	1.954 ± 0.097 $^{**, aa, bb, \#\#}$	2.158 ± 0.197 $^{\#}$
L-dopa + 6-OHDA	1.808 ± 0.052 $^{*, aa, bb, \#}$	2.137 ± 0.074 $^{\#}$
Vitamin C + 6-OHDA	1.866 ± 0.207 $^{*, aa, bb, \#}$	1.984 ± 0.142 $^{\#}$

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the activity of GPx. Data were presented as mean ± S.E.M. (n=5 per group).

*	p-value <0.05 compared with control
***	p-value <0.001 compared with control
aaa	p-value <0.001 compared with vehicle
bb	p-value <0.01 compared with vehicle + NSS
bbb	p-value <0.001 compared with vehicle + NSS
#	p-value <0.05 compared with vehicle + 6-OHDA
##	p-value <0.01 compared with vehicle + 6-OHDA
###	p-value <0.001 compared with vehicle + 6-OHDA

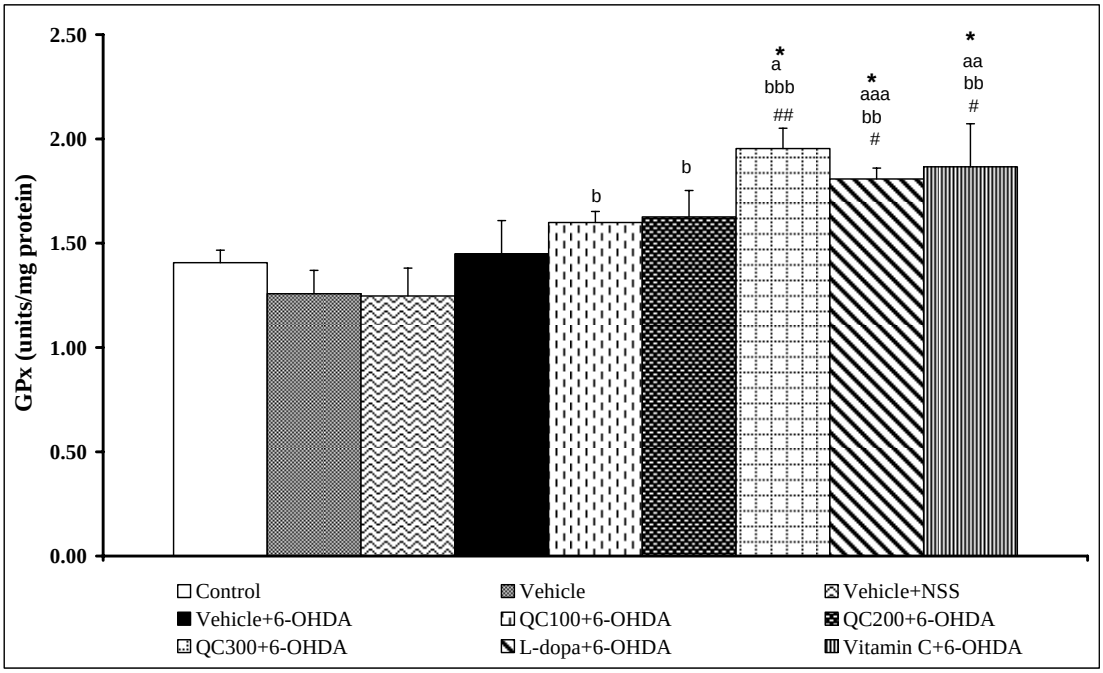


Figure 34 The effect of oral quercetin administration on the activity of glutathione peroxidase (GPx) in right striatum. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

*	p-value <0.05 compared with control
a	p-value <0.05 compared with vehicle
aa	p-value <0.01 compared with vehicle
aaa	p-value <0.001 compared with vehicle
b	p-value <0.05 compared with vehicle
bb	p-value <0.01 compared with vehicle + NSS
bbb	p-value <0.001 compared with vehicle + NSS
#	p-value <0.05 compared with vehicle + 6-OHDA
##	p-value <0.01 compared with vehicle + 6-OHDA

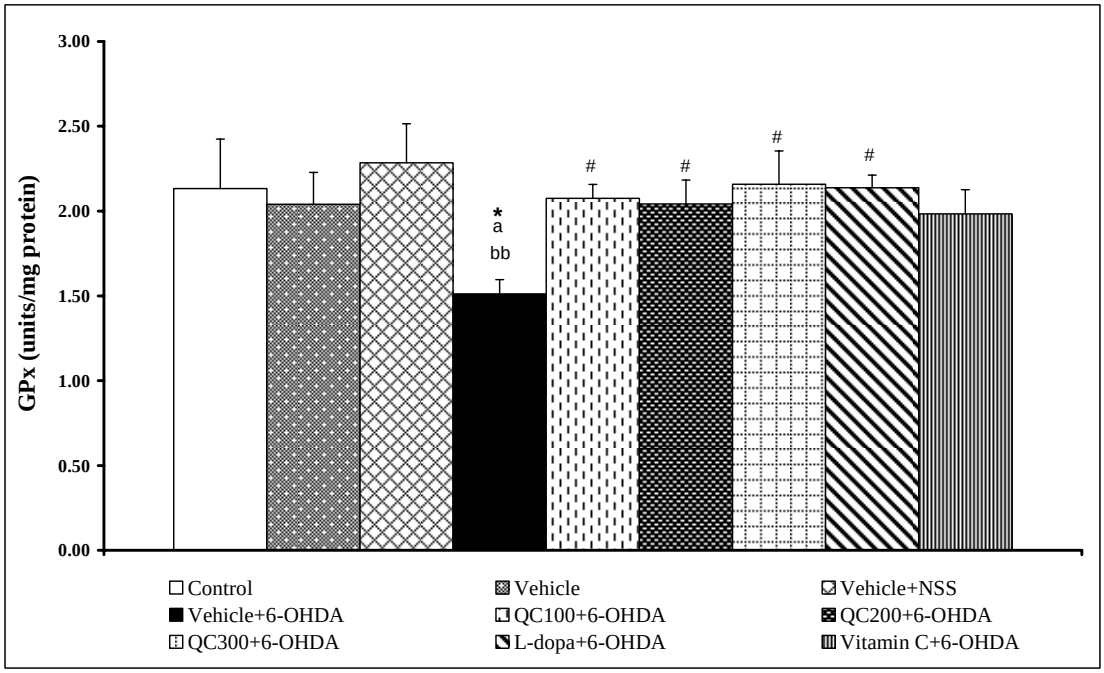


Figure 35 The effect of oral quercetin administration on the activity of glutathione peroxidase (GPx) in right hippocampus. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

a p-value <0.05 compared with vehicle

bb p-value <0.01 compared with vehicle + NSS

\# p-value <0.05 compared with vehicle + 6-OHDA

Table 18 The effect of oral quercetin administration on the activity of CAT (catalase) in right striatum and hippocampus.

Group (Treatment)	CAT (units/ mg protein)	
	Striatum	Hippocampus
Control	20.800 ± 1.996	15.888 ± 1.760
Vehicle	18.023 ± 1.114	13.116 ± 0.483
Vehicle + NSS	17.612 ± 1.521	14.402 ± 1.390
Vehicle + 6-OHDA	14.871 ± 1.024 *	14.268 ± 1.325
QC100 + 6-OHDA	19.018 ± 1.341 #	19.609 ± 2.117
QC200 + 6-OHDA	19.627 ± 1.587 #	17.795 ± 1.081
QC300 + 6-OHDA	19.476 ± 0.869 #	20.830 ± 2.770 #
L-dopa + 6-OHDA	19.350 ± 0.967 #	21.464 ± 1.440 #
Vitamin C + 6-OHDA	20.708 ± 1.728 #	19.067 ± 2.128

Rats were orally administered quercetin at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the activity of CAT. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with vehicle + 6-OHDA

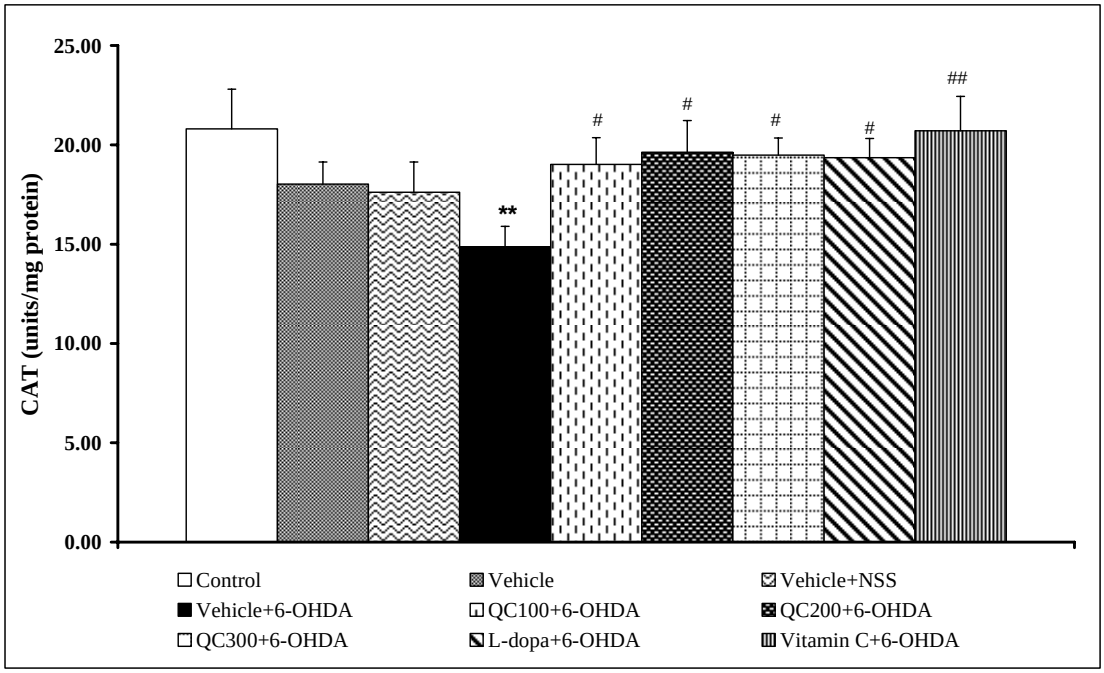


Figure 36 The effect of oral quercetin administration on the activity of catalase (CAT) in right striatum. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with vehicle + 6-OHDA

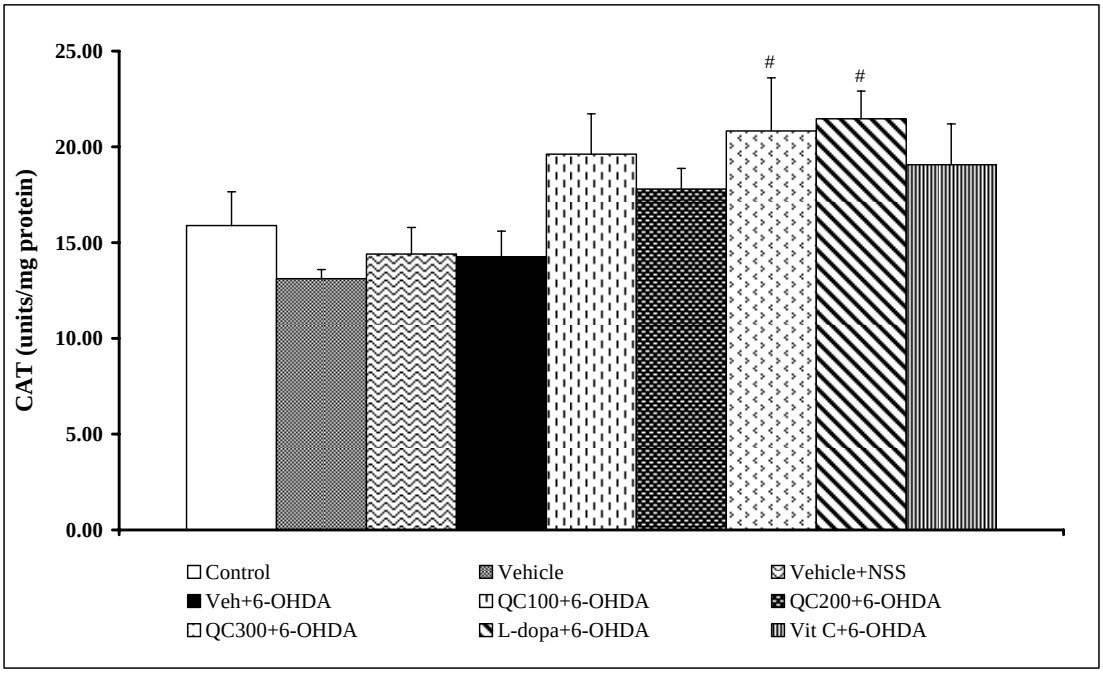


Figure 37 The effect of oral quercetin administration on the activity of catalase (CAT) in right hippocampus. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

\# p-value <0.05 compared with vehicle + 6-OHDA

Table 19 The effect of oral quercetin administration on the activity of AChE (acetylcholinesterase) in right striatum and hippocampus.

Group (Treatment)	AChE (μmole/min. mg protein)	
	Striatum	Hippocampus
Control	0.083 ± 0.045	0.048 ± 0.006
Vehicle	0.072 ± 0.025	0.047 ± 0.010
Vehicle + NSS	0.082 ± 0.040	0.046 ± 0.004
Vehicle + 6-OHDA	0.145 ± 0.034	0.055 ± 0.011
QC100 + 6-OHDA	0.070 ± 0.023	0.040 ± 0.004
QC200 + 6-OHDA	0.069 ± 0.014	0.039 ± 0.010
QC300 + 6-OHDA	0.034 ± 0.007 #	0.029 ± 0.008 #
L-dopa + 6-OHDA	0.083 ± 0.058	0.034 ± 0.006
Vitamin C + 6-OHDA	0.082 ± 0.025	0.034 ± 0.003

Rats were received quercetin via oral route at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the activity of AChE. Data were presented as mean ± S.E.M. (n=5 per group).

p-value <0.05 compared with vehicle + 6-OHDA

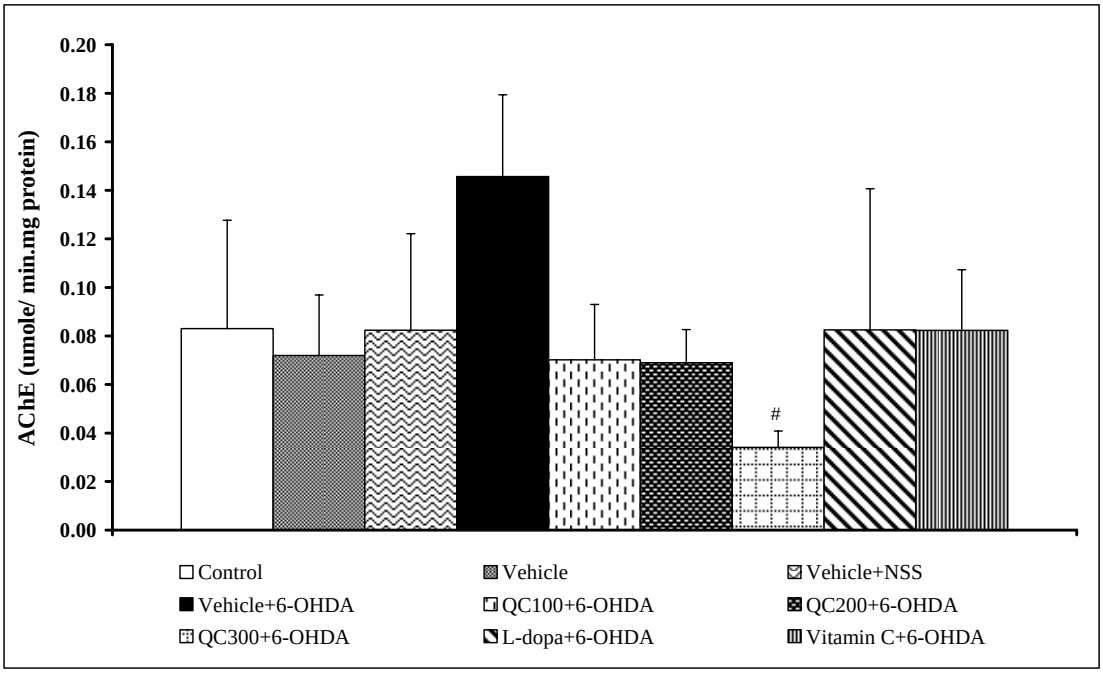


Figure 38 The effect of oral quercetin administration on the activity of acetylcholinesterase (AChE) in right striatum. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

\# p-value <0.05 compared with vehicle + 6-OHDA

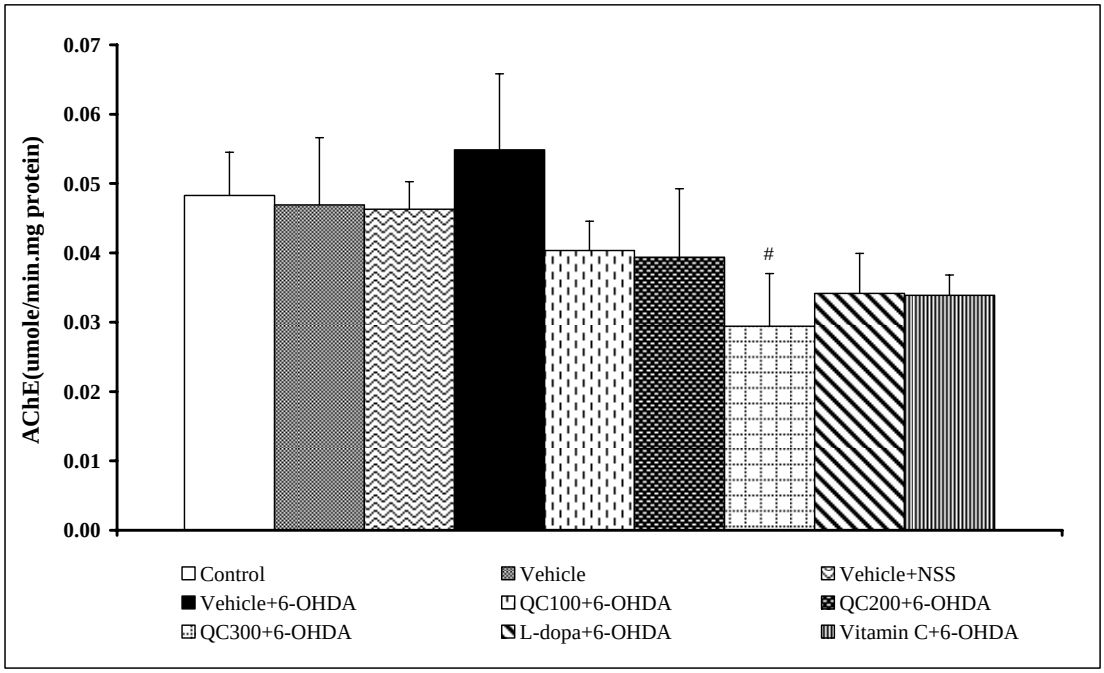


Figure 39 The effect of oral quercetin administration on the activity of acetylcholinesterase (AChE) in right hippocampus. Rats were received quercetin at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

\# p-value <0.05 compared with vehicle + 6-OHDA

Table 20 The effect of transdermal quercetin administration on the density of survival neuron in right hippocampus.

Group (Treatment)	CA1 (cells/225μm^2)	CA2 (cells/22 5μm^2)	CA3 (cells/225μm^2)	Dentate gyrus (cells/225μm^2)
Control	82.720 ± 1.628	70.920 ± 1.798	68.640 ± 0.471	145.480 ± 4.184
Zein	60.920 ± 1.768 ***	51.960 ± 2.441 ***	51.080 ± 0.516 ***	112.640 ± 1.930 ***
QC5%	63.920 ± 1.315 ***	57.160 ± 2.334 ***	52.960 ± 1.059 ***	115.200 ± 2.439 ***
QC10%	65.720 ± 1.765 ***, #	56.760 ± 1.509 ***	53.040 ± 1.076 ***	116.720 ± 0.958 ***
QC15%	68.160 ± 1.357 ***, ##	61.000 ± 2.186 **, ##	55.920 ± 0.889 ***, ###	121.640 ± 2.014 ***, #

Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed and their brains were removed to determine the density of survival neuron in right hippocampus. Data were presented as mean ± S.E.M. (n=5 per group).

** p-value <0.01 compared with control

*** p-value <0.001 compared with control

p-value <0.05 compared with zein + 6-OHDA

p-value <0.01 compared with zein + 6-OHDA

p-value <0.001 compared with zein + 6-OHDA

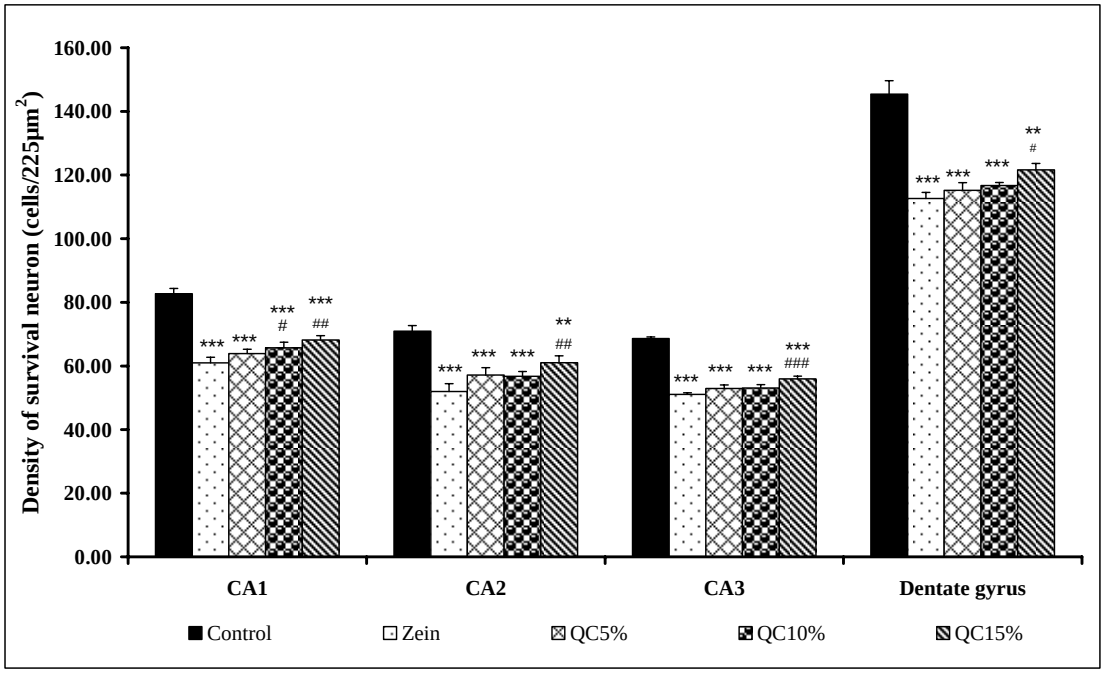
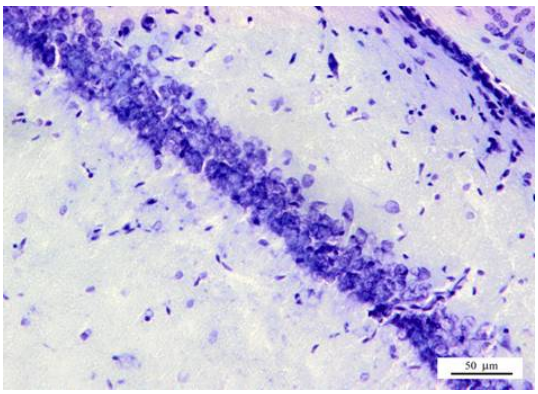


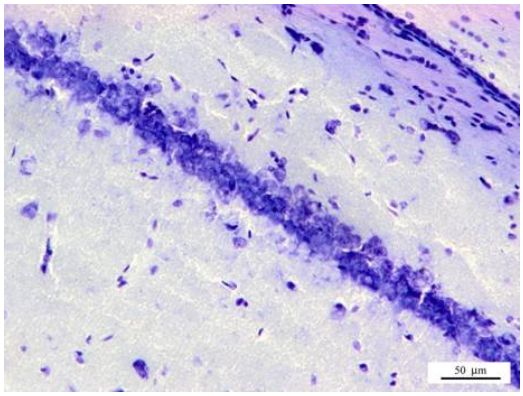
Figure 40 The effect of transdermal quercetin administration on the density of survival neuron in right hippocampus. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

**	p-value <0.01 compared with control
***	p-value <0.001 compared with control
#	p-value <0.05 compared with zein + 6-OHDA
##	p-value <0.01 compared with zein + 6-OHDA
###	p-value <0.001 compared with zein + 6-OHDA

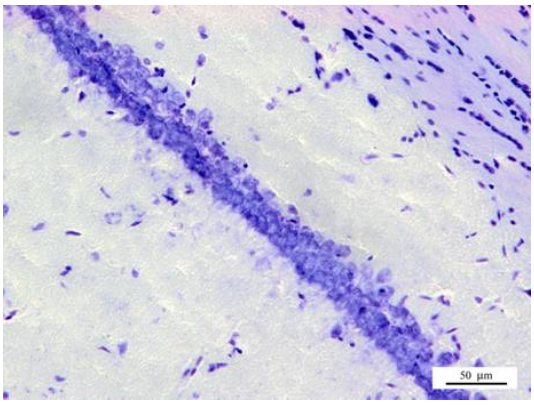
Control



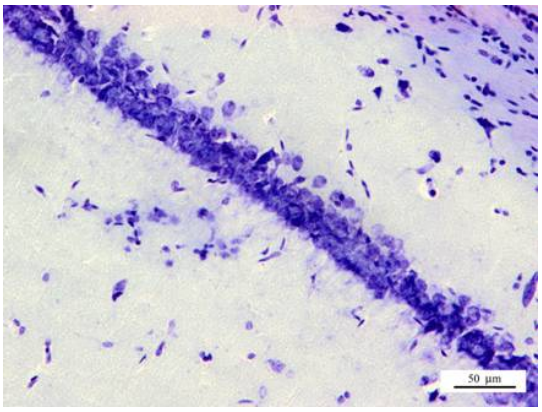
Zein



QC 5%



QC 10%



QC 15%

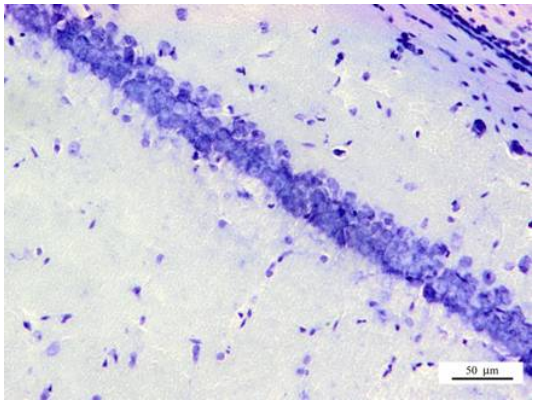
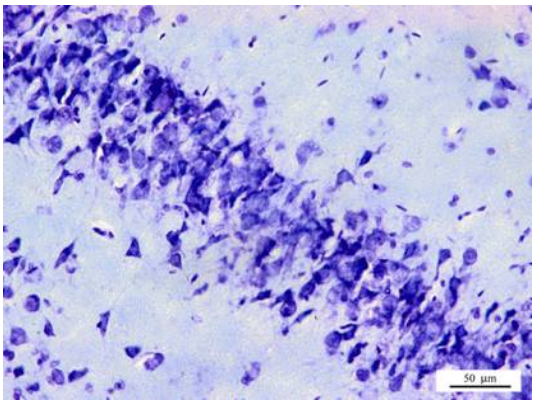
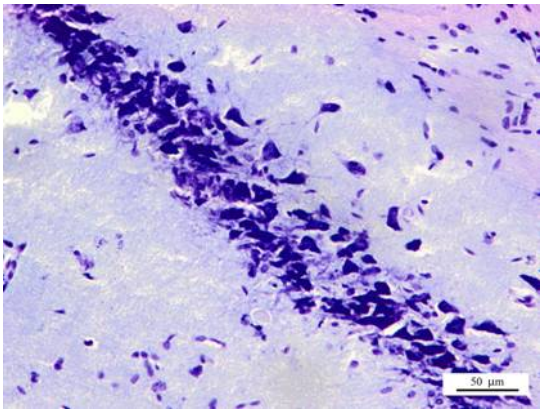


Figure 41 Photographs of coronal section of right hippocampus (CA1) stained with cresyl violet at 40X magnification.

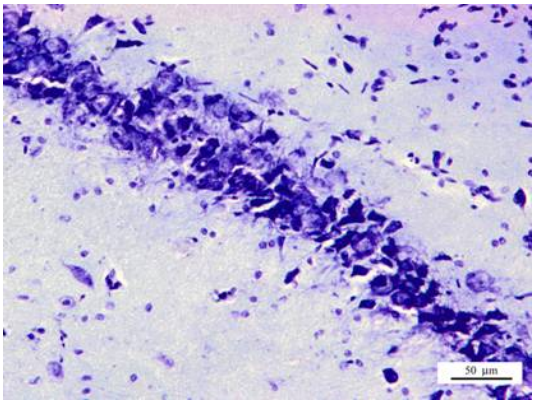
Control



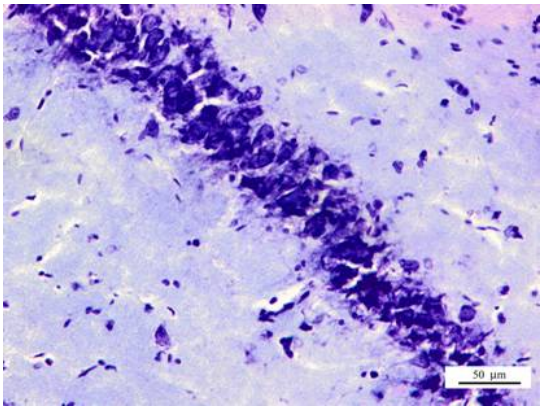
Zein



QC 5%



QC 10%



QC 15%

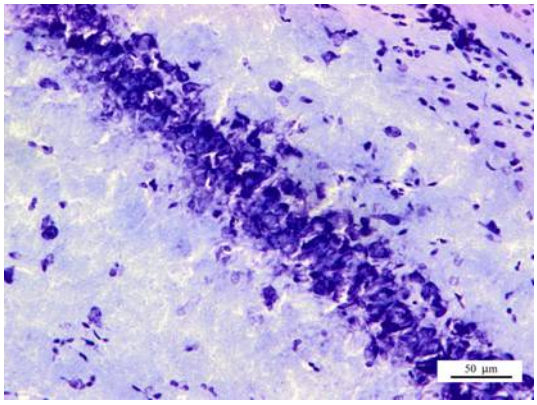
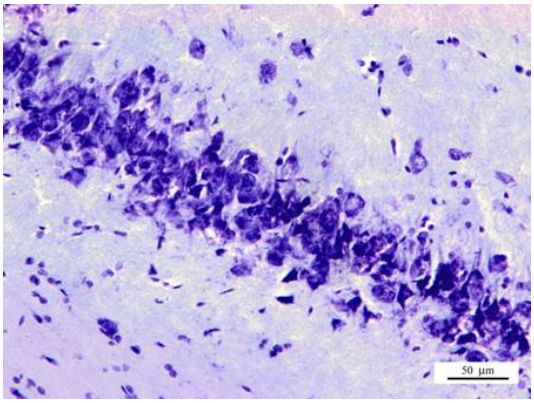
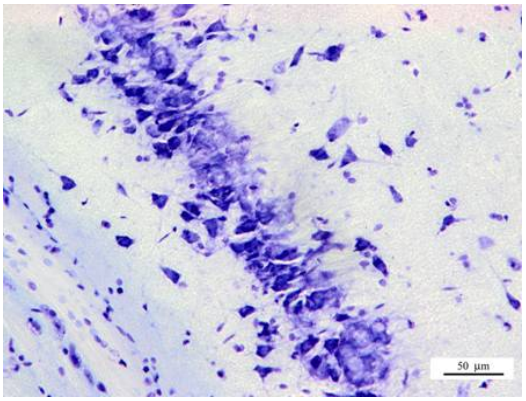


Figure 42 Photographs of coronal section of right hippocampus (CA2) stained with cresyl violet at 40X magnification.

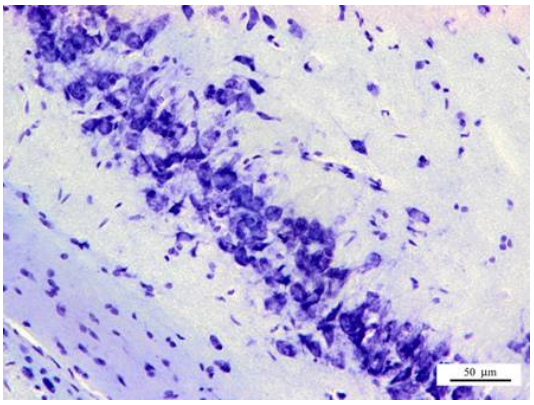
Control



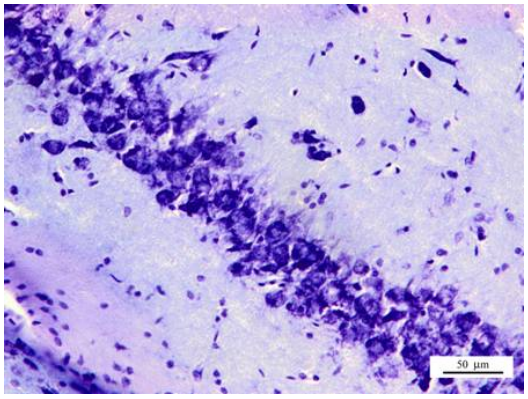
Zein



QC 5%



QC 10%



QC 15%

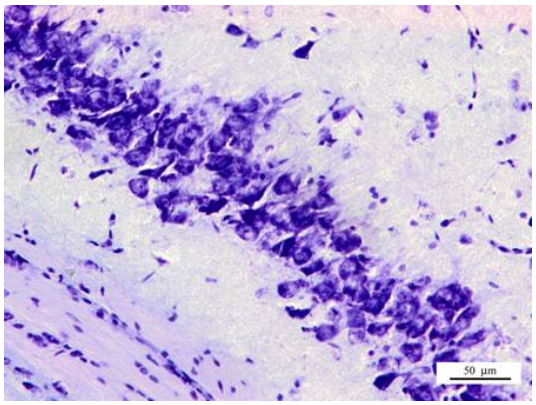
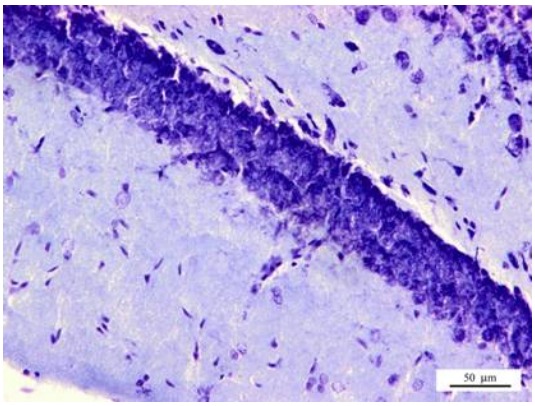
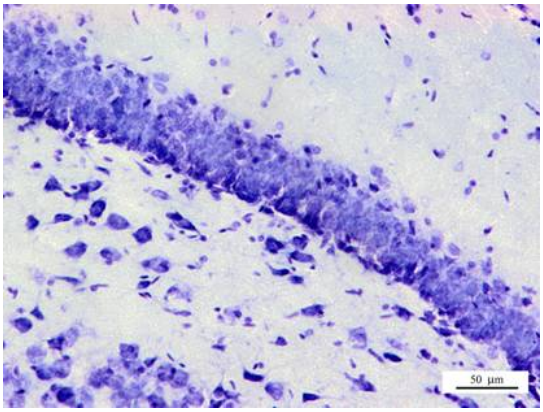


Figure 43 Photographs of coronal section of right hippocampus (CA3) stained with cresyl violet at 40X magnification.

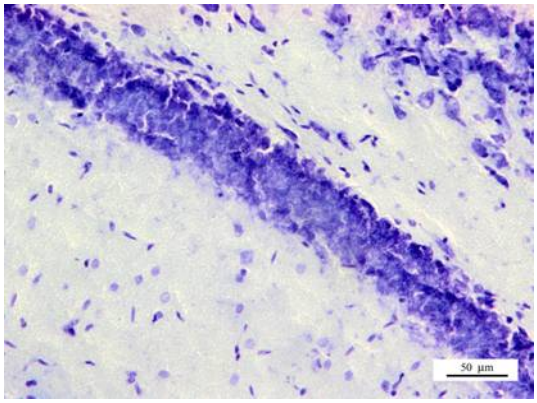
Control



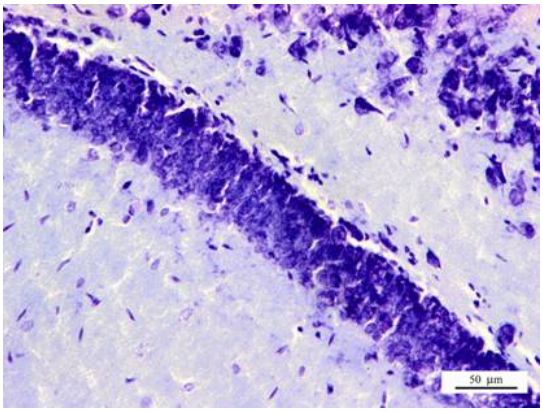
Zein



QC 5%



QC 10%



QC 15%

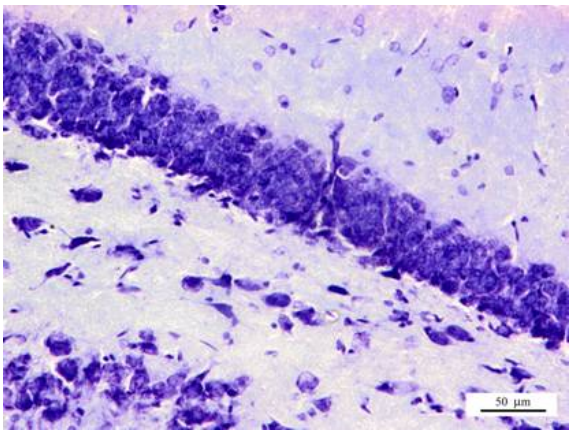


Figure 44 Photographs of coronal section of right hippocampus (dentate gyrus) stained with cresyl violet at 40X magnification.

Table 21 The effect of transdermal quercetin administration on the density of survival neuron in right substantia nigra.

Group (Treatment)	Density of neuron (cells/225μm^2)
Control	73.440 ± 2.354
Zein	50.400 ± 3.929 ***
QC5%	55.520 ± 3.395 ***
QC10%	57.360 ± 2.769 ***
QC15%	58.840 ± 3.375 **, #

Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed and their brains were removed to determine the density of survival neuron in right substantia nigra. Data were presented as mean ± S.E.M. (n=5 per group).

** p-value <0.01 compared with control

*** p-value <0.001 compared with control

p-value <0.05 compared with zein + 6-OHDA

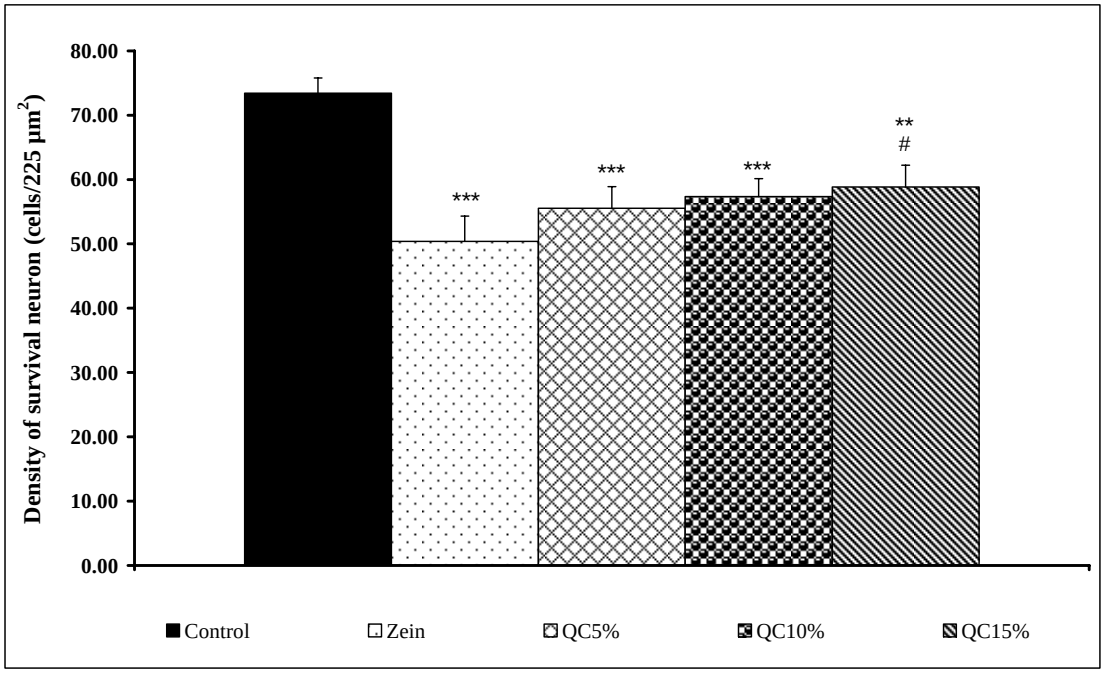


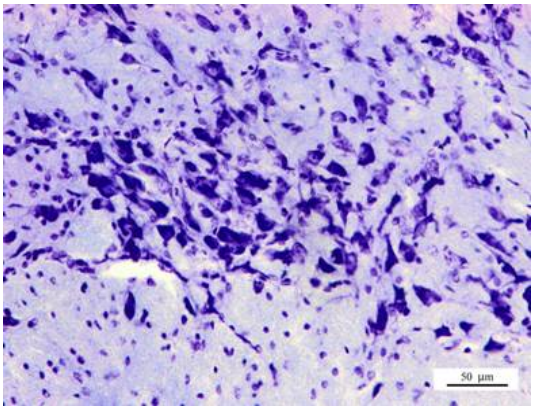
Figure 45 The effect of transdermal quercetin administration on the density of survival neuron in right substantia nigra. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

** p-value <0.01 compared with control

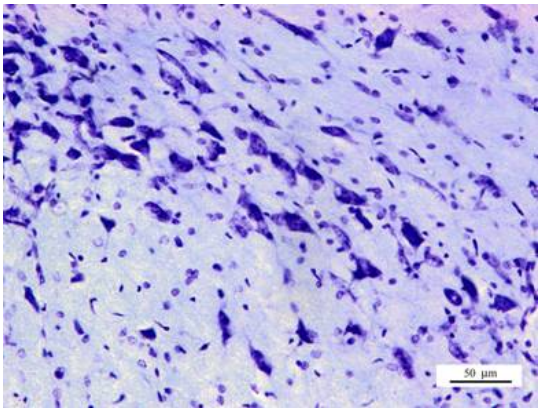
*** p-value <0.001 compared with control

p-value <0.05 compared with zein + 6-OHDA

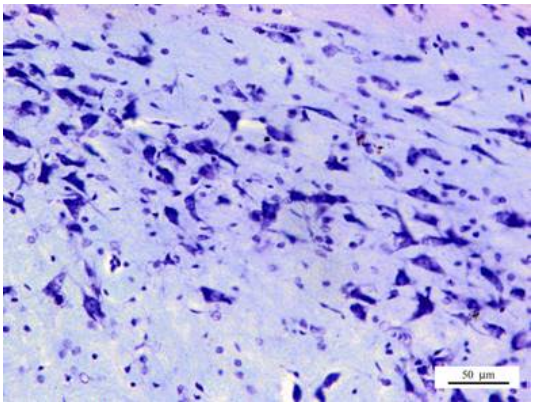
Control



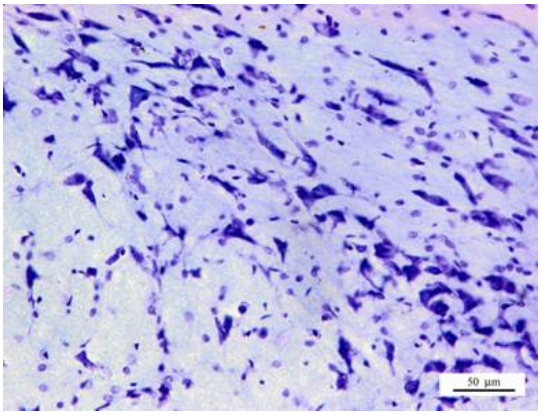
Zein



QC 5%



QC 10%



QC 15%

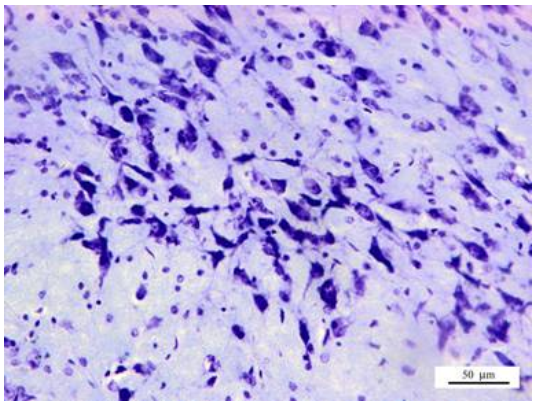


Figure 46 Photographs of coronal section of right substantia nigra stained with cresyl violet at 40X magnification.

Table 22 The effect of transdermal quercetin administration on the density of survival neuron in right striatum.

Group (Treatment)	Density of neuron (cells/225μm^2)
Control	149.280 ± 5.501
Zein	120.720 ± 2.903 ***
QC5%	123.920 ± 3.601 ***
QC10%	125.400 ± 3.146 ***
QC15%	131.480 ± 1.885 **, #

Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed and their brains were removed to determine the density of survival neuron in right striatum. Data were presented as mean ± S.E.M. (n=5 per group).

** p-value <0.01 compared with control

*** p-value <0.001 compared with control

p-value <0.05 compared with zein + 6-OHDA

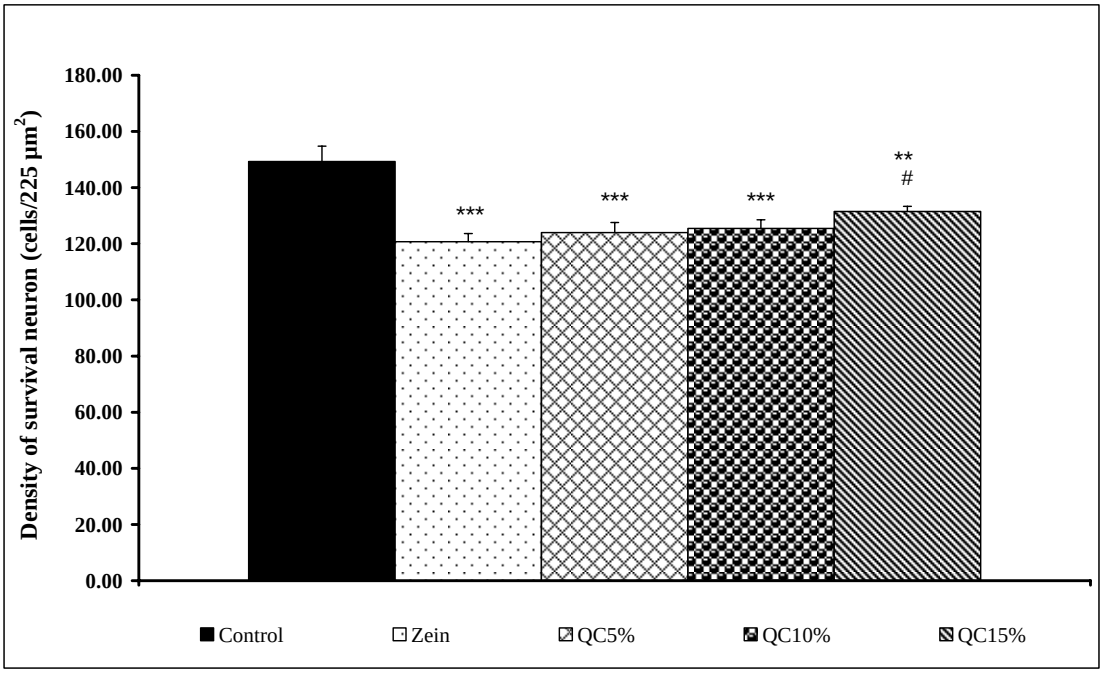


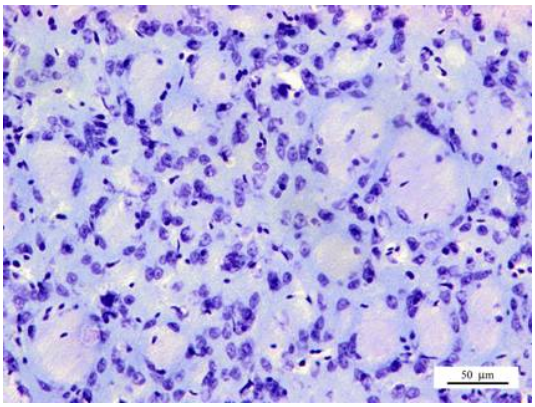
Figure 47 The effect of transdermal quercetin administration on the density of survival neuron in right striatum. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

** p-value <0.01 compared with control

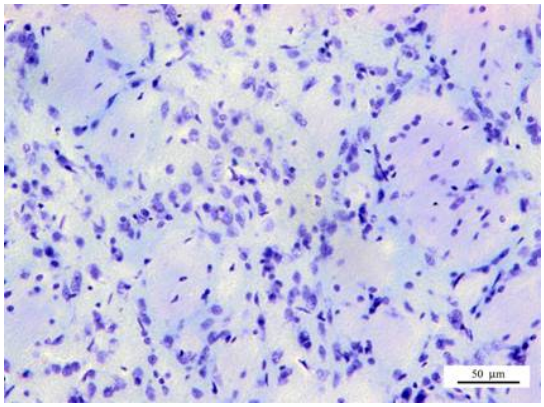
*** p-value <0.001 compared with control

p-value <0.05 compared with zein + 6-OHDA

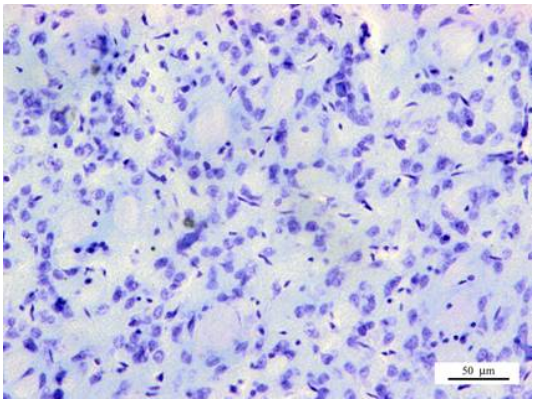
Control



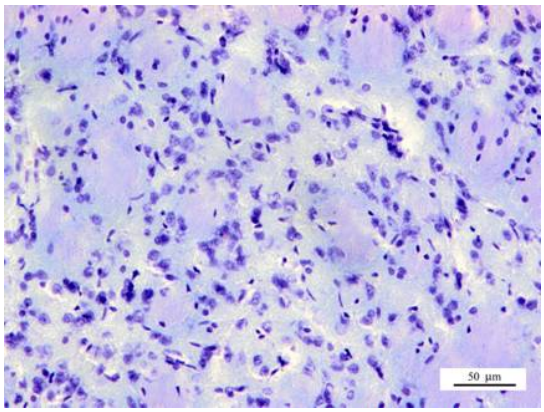
Zein



QC 5%



QC 10%



QC 15%

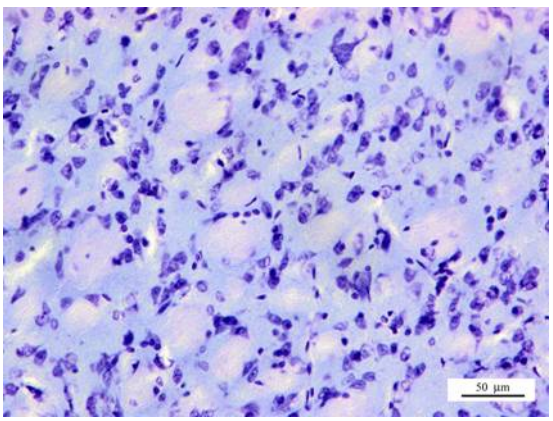


Figure 48 Photographs of coronal section of right striatum stained with cresyl violet at 40X magnification.

Table 23 The effect of transdermal quercetin administration on the density of tyrosine hydroxylase positive neuron in right substantia nigra.

Group (Treatment)	Density of neuron (cells/225μm^2)
Control	44.280 ± 0.789
Zein	11.640 ± 0.133 ***
QC5%	12.960 ± 0.354 ***
QC10%	12.840 ± 0.717 ***
QC15%	14.840 ± 0.204 ***, ##

Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed and their brains were removed to determine the density of tyrosine hydroxylase positive neuron in right substantia nigra. Data were presented as mean ± S.E.M. (n=5 per group).

*** p-value <0.001 compared with control

p-value <0.01 compared with zein + 6-OHDA

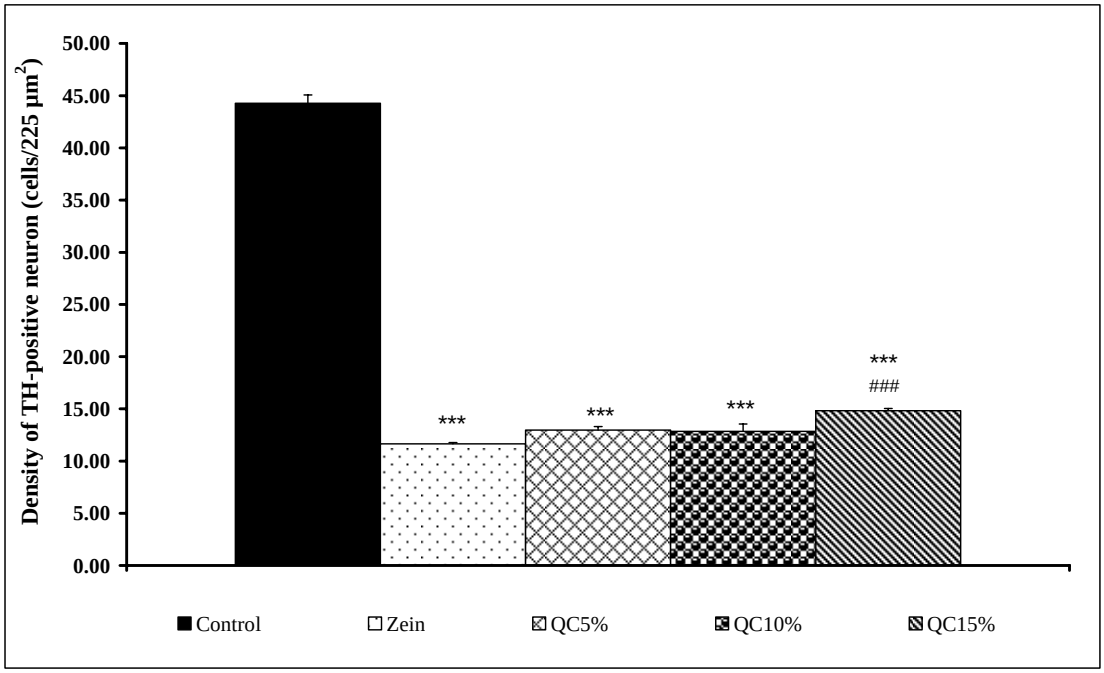
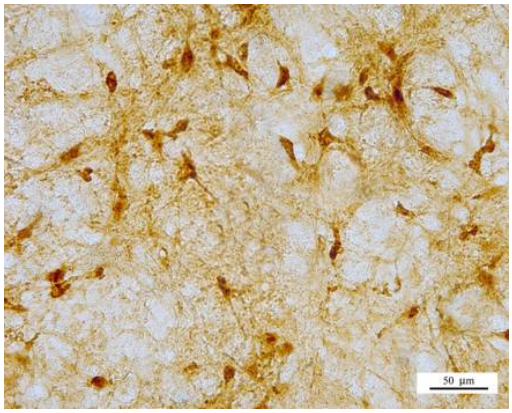


Figure 49 The effect of transdermal quercetin administration on tyrosine hydroxylase positive neuron in right substantia nigra. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

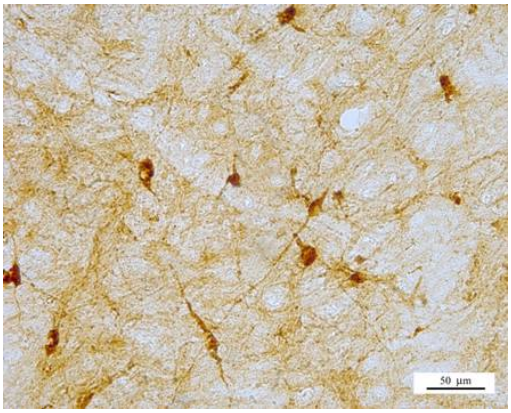
*** p-value <0.001 compared with control

p-value <0.05 compared with zein + 6-OHDA

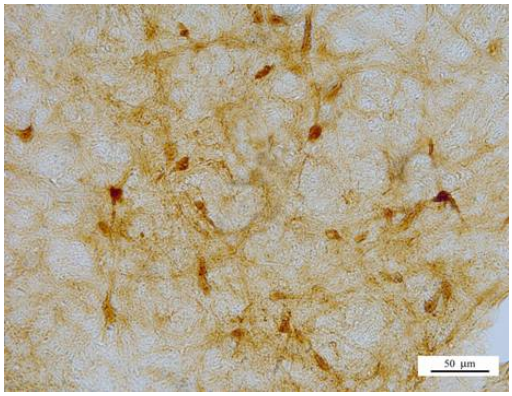
Control



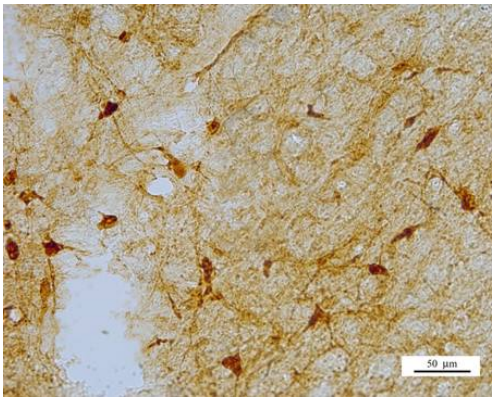
Zein



QC 5%



QC 10%



QC 15%

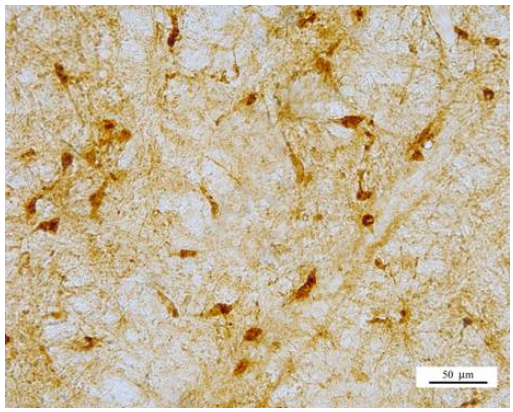


Figure 50 Photographs of coronal section of right substantia nigra stained with monoclonal antibody against tyrosine hydroxylase at 40X magnification.

Table 24 The effect of transdermal quercetin administration on the level of MDA in right striatum and hippocampus.

Group (Treatment)	MDA (nmole/ mg protein)	
	Striatum	Hippocampus
Control	0.355 ± 0.043	0.472 ± 0.151
Zein	0.536 ± 0.064 *	0.888 ± 0.107 **
QC5%	0.433 ± 0.085	0.772 ± 0.060 *
QC10%	0.337 ± 0.035 #	0.650 ± 0.078
QC15%	0.300 ± 0.019 ##	0.404 ± 0.049 ##

Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the MDA level. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with zein + 6-OHDA

\## p-value <0.01 compared with zein + 6-OHDA

** p-value <0.01 compared with control

\## p-value <0.01 compared with zein + 6-OHDA

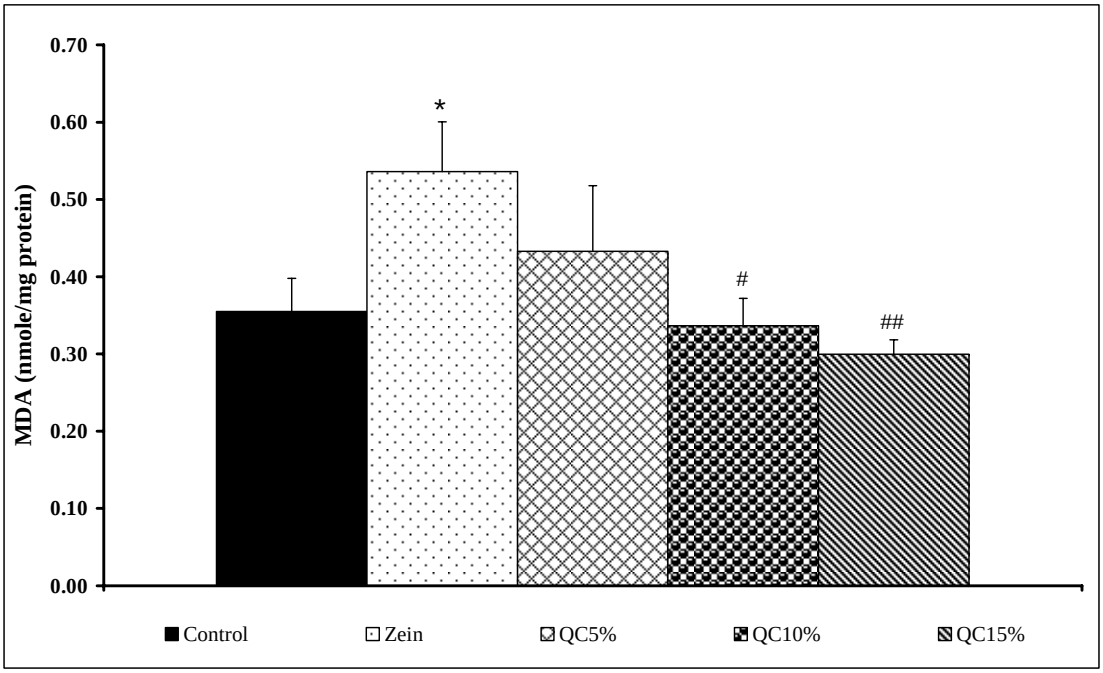


Figure 51 The effect of transdermal quercetin administration on the level of malondialdehyde (MDA) in right striatum. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with zein + 6-OHDA

\## p-value <0.01 compared with zein + 6-OHDA

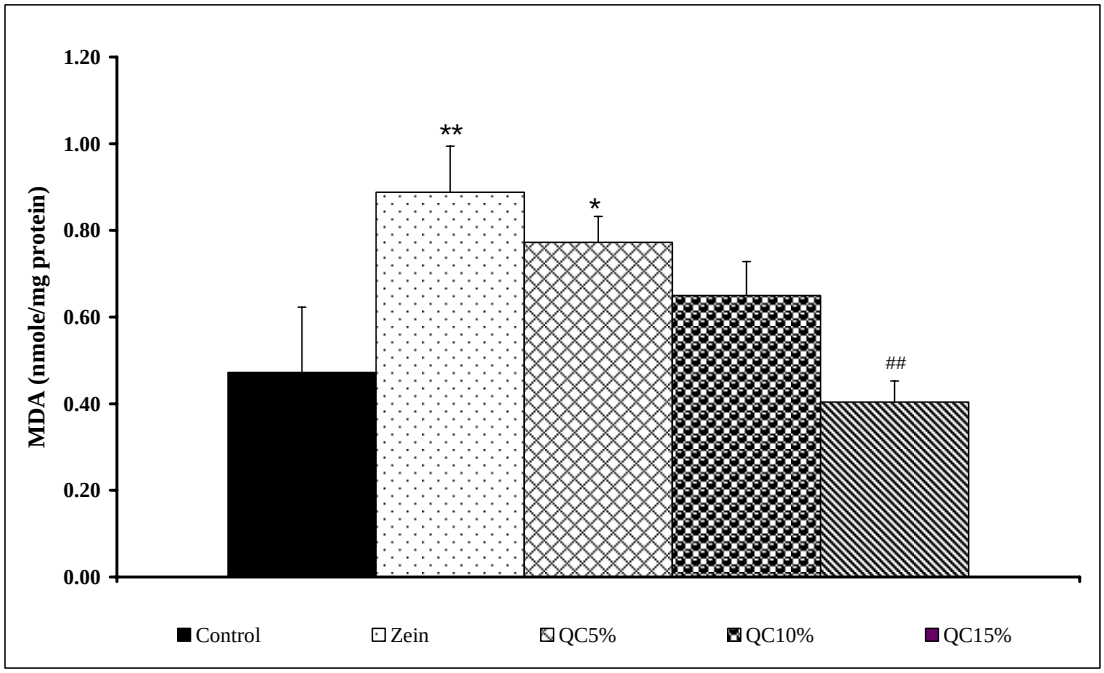


Figure 52 The effect of transdermal quercetin administration on the level of malondialdehyde (MDA) in right hippocampus. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

** p-value <0.01 compared with control

p-value <0.01 compared with zein + 6-OHDA

Table 25 The effect of transdermal quercetin administration on the activity of SOD (superoxide dismutase) in right striatum and hippocampus.

Group (Treatment)	SOD (units/ mg protein)	
	Striatum	Hippocampus
Control	1.836 ± 0.477	3.212 ± 0.622
Zein	0.597 ± 0.210 *	1.677 ± 0.500 *
QC5%	0.992 ± 0.332	2.788 ± 0.312
QC10%	1.219 ± 0.241	2.928 ± 0.394
QC15%	1.575 ± 0.278 #	3.408 ± 0.358 #

Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the level of MDA. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with zein + 6-OHDA

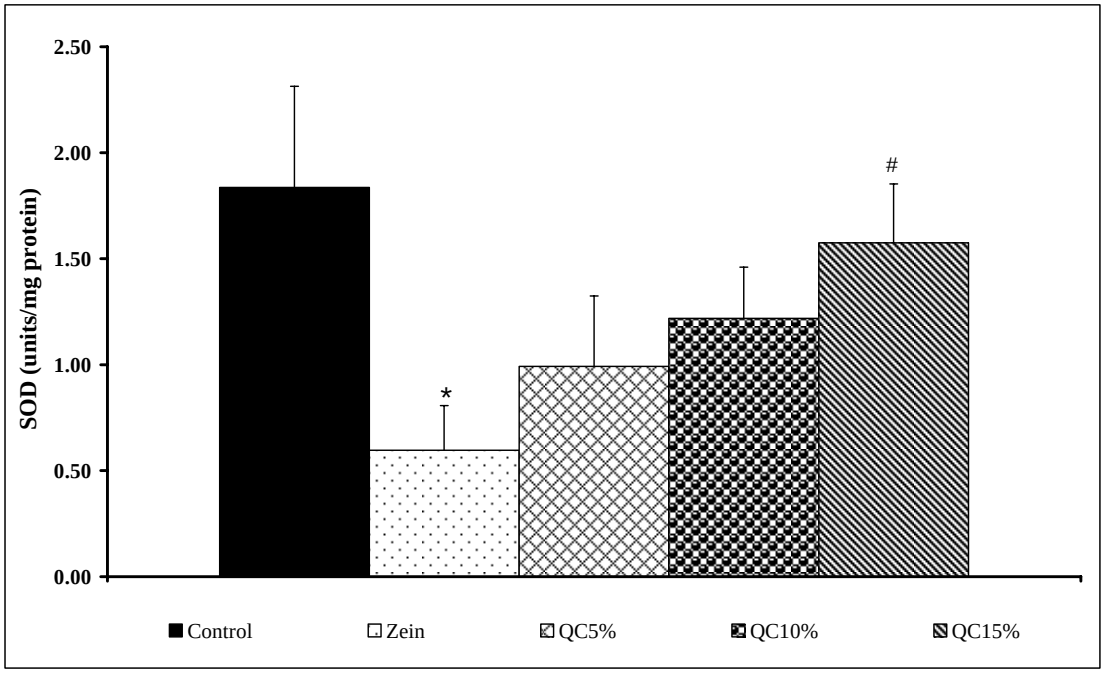


Figure 53 The effect of transdermal quercetin administration on the activity of SOD (superoxide dismutase) in right striatum. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with zein + 6-OHDA

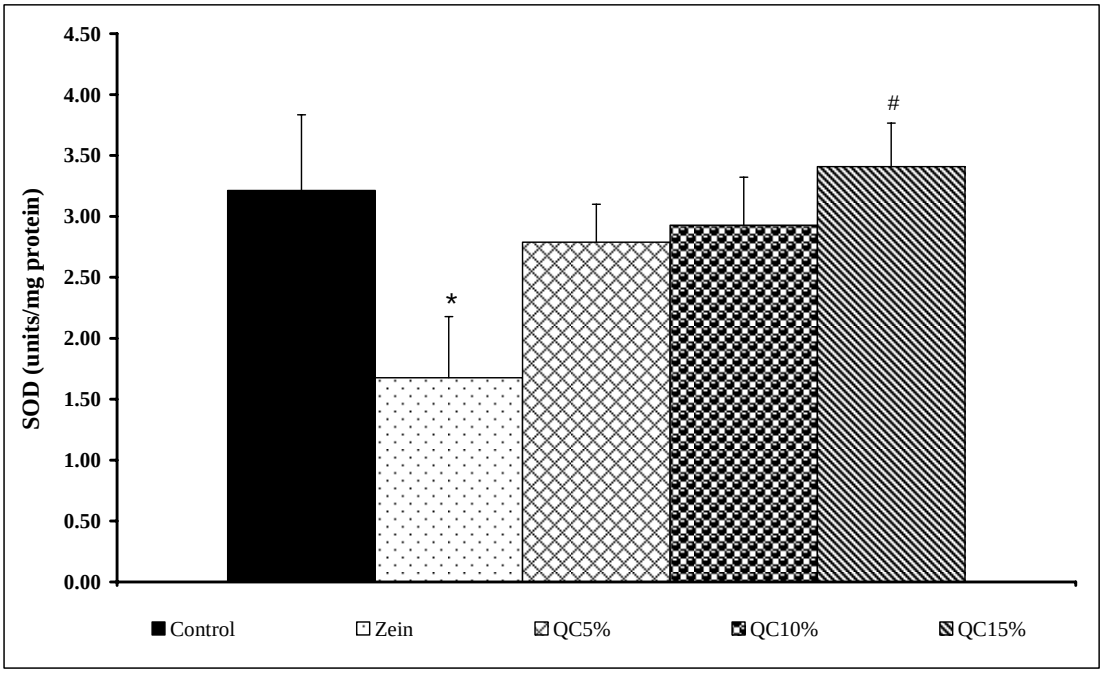


Figure 54 The effect of transdermal quercetin administration on the activity of SOD (superoxide dismutase) in right hippocampus. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with zein + 6-OHDA

Table 26 The effect of transdermal quercetin administration on the activity of GPx (glutathione peroxidase) in right striatum and hippocampus.

Group (Treatment)	GPx (units/ mg protein)	
	Striatum	Hippocampus
Control	3.927 ± 0.959	4.638 ± 1.370
Zein	2.423 ± 0.301	3.251 ± 0.933
QC5%	4.137 ± 0.575	5.040 ± 0.673
QC10%	4.393 ± 0.773	4.177 ± 0.667
QC15%	6.664 ± 1.035 $^{*, \#\#}$	6.818 ± 0.549 $^{\#}$

Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the activity of GPx. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\# p-value <0.05 compared with zein + 6-OHDA

\#\# p-value <0.01 compared with zein + 6-OHDA

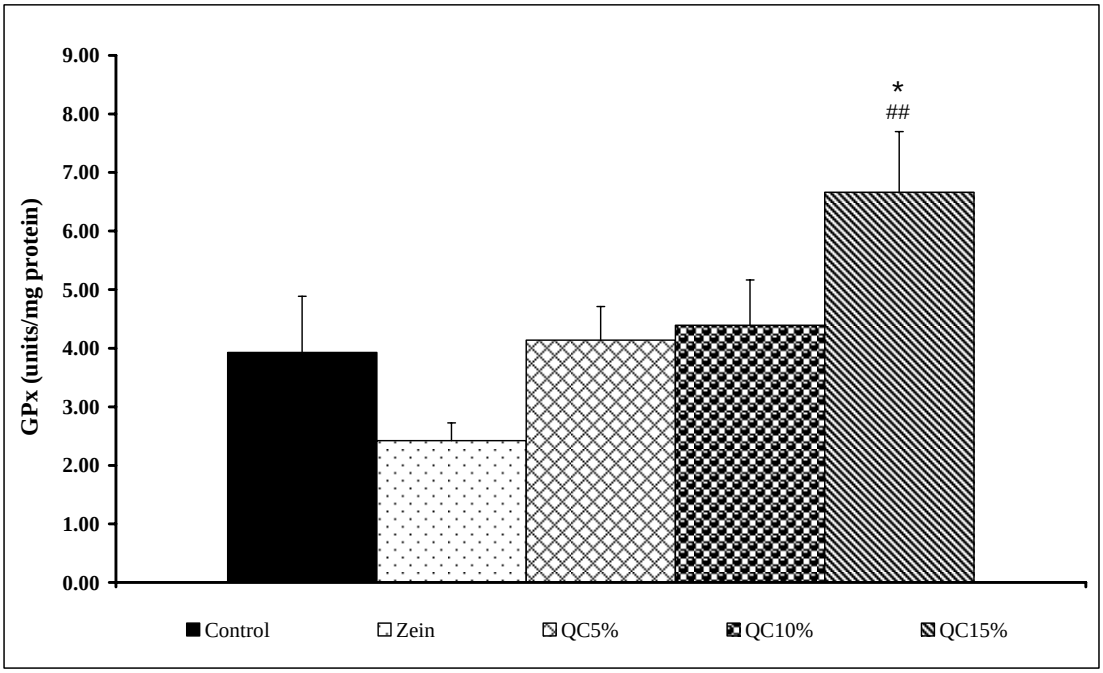


Figure 55 The effect of transdermal quercetin administration on the activity of GPx (glutathione peroxidase) in right striatum. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\## p-value <0.01 compared with zein + 6-OHDA

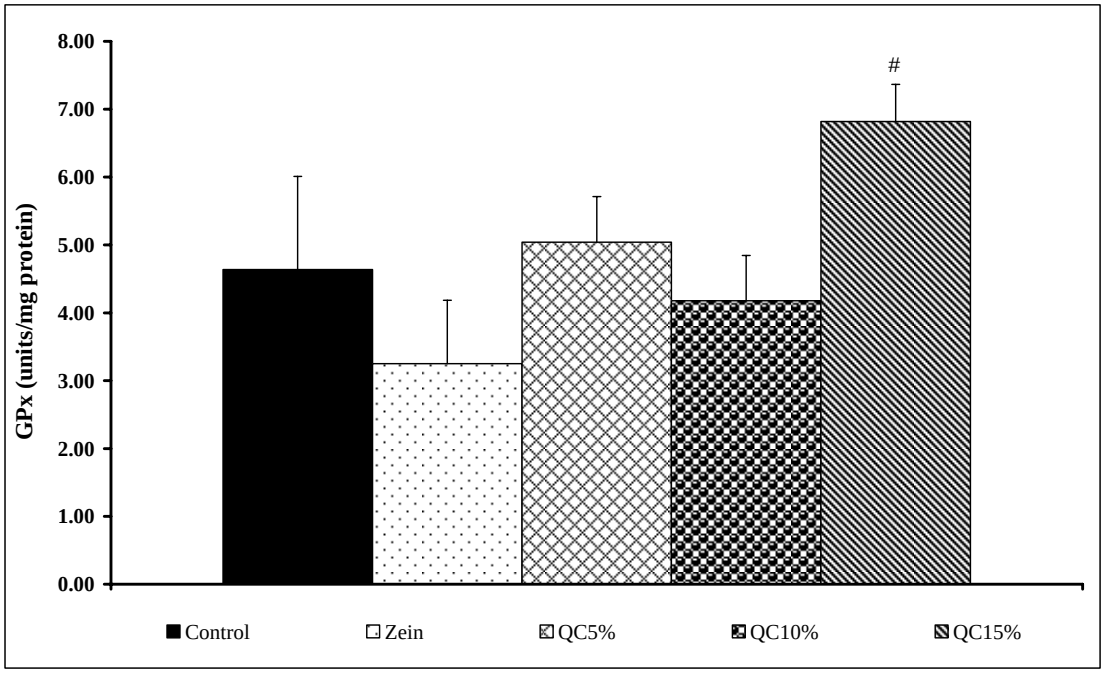


Figure 56 The effect of transdermal quercetin administration on the activity of GPx (glutathione peroxidase) in right hippocampus. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

p-value <0.05 compared with zein + 6-OHDA

Table 27 The effect of transdermal quercetin administration on the activity of CAT (catalase) in right striatum and hippocampus.

Group (Treatment)	CAT (units/ mg protein)	
	Striatum	Hippocampus
Control	17.724 ± 1.871	31.086 ± 3.453
Zein	15.968 ± 1.160	31.546 ± 4.830
QC5%	19.895 ± 1.794	31.171 ± 3.375
QC10%	20.464 ± 1.244	22.679 ± 2.359
QC15%	21.790 ± 2.216 #	19.514 ± 0.990

Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the activity of CAT. Data were presented as mean ± S.E.M. (n=5 per group).

p-value <0.05 compared with zein + 6-OHDA

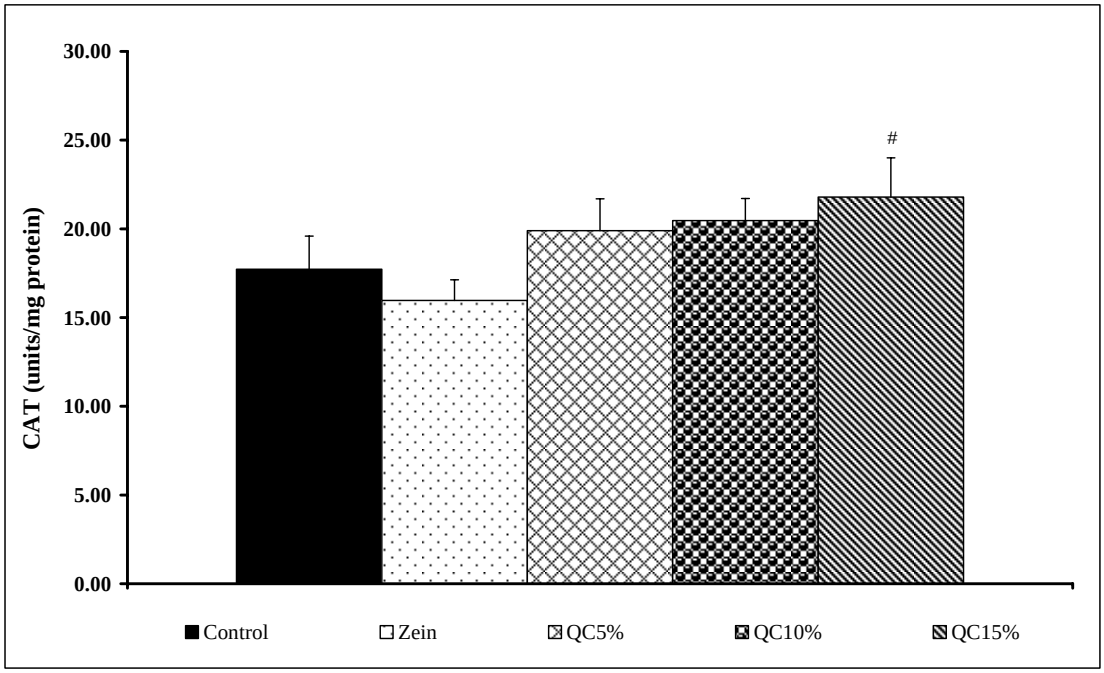


Figure 57 The effect of transdermal quercetin administration on the activity of CAT (catalase) in right striatum. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented mean ± S.E.M. (n=5 per group).
p-value <0.05 compared with zein + 6-OHDA

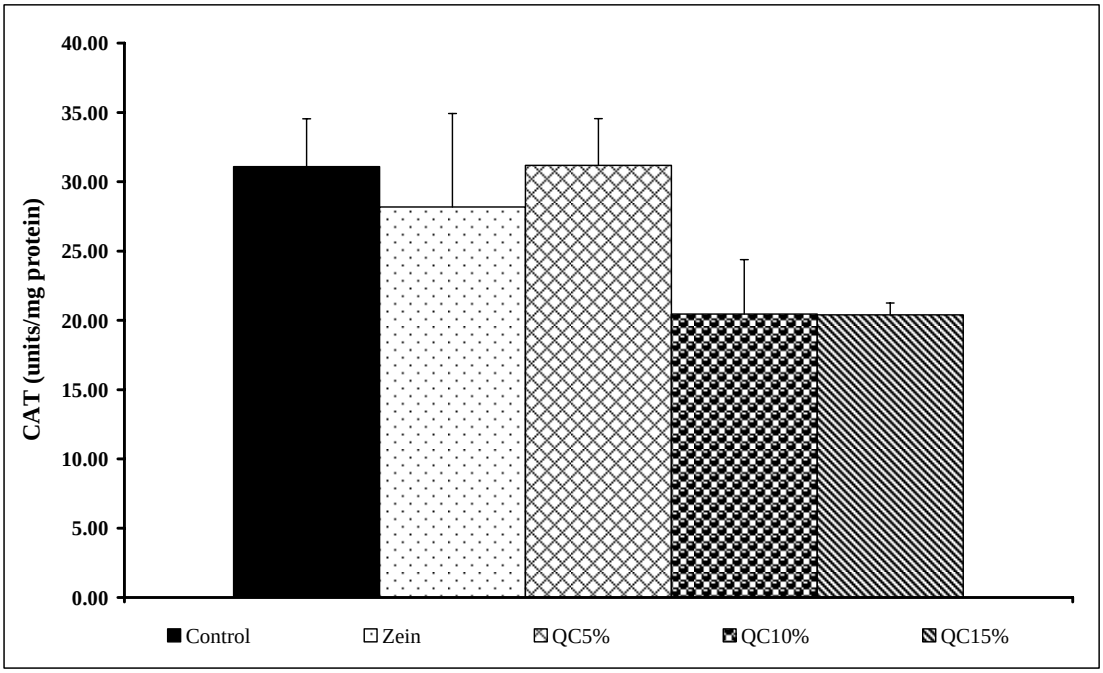


Figure 58 The effect of transdermal quercetin administration on the activity of CAT (catalase) in right hippocampus. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

Table 28 The effect of transdermal quercetin administration on the activity of AChE (acetylcholinesterase) in right striatum and hippocampus.

Group (Treatment)	AChE (umole/min. mg. protein)	
	Striatum	Hippocampus
Control	0.0825 ± 0.0264	0.0512 ± 0.0083
Zein	0.0860 ± 0.0131	0.0601 ± 0.0108
QC5%	0.0616 ± 0.0083	0.0483 ± 0.0143
QC10%	0.0484 ± 0.0183	0.0329 ± 0.0061
QC15%	0.0354 ± 0.0054 #	0.0213 ± 0.0017 **, #

Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. After the last dose of administration the rats were sacrificed, right striatum and hippocampus were separated and collected to determine the activity of AChE. Data were presented as mean ± S.E.M. (n=5 per group).

** p-value <0.01 compared with control

p-value <0.05 compared with zein + 6-OHDA

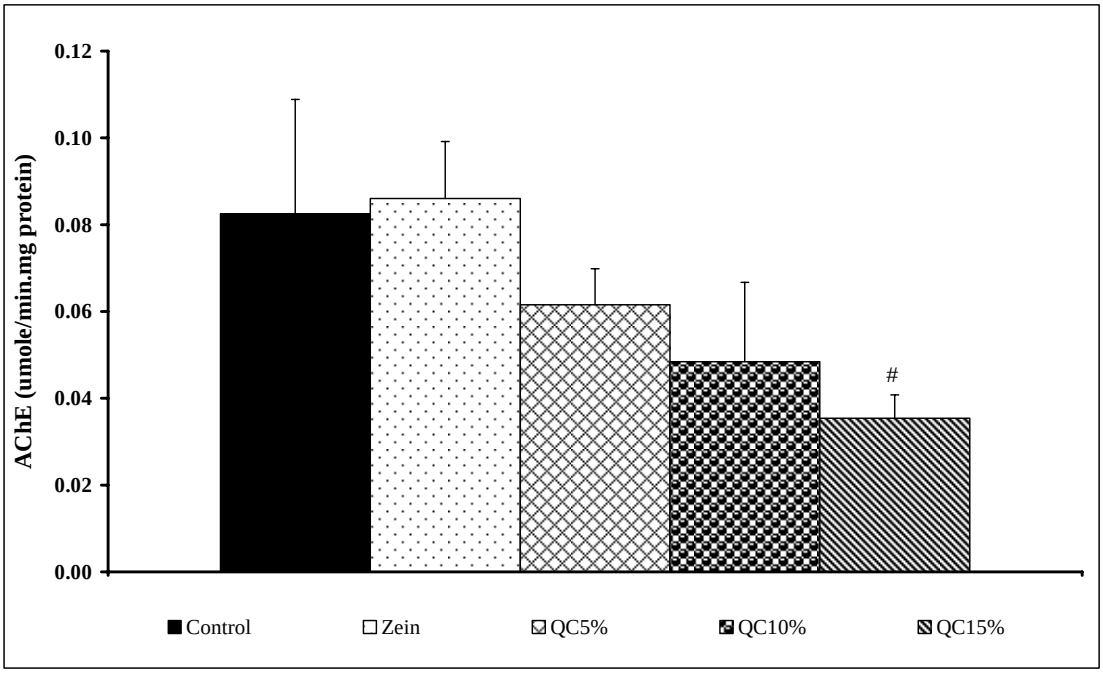


Figure 59 The effect of transdermal quercetin administration on the activity of AChE (acetylcholinesterase) in right striatum. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

p-value <0.05 compared with zein + 6-OHDA

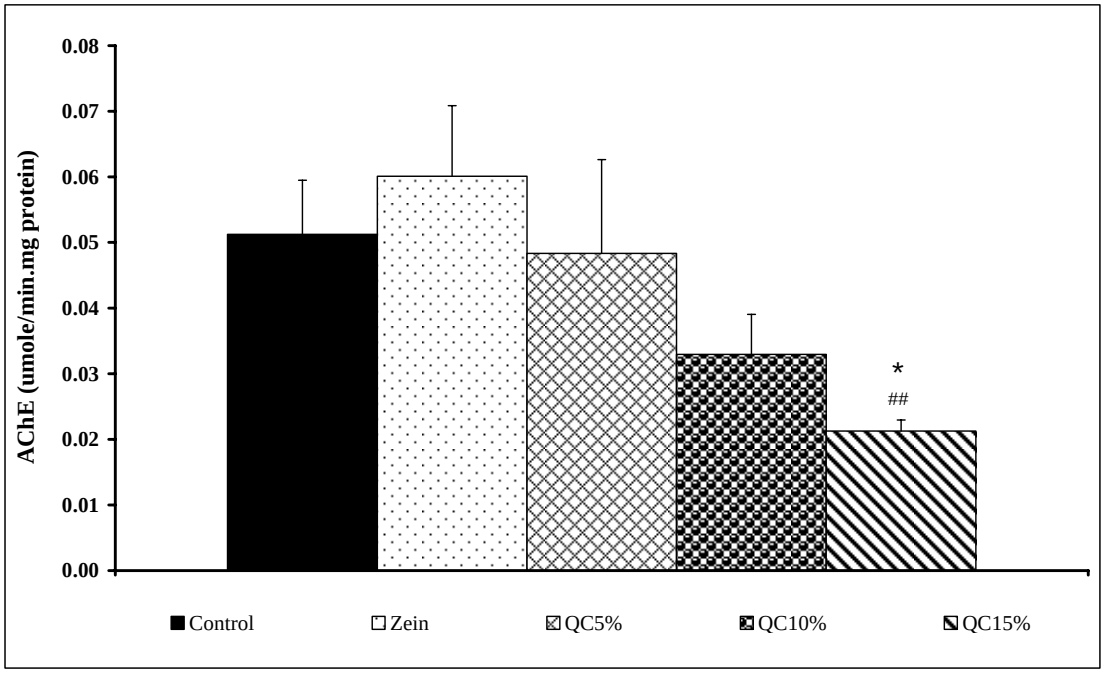


Figure 60 The effect of transdermal quercetin administration on the activity of AChE (acetylcholinesterase) in right hippocampus. Rats were received transdermal zein based quercetin nanofiber patch at a period of 14 days before and 14 days after 6-OHDA injection. Data were presented as mean ± S.E.M. (n=5 per group).

* p-value <0.05 compared with control

\## p-value <0.01 compared with zein + 6-OHDA