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SESAMOL IN ASSOCIATION WITH FOLIC ACID SHOWS ANTI-PARKINSON EFFECT ON 6-OHDA INDUCED PARKINSONIAN ANIMAL BY REGULATING THE PARK GENES

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ABSTRACT

Parkinson disease (PD) is a progressive neurodegenerative disorder which leads to motor impairment. Sesamol (SA) is a potent antioxidant, present in sesame oil and Folic acid (FA) involved in dopamine synthesis was combined together in this study and their impact on 6-OHDA induced animals was to be studied. The gene and protein expression of DJ-1, LRRK-2 and parkin were analysed by RT-PCR and western blotting. The level of dopamine was estimated by fluorimetric analysis. The presence of tyrosine hydroxylase positive (TH^+) neurons was analysed by immunohistochemistry. On comparison with L-dopa, the SA and FA treated animals shows a protective effect on neurons toxicated with 6-OHDA. SA and FA suppress LRRK-2 and trigger the DJ-1 and parkin synthesis by regulating their respective gene. SA and FA have regulated dopamine level and TH^+ neurons. Thus SA and FA may serve as a novel combined drug for treatment of PD.

KEY WORDS: Parkinson's disease, Sesamol, Folic acid, DJ-1, LRRK-2, parkin

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INTRODUCTION

Parkinson disease is a progressive neurodegenerative disorder which leads to motor impairment. The prevalence of the disease is of about 1-2% of age above 60 and it rises to ~4% of population above 80 ages. The pathology of the disease is the degeneration of dopamenergic neurons of substantisa nigra in Basal ganglia, which synthesise the neurotransmitter called Dopamine. The depletion of these neurons will reduce the dopamine levels which were mainly involved in locomotary event of the body. Thus the preliminary symptoms of the disease are motor impairment like difficult in walking, rigidity, tremor and braykinesia[1]. The progression of PD also develops cognitive and autonomic functional complications, which affects the quality of life of the patients[2]. The clear mechanism for the cause of degeneration is still a mystery, but certain causative factors like oxidative stress, protein aggregation, environmental pesticides and genetic factors are identified by the researchers. Oxidative stress is found to be a key cause of almost all the deadly diseases. The generation of free radical in the cell can damage the cell integrity. In Parkinson's disease oxidative stress plays a critical role which was evidenced by several studies[3,4]. The recent research showed that several genes have been linked to Parkinson's disease. Six among them are in particular, which are α- synucline, UCHL-1, PARK2 (Parkin), PARK 7 (DJ-1), PINK-1, and LRRK-2[5, 6]. DJ-1 gene (PARK 7) plays a role in protecting the cell by various mechanisms and prevents the neurons from Daxx induced apoptosis after oxidative stress[7]. In Parkinson's disease cases the DJ-1 is down regulated than those of non-Parkinson control[8]. The other gene called LRRK2 has been mutated in PD and more than 8 mutations have been identified[9,10]. A study also demonstrates that the LRRK2 play a critical role in lewy body formation and disease pathology of PD[11]. The parkin gene has a protective effect on dopamenirgic neuron which involve in protein degradation process[12,13]. Thus mutation in parkin gene leads to protein aggregation. The inactivation of native protein (parkin) was due to the oxidative stress and s-nitrogylation[5]. The modern medications like levodopa and dopamine antagonist for the disease help to manage the early motor symptoms but not to arrest the degeneration of neurons. When the disease progress the degeneration continues and the drugs become impotent to treat even the symptoms and create several other complications like sleeping disturbance and emotional problems. At this situation there comes the need for novel therapeutic drugs which should scavenge the free radicals and protect the neurons from degeneration. Recent studies show that many phenols and flavonoids play an important role in treating neurodegenerative disorders including PD[14]. Sesamol (SA) is one of the potent antioxidant, present as a constituent of sesame oil. This oil is one of the functional foods around worldwide obtained from the plant sesame (*Sesamum indicum* L.). SA has anti-photo oxidative activity because of its ability to scavenge singlet oxygen[15]. In glail astrocyte cells, SA also prevents the production of nitric oxide and hydrogen peroxide and reduces monoamine oxidase activity[16]. This monoamine oxidase activity play important role in development of neurodegenerative disorder. The bioavailability and tissue distribution study of SA in rats shows that sesamol can cross the blood brain barrier[17]. Folic acid (FA) also come into the picture of study because its essentiality in Parkinson's disease. FA is mainly involved in the mechanism of dopamine synthesis. It is reported that the deficiency of FA can endanger Parkinson's disease[18]. Another study shows that a high intake of vitamins-B has anti-parkinson effect[19]. Thus SA and FA have brought together may provide a better result in treating Parkinson's disease. 6-hydroxy dopamine (6-OHDA) a well-known neurotoxin was used as a model to demonstrate this study. 6-OHDA is used as a hydroxylated analogue for natural dopamine. On intrastriatal administration of 6-OHDA generate hydrogen peroxide and hydroxyl radical and produce oxidative stress which was proven by several studies[20,21]. The preliminary behavioural study and antioxidant profile of rats were analysed and the results

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have been published[22]. So the study has been extended to show the effect of SA and FA on 6-OHDA induced animal at the gene and protein levels. The gene expression of DJ-1, LRRK-2 and parkin were analysed by RT-PCR and their protein levels were determined by western blotting. The level of dopamine was estimated by fluorimetric analysis. The presence of tyrosine hydroxylase positive (TH^+) neurons was analysed by immunohistochemistry.

MATERIALS AND METHODS

(i) Chemicals used for the study

6-Hydroxydopamine, Sesamol (SA), L-Dopa, Apomorphine, Folic acid (FA) and ascorbic acid were purchased from Sigma-Aldrich. All the other chemicals used for the study were of analytical grade.

(ii) Experimental protocol

Male Wistar rats of weight 200–250 g was purchased and maintained at 25±2ºC in 12 h light/dark cycle with free access to food and water. The animal protocol was approved by the Institutional Animal Ethical Committee of Saveetha University (SU/BRULAC/RD/004/2013). The rats were segregated into five groups having 6 rats in each group, Group 1 (control), Group 2 (Lesion), Group 3 (Lesion+ SA), Group 4 (Lesion + SA+ FA) and Group 5 (Lesion+ L-dopa). The rats were anesthetized and infused with 6-hydroxydopamine at the rate of 1µl/min, 2µl of 6-hydroxydopamine (10µg/2µl in 0.1% ascorbic acid) was injected intrastriatally in right striatum once for the development of PD. The regions were located according to rat brain atlas (antero-posterior 0.5 mm, lateral 2.5 mm, dorso-ventral 4.5mm relative to bregma and ventral from dura). After 21 days the disease development was confirmed by Apomorphin induced contra lateral rotational test[23]. The animals were treated with SA (30mg/kg body weight, intra peritoneally with saline as vehicle), FA (5mg/kg body weight dissolved in water given orally) and L-dopa (100mg/kg body weight dissolved in water given orally) for the next 24 days.

(iii) Estimation of Neurotransmitter level in striatum

The animals were sacrificed by cervical dislocation and the brains were removed immediately. The striatum was separated, weighed and homogenated with 6ml of cold acidified butanol at 800×g. Aliquots of each homogenate serve as tissue sample. The known amount of dopamine was prepared in parallel with tissue sample. The blank, standard and tissue samples were estimated for dopamine levels by spectrofluorimetric analysis following the method described by Kari et al., [24] and the level was expressed as ng/ g wet tissue.

(iv) Immunohistochemistry analysis

The brains of the sacrificed animals were removed, the striatum was separated and fixed in 4%of paraformaldehyde in PBS (phosphate buffer solution) at pH 7.4 and then immersed in 10%-30% of sucrose until they sunk. About 30µm thickness of tissue was sliced and mounted on gelatine coated slide. The slides were washed in decreasing concentration of ethanol (100%-10%) at 5min interval and incubated in citrate buffer at pH 6.0. After three wash with PBS the slides were treated with 20:1 mixture of 0.3% hydrogen peroxide and Triton X-100 to block endogenous peroxidase activity. The slides were washed with 0.5% bovine serum albumin and the sections were incubated with monoclonal (mouse) anti-tyrosine hydroxylase antibody (1:500). After 24hrs the section were washed with PBS and then incubated with appropriate biotinylated and avidin-biotin complex for 1 hr at room temperature. The immune stained slides were analysed by bright field microscopy.

(v) Expression of genes by RT-PCR

Total RNA was isolated from the homogenated brain tissue (striatum). RT-PCR was carried out by denaturing the isolated RNA along with primer at 65ºC. cDNA was synthesised and amplified by PCR(Polymerase chain reaction) method. Amplified PCR samples were analysed in agrose gel electrophorosis. The following primers are used for the respective gene.

DJ-1 Primer Forward - 5'-GGATGCTGGGAACCGAACCTGGGTC-3'

	Primer Reverse - 5'-CTGGGCTACAGCCTGAACCCCACAC-3'
LRRK2	Primer Forward - 5′-TGGGTTGGTCACTTCTGTGC-3′
	Primer Reverse - 5′-CATTGGCTGGAAATGAGTGC-3′
Parkin	Primer Forward - 5′-CCAAACCGGATGAGTGGTGAGTGC-3′
	Primer Reverse - 5′-ACACGGCAGGGAGTAGCCAAGTTG-3′
β-actin	Primer Forward - 5′-GTAGACAAAATGGTGAAGGTCGGTG-3′
	Primer Reverse - 5′-CTCGCTCCTGGAAGATGGTGATGGG-3′

(vi) Western Blot analysis for protein expression

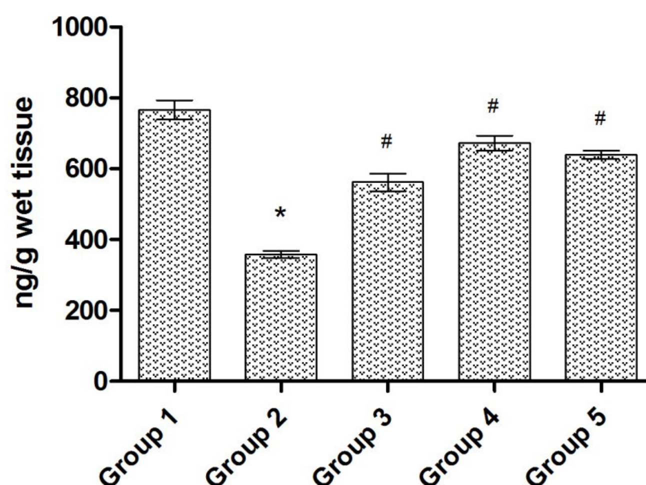
The brain tissue (striatum) of rats were homogenised in PBS at pH of 7.4 with protease inhibitor. The proteins were separated on 10%SDS-PAGE gel and transferred to a nitrocellulose membrane. After blocking the non-specific binding protein with non-fat milk, membranes were incubated with respective mouse monoclonal antibodies like anti-DJ-1, anti- LRRK-2, anti- parkin and anti-actin at 1:1000 dilutions. The secondary antibodies, horseradish peroxidase-conjugated with either anti-mouse or anti-rabbit were used at 1:2000 dilutions. The conjugated antigen-antibody complex were visualised in chemiluminescence system.

RESULTS

1. Dopamine level in striatum

The level of dopamine was estimated by spectrofluorimetric analysis (Graph.1). In comparison with control animals the dopamine level in lesion group was reduced significantly of $p<0.001$ and it is restored by SA and FA treatment. In SA treated group and L-dopa treated group the dopamine level was increased but not as much as SA and FA treated group of rats.

Graph 1
Dopamine level in striatum



Dopamine levels in striatum of animals. Group1-control, Group 2- Lesion, Group 3- Lesion+SA, Group 4- Lesion+SA+FA and Group 5- Lesion+L-Dopa.
The value are expressed in mean ±S.E.M, *p<0.001 Lesion vs Control and #p<0.001 SA, SA+FA, L-Dopa vs Lesion.

2. Immunohistochemistry study for Tyrosine hydroxylase activity in right striatum

The immunohistochemical analysis (Figure.1 A-E) shows there is a depletion in TH^{+ve} cells in right striatum due to lesion with 6-OHDA when compared with the control group animals. On SA and FA treatment tyrosine hydroxylase activity was restored and the number of TH^{+ve} cells was higher when compared with the SA treated group and L-Dopa treated group animals.

Immunohistochemistry study

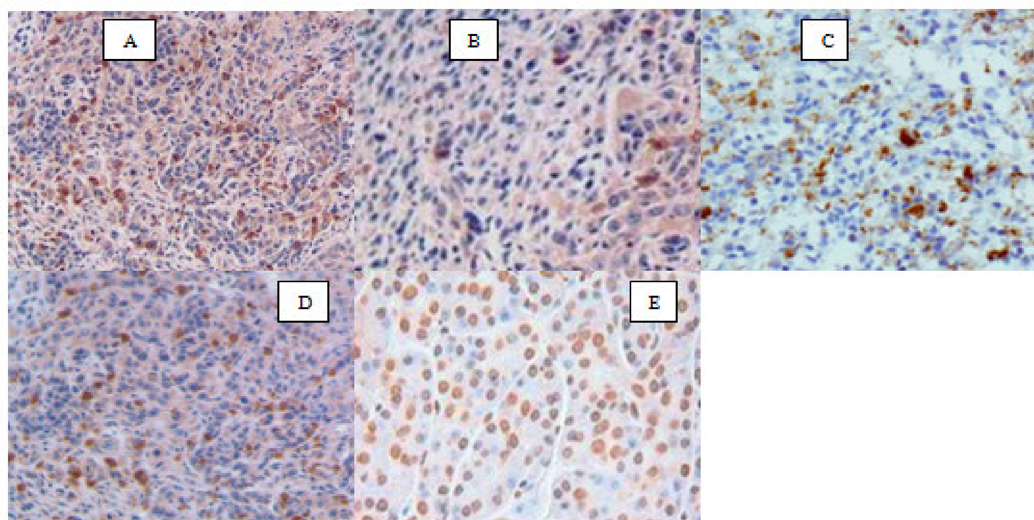


Figure 1 A-E

Immunohistochemical analysis to estimate activity of Tyrosine hydroxylase in striatum of Rats. A. Control animal shows normal structure of neurons and TH+ cells. B. Lesion animal there is reduced number TH+ cells. C.SA treated group shows an improved activity of TH as well as L-Dopa (E) treated group. D. Shows improved TH activity in the cells and restore the normal structure of neurons.

3. Expression of DJ-1, LRRK-2 and parkin gene by RT-PCR

On 6-OHDA lesion it is found that DJ-1 and parkin in right striatum of lesion animals was down-regulated, whereas LRRK-2 gene was overexpressed when compared with the control group animals this could be visualised from the Figure 2. Though the SA treated and L-dopa treated animals shows some improvement in up-regulation of DJ-1 and parkin and in suppressing the LRRK-2 gene, the SA and FA treated group animals have shown a significant regulation of these genes when compared with the lesion group animals.

Gene expression by RT-PCR

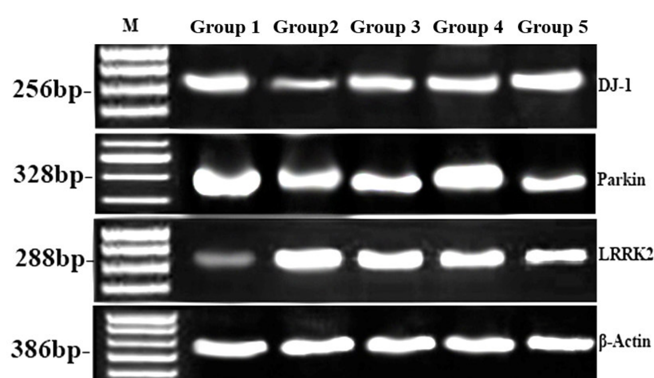


Figure 2

RT-PCR analysis for gene expression of DJ-1, parkin, LRRK2 and β-actin. Group 1 is the control rats. Group 2. Lesion group, Group 3. Lesion +SA treated group. Group 4. Lesion+SA+FA treated group. Group 5. Lesion+L-dopa treated group. On comparison with control group DJ-1& parkin gene was down-regulated and LRRK2 gene was up-regulated in Lesion group this was regulated on SA and FA treatment.

4. Protein expression of DJ-1, dardarin (LRRK-2) and parkin by Western Blotting

Figure 3 shows protein expression of DJ-1, dardarin (LRRK-2) and parkin. The band-width shows the levels of protein in brain of the animals. Lane.1 represents the control group in which protein expression of control animals were expressed. Lane.2 repersents the induced animals in which DJ-1 and parkin levels were reduced and dardarin levels were over expressed when compared with control group.

Protein expression by western blotting analysis

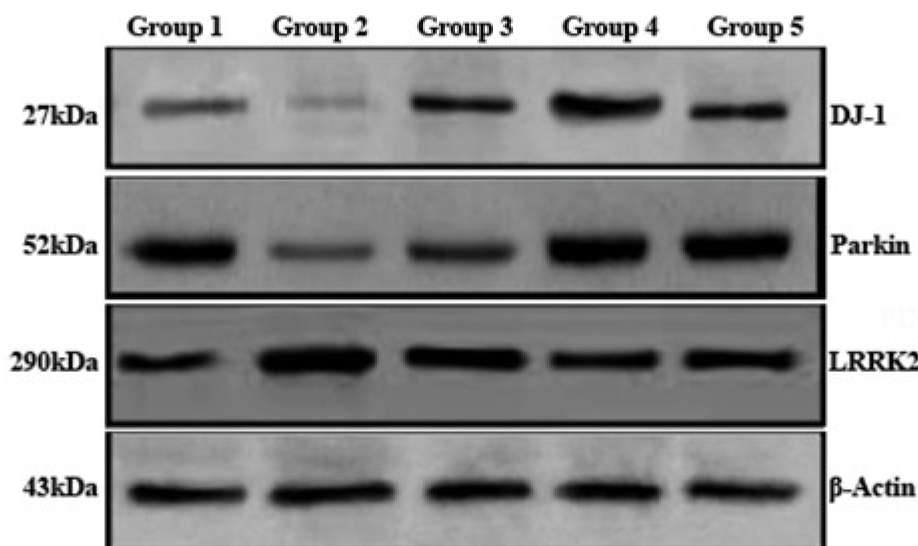


Figure 3

Protein expression of DJ-1, parkin, LRRK2 and β-actin by Western Blotting. Group 1 is the control rats. Group 2. Lesion group, Group 3. Lesion +SA treated group. Group 4. Lesion+SA+FA treated group. Group 5. Lesion+L-dopa treated group. On comparison with control group DJ-1& parkin levels was reduced whereas dardarin level was increased by 6-OHDA lesion and this was regulated on SA and FA treatment.

On SA (Lane3) and L-dopa (Lane 5) administration shows slight variation in the protein expression were DJ-1 and parkin were mildly up-regulated and dardarin level was suppressed. But in the case of SA and FA administrated animals the protein levels were brought to near normal on comparison with control and lesion groups. In brief on SA and FA administration DJ-1 and parkinwas up-regulated and dardarin level was reduced and regulated.

DISCUSSION

The neuronal degeneration in PD was an unrevealed puzzle, but certain clues have been found by many researches. The degeneration of neurons may be due to oxidative stress, environmental toxins, mitochondrial dysfunction, protein aggregation (lewy body formation), iron accumulation[25] and genetic factor. The present medical strategy shows that there are several medications and treatment like dopamine antagonist, deep brain stimulation and gene therapy are provided[26,27]. These treatments are mainly targeted to reduce the symptoms but not to prevent the degeneration. L-dopa is the gold standard drug served for past four decades in treating PD. Though many dopamine antagonists have identified to treat PD, L-dopa was found to be the best in reducing the symptoms of the disease. But its prolong use will lead to high risk of motor fluctuation, dyskinesia and dopamine dysregulation syndrome[28]. As the oxidative stress is a hallmark of PD, the recent studies were focused on identifying a novel therapeutics drug to arrest or to delay the degeneration process[29]. SA is one of the power full antioxidant, which scavenges the free radicals very effectively in both *in-vitro*[30] and *in-vivo* studies[31, 32]. Here in this study we demonstrated that SA has anti-parkinson

effect in association with FA. SA has protected the neurons from further neuronal degeneration by regulating the antioxidant profile of rats and improved the behavioural activity of rats[21]. SA's impact on neuronal protection was also proven by analysing dopamine level in the striatum of animals which was shown in Figure1. This kind of activity emphasise that SA may have anti–parkinson effect and this was supported by several other antioxidant investigation for PD[33-35]. It is found that 6-OHDA has induced the degeneration of neurons by down regulating DJ-1 and parkin genes. DJ-1 protects the cell from oxidative stress by activating master regulator of oxidative stress, Nrf2[36]. On other hand parkin gene involve in ubiquitin ligase activation which prevents protein aggregation[12]. Down-regulation of these genes will obviously lead to oxidative stress and protein aggregation. This was regulated by SA administration in which the gene expression and protein levels were improved. As α-Synuclin is known to be the major component of Lewy body, dardarin is also a component of Lewy body. Mutation in LRRK2 will leads to protein aggregation[37]. SA has down-regulated LRRK2 gene by which the protein aggregation may be prevented due to this action. Degeneration of neuron occurs due to 6-OHDA toxication and the neuron density was reduced in which reduces tyrosine hydroxylase (TH) activity this was clearly monitored by immunohistochemistry. The TH^+ neurons are reduced in lesion group where it is restored by SA and FA administration and this was visualised by immunohistochemistry image in Figure.2. FA has been used as a supporting drug along with SA. The combined treatment of SA and FA showed better result than SA alone treated group and L-dopa treated group.

CONCLUSION

Our study has demonstrated that Sesamol is power full antioxidant which cross the brain blood barrier and enter into the regulatory mechanism of oxidative stress and protein aggregation process by regulating DJ-1, parkin and LRRK2 genes and protects the neurons form 6-OHDA toxicity. Thus, Sesamol in association with folic acid shows significant anti-parkinson effect in rats. Further investigation and clinical trials are required to justify the same.

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