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Research Article

Impact of Bioactive Compounds of *Mucuna monosperma* on Antioxidant Enzymes in PD Lines *Drosophila melanogaster*

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ABSTRACT

Parkinson's disease (PD), the most common neurodegenerative ailment, is caused by progressive damage in dopamine-secreting cells in the substantianigra. Oxidative stress plays a major role in the degeneration of dopaminergic neurons in PD. All organisms have developed adaptive responses to oxidative stress that result in increased production of defensive enzymes and antioxidant molecules. The mutations in α-synuclein protein have a role in modulating the dopamine activity. In this study, we have illustrated the protective effects of bioactive compounds of *Mucuna monosperma* (MM) against paraquat (PQ)-induced oxidative stress in a transgenic Parkinson's disease model (Elav/SNCA^{A30P}) of *Drosophila melanogaster*. The isolated L-Dopa and Ursolic compounds exhibit antioxidant properties. The activity of antioxidant enzymes and LPO has been measured in L-dopa and Ursolic acid-supplemented PD lines under oxidative stress conditions. The oxidative stress caused by PQ was averted and antioxidant enzyme activity was significantly increased in flies that were fed with a mixture of L-Dopa and Ursolic acid. SOD activities were elevated by 4.2 fold, CAT activates increased by 3.8 fold and G6Pd activates were increased by 4.6 fold under stress conditions. The synergetic effect of these bioactive compounds decreases the LPO activity by 2 fold with the increase of glutathione by 3.36 fold in transgenic PD flies. Based on the findings, we speculate that L-Dopa with Ursolic acid of *M. monosperma* prevents oxidative stress-related disorders and can be used as a possible therapeutic agent against PD disorder.

Keywords: Parkinson's disease, Oxidative stress, *Mucuna monosperma*, *Drosophila melanogaster*, Paraquat, L-Dopa, Ursolic acid, Antioxidative enzymes.

INTRODUCTION

Parkinson's disease is a neurodegenerative disorder resulting from progressive damage in dopamine-secreting cells in the substantia nigra.[1] Oxidative stress and neuro-inflammation have been recognized as key causes of dopaminergic neuron death in various forms of Parkinson's disease.[2] Dopaminergic neurons are susceptible to oxidative damage due to dopamine's inherent metabolism, which is oxidized and generates reactive oxygen species (ROS), leading to cellular oxidative stress. The elevated intracellular levels of ROS lead to free radical attacks on neural cells and contribute a calamitous role to neurodegeneration and cellular damage that includes damage of lipids, protein and DNA.[3]

The brain consumes about 20% of the oxygen supply of the body, and a significant portion of that oxygen is converted to ROS.[4] that can be generated in the brain from several sources, both in neurons and glia, with the electron transport chain being the major contributor at the mitochondrial level.[5,6] Hence ROS is the significant contributor to dopaminergic neuronal loss in the PD brain which results from dopamine metabolism, low glutathione (GSH), and high levels of iron and calcium in the SNpc.[7] The postmortem studies of PD patients' brains prove the support of a conclusive association between PD and oxidative stress, where increased oxidative activity and macromolecule damage were found in dopaminergic neurons.[7, 8]

All organisms have developed adaptive responses to oxidative stress that result in increased production of defensive enzymes, molecular chaperones, and antioxidant molecules.[9] Antioxidant and anti-inflammatory agents have been shown to play a vital role in the survival of neurons and the alleviation of PD symptoms.[10] The glial cells are capable of regulating various enzymatic systems.[10,11] with the subsequent production of cytotoxic factors. The glial cells contribute efficient antioxidative defense mechanisms for self-protection against oxidative damage, which contains glutathione in high concentrations, substantial activities of the antioxidative enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, as well as NADPH-regenerating enzymes. Their antioxidative potential protects neural cells against oxidative damage. Superoxide anions are highly reactive, that is produced mainly by mitochondrial complexes of the electron transport chain, and can easily cross the inner mitochondrial membrane, where it can be reduced to H_2O_2 by Super oxidase dismutase (SOD), and

further, catalase converts this H_2O_2 to water. Another important effective antioxidant involved in the removal of peroxides and many xenobiotic compounds is GSH, which is a tripeptide consisting of glutamate, cysteine, and glycine, with the reactive thiol group of its cysteine residue serving as an antioxidant. GSH is synthesized in the cytoplasm but has to be transported to the mitochondria, where it functions as an antioxidant molecule.[12]

GSH levels are regulated in healthy neurons, and alterations from the physiological basal levels can induce cell death. Analysis of postmortem brain tissue from PD patients shows a decreased amount of GSH. Down-regulation of GSH synthesis in the rat brain has been shown to result in progressive degeneration of nigral dopaminergic neurons.[13]

In recent studies, it has been proved that medicinal plant extracts and phytochemicals with strong neuro-protective properties reduce the signs of PD.[14,15] The neuroprotective effect of medicinal plants, including *Mucuna pruriens, Vicia faba, Nigella sativa* and *Crocus sativus* has been studied for the reduction of oxidative stress.[16]

Phytochemicals such as polyphenols, thymoquinone and curcumin have considerable protective effects on the nervous system under oxidative stress.[17] Polyphenols like curcumin, resveratrol, catechin, and oleuropein inhibit the formation of Lewy bodies.[18]

L-DOPA is a large neutral amino acid that is the precursor for catecholamines, dopamine, norepinephrine, and epinephrine, can be taken up by large neutral amino-acid transporters and decarboxylated to dopamine by aromatic amino acid decarboxylase present within neurons and glia. Thus L-Dopa contributes to its clinical efficacy in the treatment of Parkinson's disease.[19] Normally L-dopa is not found in the human body and must be synthesized from the dietary phenylalanine and tyrosine. L-dopa is commonly used for managing PD symptoms because L-DOPA can easily cross the blood-brain barrier and gets converted into dopamine. Hence, till today, L-Dopa is still the cornerstone of Parkinson's treatment.[20] Further, it has been reported that L-DOPA is the drug of choice in degenerative neurological disorders like PD, which has been used as medication.[21,22] Chemically synthesized L-Dopa creates various side effects. The treatment with oral L-Dopa induces plastic changes in basal ganglia circuits that can lead to the development of motor response complications.[23] Plant source L-DOPA can be used as an alternative for chemically synthesized drugs against the PD disease. Natural best plant sources of L-DOPA are Fava bean (*Vicia faba*), seed sprouts, pods, and broad beans, cultivated legumes, which have anti-Parkinson's effect.[24] L-DOPA and ursolic acid of *Mucuna puriens* exhibit potent anti-parkinsonian properties.[25] Another rich source of L-Dopa is *Mucuna monosprma* of family *Fabaceae,* which contains 5.48% L-DOPA, and the content increases by 6.58% when beans are soaked in water.[26] L-dopa and ursolic acid are the main bioactive polyphenolic compounds that is present in *M. monosperma.* In our previous study it has been shown the anti-Parkinson's properties of L-Dopa and ursolic acid of *M. monosperma* (MM) in PD lines of *Drosophila*. With all the background information, in the present study, we have chosen L-DOPA and ursolic acid of MM seed to know the synergetic effect on antioxidant enzyme activities in PD lines of *D. melanogaster* under oxidative stress conditions.

MATERIALS AND METHODS

Chemicals

Paraquat dichloride, methionine, EDTA, nitro blue tetrazolium (NBT), hydrogen peroxide, nicotinamide adenine dinucleotide phosphate (NADP), trichloroacetic acid (TCA), reduced glutathione, 5, 5'- dithio-bi's (2- nitrobenzoic acid) (DTNB), bovine serum albumin (BSA) were procured from Sigma Aldrich, India. All the chemicals used were of analytical grade (AR).

Preparation of seeds extract

The seeds of *M. monosperma* are collected from Koppa (Western Ghats), Chikamagalore District, Karnataka, India. The seeds were washed with water to remove the unwanted content present in the seeds and dried under sunlight and a hot air oven to remove moisture content. Further, the seeds were made into a fine powder using an electric blender. The powder obtained was subjected to the Soxhlet apparatus for extraction in methanol solvent.

Isolation of L-dopa and ursolic acid

Isolation of L-Dopa and ursolic acid from the crude extract of MM was made through Preparative HPLC and column chromatography, respectively and HPLC was done to identify and quantify the isolated compounds.

Culturing and crossing of *Drosophila melanogaster*

The transgenic fly lines that express wild type h-αS under upstream activation sequence (UAS), control in neurons UAS–SNCA and Elav-GAL4 were obtained from *Drosophila* Stock Center, Department of Zoology, Manasagangothri, University of Mysore, Mysuru, Karnataka. The flies were cultured in a standard wheat cream agar media seeded with yeast granules and maintained at 22 ± 1°C diurnal cycle (12 hours light and 12 hours dark) of relative humidity 70 to 80% and flies were maintained in 30 mL culture bottles. For all the analyses, synchronized *D. melanogaster* subcultures were used.

Crosses were set up using virgin females of Elav- Gal4 was mated to males of UAS-$SNCA^{WT}$ and UAS-$SNCA^{A30P}$. The progeny expressed the human α-synuclein in the neurons and the flies are referred to as Elav/$SNCA^{wt}$ as control and Elav/$SNCA^{A30P}$ as PD flies. Oxidative stress test and biochemical analyses were carried out using the F_1 generation of PD flies (Fig. 1).

Induction of oxidative stress by Paraquat (PQ)

To know the neuroprotective potentiality in L-DOPA and ursolic acid of MM, flies were subjected to oxidative stress conditions. Paraquat dichloride (PQ) has been employed as OS molecule by following the method of Hosamane and Muralidhara.[27] About 15 days PD line flies were used for OS induction. The flies were starved in empty vials of size 9 x 3 cm for 2 hours. Then, flies were exposed to 15 mM PQ in 5% sucrose solution through a soaked filter paper for 2 hours duration. Survival was determined after 24 hours and survived flies were used for homogenization for biochemical assays. About 50 flies were maintained in each batch (10 flies/vial) and each assay was repeated thrice.

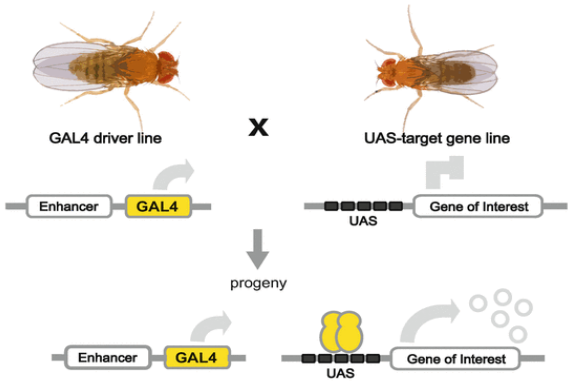

Fig.1: GAL4 driver and UAS-target gene fly lines are generated and maintained as separate stocks. In the absence of GAL4 there is no expression of the target gene. Crossing a fly expressing GAL4 to a fly carrying UAS-target genes results in targeted gene expression in the progeny of the cross.

Biochemical assay

All the biochemical assays were carried out in six different batches. Elav/SNCA^{wt} was considered as control batch, Elav/SNCA^{A30P} was the transgenic PD line, OS induced control group and PD line. L-Dopa alone fed batch to PD with OS induced batch and L-Dopa with Ursolic acid fed-batch to PD with OS induced batch.

Antioxidant enzyme assay

All the antioxidant enzyme (SOD, CAT, G6PD) activities were measured in the L-Dopa and ursolic acid-supplemented PD flies with a concentration of 4 mg/mL. All the experiments were carried out in 20 days age grouped flies under stressed conditions. The extract treated with oxidative stress molecule (PQ) induced flies were considered as a stressed group.

Superoxide dismutase(SOD)

SOD activity was measured as per the standard procedure Beyer and Fridovich, (1987).[28] Fly homogenate was used for the preparation of samples. 3ml mixture was prepared by adding phosphate buffer of pH 7.8, 100 mM methionine, 10mM riboflavin, 5mM EDTA, 750mM NBT and enzyme extract with distilled water. The reaction mixture was gently mixed and incubated in dark at 400W bulbs for 15 minutes. Absorbance was measured at 560 nm in a UV spectrophotometer against a blank. SOD activity was calculated per mg of protein.

Catalase(CAT)

The catalase activity was conducted by following the standard protocols (Aeibi and Bergmeyer, 1974).[29] About 100 µL of fly homogenate was added to a mixture of phosphate buffer with 100 µL of hydrogen peroxide and the absorbance was read at 240 nm in a UV spectrophotometer. Catalase activity was calculated using the following formula: Units/mL of enzyme = Δ A (min)/(E ×mg of protein) = µm H_2O_2 Consumed/min/mg of protein.

Glucose- 6 -phosphate dehydrogenase (G6PD) Assay

The total activity of G6PD was measured in MM Crude extract, L-Dopa and L-Dopa with Ursolic acid supplemented flies by following the modified method of Kumar *et al.,* (1991).[30] About 100 µL of supernatant was mixed with 0.4 mL of 1.5M Tris HCL (pH7.5) containing 3.8×10^{-4} M NADP, 0.01 ml of 0.3 M $MgCl_2$ and 0.5 mL of 0.03 M Dglucose 6 phosphate. The activity of the reaction mixture was measured at one-minute intervals for 3 minutes at 340 nm using UV spectrophotometer. The activity was calculated based on a molar extinction coefficient 6.22 mM^{-1} cm^{-1}.

Glutathione (GSH)

To measure the antioxidant in the bioactive compounds fed flies glutathione was measured. The activity of GSH was measured by following the standard method [Buege, 1978].[31] About 200 µL of test sample was used in each group. The absorbance was read at 412 nm and the activity was expressed as µg/mg protein. GSH level was expressed as µg/mg protein. It was measured in the L-Dopa and ursolic acid-supplemented PD flies with a concentration of 4 mg/mL in 20 days flies under stress and non-stress conditions.

Lipid peroxidation assay

Lipid Peroxidation assay was measured by employing thiobarbituric acid (TBA) as per the standard procedure (Buege, 1978).[31] The assay was carried out in 20 days aged fly groups. The reaction mixture consisted of 0.2 µl of homogenate sample, 0.2 µL of SDS (8.1% w/v), 1.5 mL of acetic acid (pH 3.5, 20%), 1.5 ml of TBA (0.8% w/v) and the reaction mixture was made up to 4 mL with distilled water, mix well. The mixture was incubated in a water bath at 90°C for 60 minutes and then cooled in an ice bath. After cooling, samples were mixed with 3 mL of n-butanol and centrifuged at 5000 rpm for 10 minutes. Further, the supernatant was carefully transformed to another test tube and the absorbance was measured at 532 nm. Lipid peroxidation was quantified as malondialdehyde (MDA) equivalents using 1,1,3,3- tetramethoxypropane as the standard (molar extinction coefficient value is 15600 M-1 cm^{-1}). A blank solution was prepared by mixing all the reagents except the sample homogenate.

Determination of total protein: The total quantity of protein in *Drosophila* head homogenates prepared from MM Crude Extract, isolated L-Dopa and L-Dopa with ursolic acid supplemented flies was measured as per standard protocol (Lowry *et al.*, 1951).[32] Estimation was carried out by taking BSA as standard. The quantity of protein was estimated through the standard graph.

Statistical analysis

The data obtained from all the experiments will be subjected to statistical analysis using SPSS software. To know the level of significance among the different groups, data will be subjected to one-way ANOVA, followed by DMRT. A probability of $p < 0.05$ will be considered as significant. Data from biochemical estimations will be expressed as mean ± SEM.

RESULT AND DISCUSSION

Parkinson's disease (PD) is characterized by the deposition of inclusion bodies (Lewy bodies) of α-synuclein in substantianigra that is ubiquitously expressed in the brain.[33] Synuclein is a presynaptic neuronal protein encoded by the SNCA gene that is linked genetically and neuropathologically to PD. Evidence indicate that mutations in α-synuclein protein have a role in modulating dopamine activity but

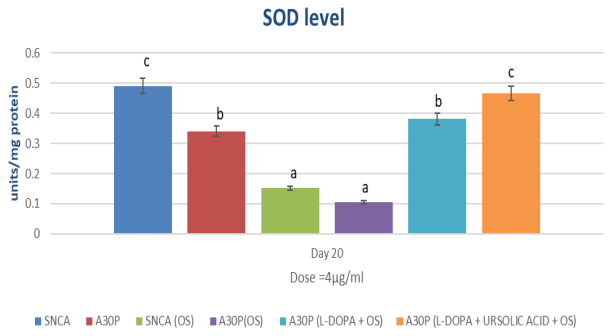

Fig. 2: Effect of L-Dopa and L-Dopa with ursolic acid on SOD activity in flies exposed to PQ. PQ decreases the activity of SOD. L-Dopa and L-Dopa with ursolic acid-treated flies showed a significant increase in the activity of SOD after PQ exposure.

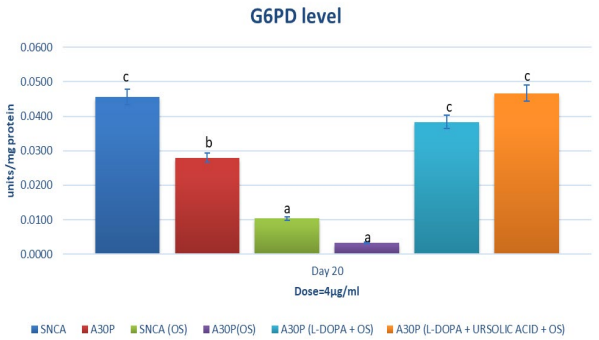

Fig.4: Effect of L-DOPA and L-DOPA with ursolic acid on G6PD activity in control and PD line *D. melanogaster* under stress condition.

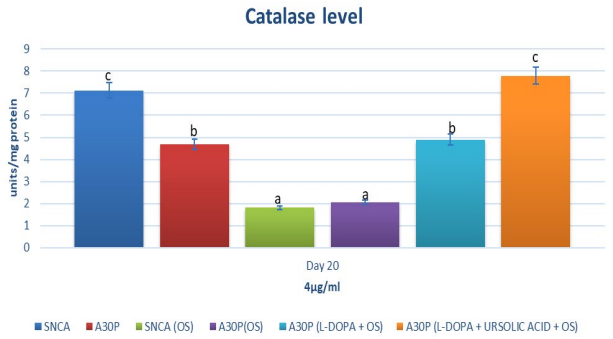

Fig.3: Effect of L-Dopa and L-Dopa with ursolic acid on CAT activity in flies exposed to PQ. PQ decreases the activity of CAT. L-Dopa and L-Dopa with Ursolic acid treatment returned the activity of CAT to a nearly normal state compared to control.

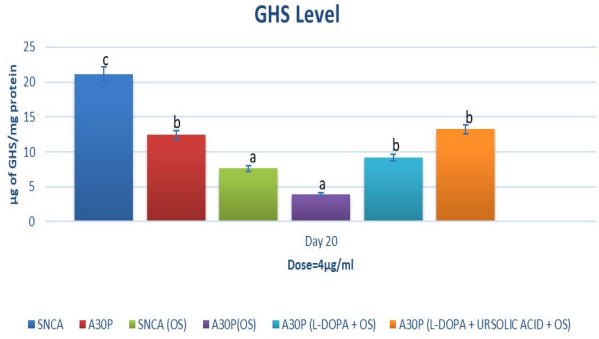

Fig.5 : Effect of L-DOPA and L-DOPA with ursolic acid on PQ induced alterations in GSH. L-DOPA and L-DOPA with Ursolic acid reversed PQ-induced GSH depletion and by itself enhanced the GSH level.

in a negative way that initiates neuronal cytoplasmic accumulation and interaction of dopamine with iron, engendering ROS production.[34] Antioxidant therapy involving enzymes constitutes upstream therapy in ROS generation and prevents downstream pathologies in advance in certain neurodegenerations. It has been reported that a bioactive compound, curcumin, prevents α-synuclein aggregation,[35] which increases the nuclear translocation of the transcription factor, potentially promoting the degradation of α-synuclein.[36] L-Dopa has been used as the single most effective drug for PD for its many years. The antioxidant enzymatic and non-enzymatic defense factors maintain a balance and reduce oxidative stress. In the present study, we have test the L-dopa and ursolic acid to know the effect of antioxidant enzymes and LPO in PD lines of *D. melanogaster* under oxidative stress conditions.

The major antioxidant enzyme activities such as superoxide dismutase, catalase and G6PD were assessed, whereas in non-enzymatic endogenous antioxidants, glutathione (GSH) was measured. The result showed that all the antioxidant enzyme activities in PD lines (Elav/SNCA^{A30P}) were significantly less when compared to the control batch (Elav/SNCA^{wt}). Further, it was noticed that PQ-induced control groups, as well as PD lines, exhibited a further reduction of all the enzyme activities compared to untreated PD lines. SOD activity in the control SNCA batch was 0.49 unit/mg protein. PQ-induced control (SNCA) group showed less activity. It was decreased by 69.19% in a control group. The enzyme activity in PD line A30P was decreased by 30.61% than the control group. Further, the data reveals that OS induced PD line decreases the SOD activity by 77.55 than the without OS treated group. In contrast to this, bioactive compounds fed batches to PD lines with OS treatment showed significantly increased SOD activity. The L-Dopa supplemented batch increase the enzyme activity by 3.5-fold while L-Dopa with Ursolic acid supplemented groups increased by 4.2-fold.

The catalase activity in the control group was 7.13 unit mg protein, which was decreased by 74.21% in OS induced control group 34.22% in PD transgenic group. Similarly, the OS-induced PD line showed the greatest reduction in CAT activity, decreasing by 56.50% compared to uninduced PD lines. However, the bioactive compounds of MM-fed batches in OS-treated PD lines exhibit increased catalase activity. The batch supplemented with L-Dopa showed 2.4 fold increase CAT activity. The highest level of enzyme activity was observed in the groups supplemented with L-Dopa with ursolic acid, which was increased by 3.8 fold when compared to OS induced PD line batch.

A similar observation was noticed in the G_6Pd activity. OS-induced control group decreases the G_6Pd activity by 77.77% than the control group. The PD line with OS-induced flies decreased 64.28% enzyme activity than the uninduced PD line. L-Dopa and L-Dopa with ursolic acid fed PD line with OS treatment showed

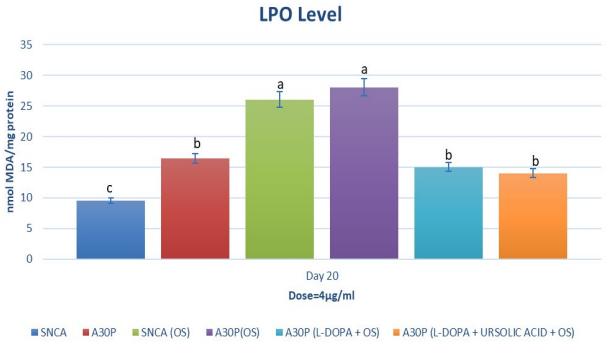

Fig.6: Protective effect of MM extract on LPO as a marker of oxidative stress in adult *Drosophila* after exposure to 15 mM PQ. L-DOPA and L-DOPA with Ursolic acid supplementation significantly decreased when compared to PQ-exposed flies.

increased G_6PD activity. L-Dopa alone fed group increased by 3.8 fold, L-Dopa with ursolic acid fed group increased 4.6 fold enzyme activity of OS induced PD line. In the present study it shows that L-Dopa, in combination with ursolic acid elevates of activities of SOD (4.2 fold), CAT (3.8 fold) and G6Pd) (4.6 fold). Wang *et al.*, 2023[35] have shown the bioactive compound of cinnamon leaves elevates the antioxidant enzymes and improves the PD in Rats. This indicates that a potent antioxidant L-Dopa and ursolic acid increases the antioxidant enzymes and reduces the risk of PD.

GSH is another major antioxidant that protects the brain cells from neurodegeneration disorders. SNCA grouped with OS-treated flies reduced the GSH by 63.25%, while OS OS-induced PD line reduced by 68.25% of GSH. However, the treatment of L-Dopa and with ursolic acids increases the GSH amount significantly by 2.32 fold and 3.36 fold, respectively. This observation indicates in a combination of L-Dopa and ursolic acid elevates the antioxidant glutathione, thus reducing the risk of PD. It has been reported that curcumin of *curcumin longa* acts as direct scavenging of ROS and exerts its antioxidant properties by increasing SOD, CAT activities and GSH levels.[37,38] In our earlier report (Sneha *et al.*, 2024), we have shown that L-Dopa and ursolic acids increase the locomotory as well as negative geotaxis behavior PD line of *D. melanogaster*. In the present investigation, we have demonstrated that the supplementation of L-Dopa and with Ursolic acids is associated with the elevation of antioxidant enzyme activities. Thus, bioactive compounds of MM improvise the behavioral activities by increasing SOD and CAT, G6Pd activities and GSH levels in PD line under stress conditions. The present result is similar to the findings of earlier studies conducted on curcumin (Figs 2-5).[37,38]

In contrast to this, LPO is another oxidative stress marker that induces the generation and accumulation of misfolded α-synuclein, thus resulting in insufficient formation of dopamine production, causing PD. LPO activity was measured by TRBS method in bioactive compounds fed groups (Fig. 6). It is a very good marker for the detection of oxidative damage. LPO is associated with Neurodegenerative diseases The least LPO activity was observed in the control group (Elav/$SNCA^{wt}$). Further, it was increased by 63.46% in OS OS-induced control group. The LPO activity in PD line (Elav/$SNCA^{A30P}$) was found to be high, increased by 63.45% than the control group, and increased by 41.43% in the batch with OS induction. However, the bioactive compound fed group of OS-induced PD line decreased the LPO activity. It was decreased by 1.87 fold in the L-Dopa fed-batch, and decreased by 2 fold in L-Dopa with ursolic acid fed-batch. This result confirms that L-Dopa and ursolic acid have ability to reduce oxidative stress by decreasing LPO, thus reducing the risk of PD. This result is in line with the observation of Jaing and Yen, (2013),[39] who have shown that dopamine prevents lipid peroxidation in the PD line.

The generation of LPO toxic products can be decreased by the activity of antioxidant enzymes, such as SOD and CAT.[40] Our present study on PD flies has also confirmed the same trend, L-Dopa with Ursolic acid increases the activity of SOD, CAT, G6Pd as well as GSH, and their by LPO toxicity was reduced. It has been proved that an increased level of LPO leads to pathogenesis. The supplementation with the antioxidants could produce beneficial effects in PD patients, increasing that oxidative stress plays a role in the pathogenesis of PD.[41]

Both L-Dopa and ursolic acid are potent antioxidants, the synergetic effect of these bioactive compounds of MM decreases the LPO activity by increasing antioxidant enzymes as well as glutathione in transgenic PD flies. L-Dopa and ursolic acid are potent in scavenging free radicals, thereby leading to the reduction in oxidative stress. Further, this can be used as a possible therapeutic agent against neurodegenerative disorders.

CONCLUSION

Neuroprotective efficiency of *M. monosperma* isolated compounds L-dopa and ursolic acid with combination approaches has been demonstrated by its ability to abrogate PQ-induced neurotoxicity and oxidative stress in SNCA and A30P mutant *Drosophila* brain. As the brain is deficient in antioxidant defenses and is rich in oxidizable substrates, it is susceptible to oxidative stress. Therefore, the attenuation of PQ-induced oxidative stress, restoration of catalase, G6PD, GSH, and SOD, and reduction in LPO levels in the fly brain demonstrated the neuroprotective effect of MM isolated compound L-Dopa and ursolic acid. The outcome demonstrated that ursolic acid and L-dopa had synergistic neuroprotective effects. Therefore, a treatment that boosts the antioxidant defense system with L-Dopa and ursolic acid could be beneficial. The neuroprotective potential of the MM-isolated compounds, L-Dopa and ursolic acid, in combination with PQ-induced oxidative stress in the *Drosophila* model, has never been reported before. To better understand the mechanisms underlying this effect, more research using genetic strains will be necessary.

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