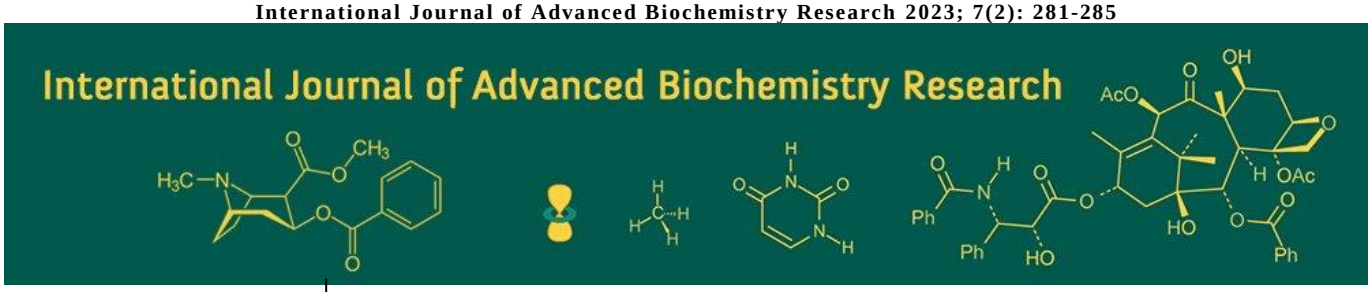

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Potential neuroprotective effect of Lauric acid on rotenone: Induced Parkinson's disease in experimental rats

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Abstract
Background: Parkinson's disease (PD) is a chronic neuro-degenerative condition characterized by impaired motor function. It is defined by a lack of dopamine in the brain and the specific degradation of dopaminergic neurons in the Substantia Nigeria. The objective of this research was to examine the regulatory impact of Lauric acid (LA) on mitochondrial biogenesis in a rat model of rotenone-induced PD.
Materials and methods: this experiment has been carried out on sixty albino male rats categorized into 4 groups; group I (control group), group II (LA-treated group) and group III (Rotenone-administered group) and Group IV (Rotenone and LA-treated group). Each group underwent catalepsy test neurobehavior and measurement of the protein carbonyl content (PCC) and (parkin interacting substrate) PARIS levels in brain tissue homogenate.
Results: This study showed that LA has significantly improved the locomotor activity in PD group with decreased PC and PARIS levels in brain tissue homogenate.
Conclusion: LA improves mitochondrial biogenesis, and possesses antioxidant effects in experimentally induced PD.

Keywords: Lauric acid, rotenone, Parkinson's disease, rats, protein carbonyl content

Introduction
Parkinson's disease (PD) is the 2nd most prevalent age-related neuro-degenerative condition, following Alzheimer's disease [1]. Globally, the general population has an average prevalence of PD of 0.3%. However, this incidence increases to 1.0% in those aged over 60 years and further rises to 3.0% in those aged over 80 years. The worldwide prevalence is projected to rise from 6.2 million instances in 2015 to 12.9 million instances by 2040 [2]. The clinical presentation includes resting tremor, bradykinesia, rigidity, and postural instability [3].

Rotenone, a pesticide derived from Leguminosae plants, selectively hinders mitochondrial-complex-I and leads to the destruction of dopaminergic neurons, resulting in a behavioral condition similar to PD [4]. Remarkably, administering a small dose of rotenone directly under the skin of rats for a duration of 4 weeks appears to accurately mimic nearly all the behavioral and neuropathological characteristics of Parkinson's disease. These include slowed movement, walking difficulties, tremors, rigidity, degeneration of dopamine-producing neurons in the nigrostriatal pathway, and formation of aggregates of α-synuclein [5]. Moreover, the rotenone model has a high level of reproducibility and might serve as an exceptional tool for exploring novel neuroprotective techniques. This model is limited by its significant morbidity, as well as the need for extensive labor and time investment [3, 6].

The primary fatty acid found in coconut oil is lauric acid (LA), that consists of a 12-carbon backbone [7]. It is often present in several types of plants and animal fats, particularly in palm nut oil and coconut, where it constitutes 45-53% of the composition. The physiological and metabolic characteristics of LA exhibit certain attributes of coconut oil. Coconut oil is efficiently digested, easily consumed, and LA is effectively distributed and aids in reducing fat accumulation. LA has substantial antibacterial activity against gram-positive pathogens and effectively combats parasites and illnesses, as shown by many experiments [8].

This experiment aimed to evaluate how LA affects certain regulators of mitochondrial biogenesis in a rat-model of rotenone-induced PD. The goal was to have a deeper comprehension of the fundamental mechanics and explore the possible utilization of LA as a neuroprotective drug in PD.

Materials and Methods

Materials

Chemicals

All solvents and chemicals utilised in this study, unless otherwise stated, have been purchased from Sigma Aldrich (Sigma, St. Louis, USA). All solvents and chemicals utilized during the experiment were of a high analytical grade.

Rotenone (99% purity, CAS NO: 83-79-4), LA (>98% purity, CAS NO: 143-07-7) and rotenone was dissolved in 1% dimethyl sulfoxide (DMSO) prior to subcutaneous injection.

Animals

The present research included a sample of 60 albino male rats, with a mean weight for their bodies ranging from 120 to 150 grams. These rats were procured from the animal colony used for research at Tanta University. Throughout the course of the investigation, the rats had been accommodated in wire mesh enclosures and provided unrestricted availability to water. The rats were maintained in a controlled-environment with consistent circumstances, including a temperature of 25 ºC and a lighting regimen of 12-h dark/12-h light cycle. The rats underwent regular weekly weighing.

This investigation had been performed in the Medical Biochemistry Department, Faculty of Medicine, Tanta University, Egypt, in adherence to the guidelines provided by the ethics committee of Medical Research, Faculty of Medicine, Tanta University, Egypt. (Approval code: 34454/2/21).

Experimental design

After acclimatization for 1 week, rats had been randomly allocated into 4 groups equally with 15 rats each as follows:

Group I (control group): animals in this group had been received a vehicle solution containing 1% DMSO at a dosage of 0.1 mL/100 grams/ day; S.C for 3 weeks.

Group II (LA-treated group): animals in this group had been received only LA via oral gavage at a dosage of 50 mg/kg/day for 3 weeks [16].

Group III (Rotenone-administered group): animals in this group received 11 S.C injecting of rotenone every other day at a dosage of 1.5 mg/kg dissolved in 1% DMSO for 3 weeks.

Group IV (Rotenone and LA-treated group): The animals in this experimental group were subjected to a combination of rotenone, administered by subcutaneous injecting every other day at a dosage of 1.5 mg/kg dissolved in a 1% DMSO solution, and LA, given orally via gavage at a dosage of 50 mg/kg/day. This combined treatment was administered daily for a duration of 3 weeks, with the LA administration occurring 1 hour before to the rotenone injection on the designated days.

Methods

At the end of the work on the 21st day rats were exposed to neurobehavioral assessment by Catalepsy test.

Catalepsy test neurobehavior

The evaluation of catalepsy included the utilization of the bar test, whereby rats had been positioned in a half-rearing stance with both forepaws resting on a bar situated 10 cm above the base. Subsequently, the duration till the removal of one or both paws was documented. The designated threshold for descent delay time was established at 180 seconds [9].

Tissue sampling

Decapitation was the method of sacrificing rats, brains had been immediately meticulously dissected, subjected to a rinsing process using ice-cold saline solution in order to eliminate any unwanted substances. The extra saline was absorbed using filter paper fragments. The brain tissues were cooled on ice and then partitioned into two halves.

Redox status parameter

Protein carbonyl content (PCC) assay: The detection of protein carbonyl contents involves their reaction with DNPH to form acid hydrazones followed by its spectrophotometric quantification.

Immunoassay of PARIS

The level of PARIS in brain tissue homogenate was identified by an ELISA employing a product that is readily accessible for purchase as a kit (Catalogue number # 201-11-2124) supplied by Sun Red Biotechnology Co., Shanghai, China.

Statistical analysis

The study's findings were analyzed utilizing the SPSS, version 16.0 for Windows (SPSS, Chicago, IL), with mean and standard deviation being the statistical measures used. The statistical technique used for conducting multiple comparisons and assessing the statistical significance across experimental groups was one-way analysis of variance (ANOVA), as well as a post hoc test. The correlation study was calculated utilizing Pearson's correlation. P-value < 0.05 was considered significant

Results

Behavioral assessment of the effect of Lauric acid on rotenone model of PD

When contrasted to the vehicle control group, rats administered with rotenone exhibited a substantial drop in rearing count (p<0.001) and a substantial rise in catalepsy (p<0.001), as shown by a reduction in the bar test's descending latency time (Figure 1).

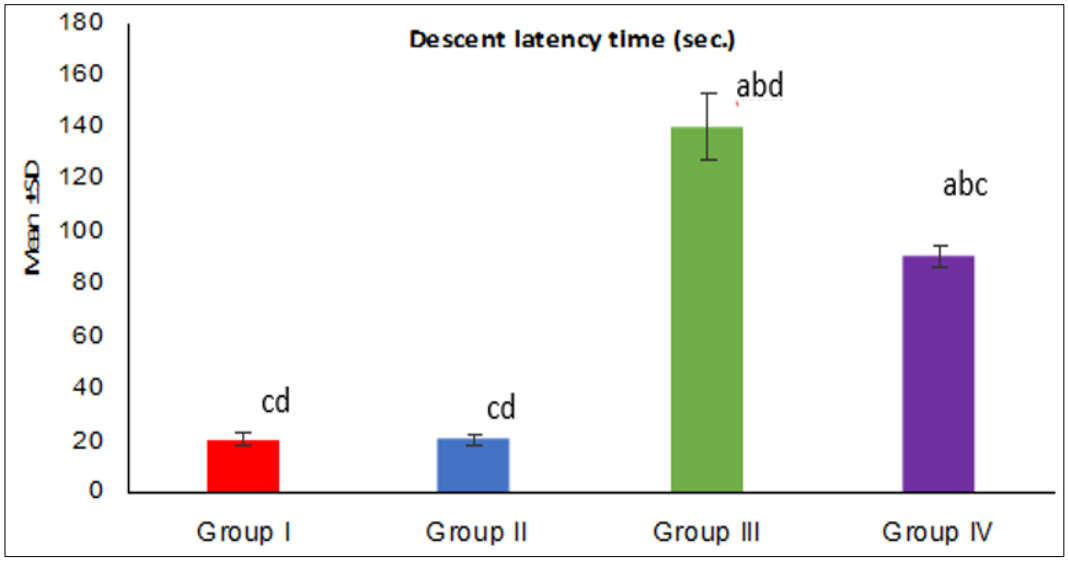

Fig 1: Effect of lauric acid on behavioral parameters among rats administered with rotenone as determined by bar test, values mean ± SD (n = 10). [a] denotes a significant difference compared to group I; [b] denotes a significant difference compared to group II; [c] denotes a significant difference compared to group III; [d] denotes a significant difference compared to group IV, by one-way analysis of variance followed by post hoc Tukey's test

The ameliorative effect of Lauric acid on redox status and mitochondrial biogenesis

PCC (nmol/mg protein) and brain PARIS level (pg/mg protein) in brain tissue homogenate of PD rats was revealed to be substantially elevated (p<0.001) as contrasted with other studied groups. However, in rotenone cotreated with LA, PCC and brain PARIS levels were significantly decreased (p<0.001). Table 1.

Table 1: Statistical comparison of protein carbonyls content (PCC) (nmol/mg tissue protein) and PARIS (pg/mg protein) levels in brain tissue homogenate among all studied groups:

	Group I	Group II	Group III	Group IV	P-value
PCC (nmol/mg protein) in brain tissue homogenate	4.65±1.92	4.28±1.68	11.44±4.27	7.36±1.88	<0.001*
PARIS level (pg/mg protein) in brain tissue homogenate	266.200±124.78	255.667±125.12	862.933±179.78	552.400±130.37	<0.001*

Data are presented as mean ±SD. * p<0.05 is statistically significant.

A substantial positive correlation was existed between PPC and PARIS levels in brain tissue homogenate of studied groups (r =0.809, P <0.001*). Table 2.

Table 2: Correlation matrix between PARIS (pg/mg protein) and PCC (nmol/mg protein) in the studied group:

Parameters		PCC (nmol/mg protein) in brain tissue homogenate
PARIS (pg/mg protein) in brain tissue homogenate	R	0.809
	P-value	<0.001*

Discussion

Parkinson's disease (PD) is a Neuro-degenerative condition characterised mostly by impairments in motor function. The process of aging is the most significant risk factor in the developing of PD. Recent molecular genetic research has provided evidence indicating that hereditary factors, alongside aging and environmental variables, significantly contribute to the onset of the condition. Furthermore, it has been shown that the death rate among those diagnosed with Parkinson's disease is three times higher compared to age-matched individuals without the condition [10].

The current research provided evidence that the injection of rotenone resulted in rigidity and bradykinesia. This was confirmed by a substantial increase in descending latency time, as seen in the catalepsy test, in the group that received rotenone in contrast to the control groups. The findings presented in this study are consistent with the results stated by Singh *et al.* [11], Shahid *et al.* [12] and Haider *et al.* [13] These previous studies demonstrated that rats administered with rotenone experienced a significant increase in latency to move (p<0.01) and a decrease in the number of squares crossed (p<0.01) contrasted to the control group.

Moreover, the current work revealed that treatment with lauric acid resulted in a substantial rise of number of rears/5 mins in rotenone and LA treated group suggesting that LA might have a positive impact on improving locomotor activity. In line with our outcomes, Zaidi *et al.* [14] showed that A reduced dosage of LA specifically enhances motor activity and has advantageous outcomes on behavioral functioning in PD caused by haloperidol.

Protein carbonyls (PCs) exhibit distinctive stability and a broad spectrum of functional effects, setting them apart from other oxidative changes. Protein carbonylation, which occurs by the direct metal-catalyzed oxidation of amino acid side chains or the addition of reactive aldehydes to amino acid side chains, is considered a reliable indicator of pathogenic reactive oxygen species (ROS) generation in several cell types and tissues [15].

In the present study, the PC concentration in brain tissue homogenate of PD rats was significantly increased as contrasted to control groups. Supporting our findings, previous studies revealed that a significant increased PC was existed in the neocortex and hippocampus in AD and in Lewy bodies of PD [15, 16].

However, our findings indicated that LA treatment showed a significant decrease in PCC level. Moreover, Shaheryar *et al.* [17] stated that LA has a neuroprotective impact through decreasing oxidative stress.

In addition, The PARIS (ZNF746) protein is a substrate of the E3 ubiquitin ligase parkin, which builds up in models where parkin is deactivated and in the brains of patients with PD. The degeneration of dopamine neurons in conditional parkin knockouts is contingent upon the presence of PARIS [18].

In the present study, the PARIS concentration in brain tissue homogenate of PD rats was substantially elevated as contrasted with control groups. Our findings were comparable to Shin *et al.* [18] who showed that The PARIS levels in the cingulate cortex of PD individuals, who have a deficiency in functional parkin, are doubled compared to age-matched controls.

However, LA treatment showed a substantial reduce in PARIS level suggesting a protective role of lauric acid against mitochondrial dysfunction. This might be explained by the finding reported previously by Tham *et al.* [19] who showed that The application of lauric acid successfully reinstated the process of creating new mitochondria in the macrophages that were resistant to insulin. This was achieved by enhancing the synthesis of ATP, consumption of oxygen, content and potential of mitochondria. Additionally, it stimulated the expression of genes responsible for regulating mitochondrial biogenesis, namely TFAM and PGC-1α.

Additionally, our results showed that a substantial positive correlation was existed among brain tissue levels of PARIS and PCC levels. That was also observed by Leathem *et al.* [20] who found that mitochondrial biogenesis defect indices were associated with a substantial rise in protein and lipid oxidation and with a substantial decline in antioxidant capacity in brain tissue of PD.

Conclusion

Lauric acid was found to restore mitochondrial function through alleviation of oxidative stress, therefore, it might provide a potentially effective neuroprotective medicinal adjuvant for the management of PD.

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