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Research Article

Purple Yam (*Dioscorea alata*) Extract Increasing Dopamine Levels and Improving the Brain's Microscopic Features in Parkinson's Model Mice

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Abstract

Parkinson's disease (PD) is a severe neurodegenerative disorder, that causes progressive motor issues from the loss of dopamine-producing neurons in the substantia nigra pars compacta (SNpc). Purple yam (*Dioscorea alata*), rich in anthocyanins, shows promise as a natural antioxidant and neuroprotectant. This study investigated the antiparkinsonian effects of *D. alata* extract on dopamine levels and brain microscopic features in a haloperidol-induced PD mouse model. Thirty-five male mice were randomly allocated into seven groups: normal (CMC-Na and aqua pro injection), haloperidol-induced negative control (CMC-Na), positive control (levodopa 39 mg/kgBW), curcumin (200 mg/kgBW), and *D. alata* extract-treated groups (100, 200, and 400 mg/kgBW). Treatments were administered daily for seven days. On day 8, all groups, except the normal control, received an intraperitoneal injection of haloperidol (2 mg/kgBW) to induce Parkinsonism. Three hours post-haloperidol injection, dopamine levels were measured from orbital vein blood. Subsequently, brains were harvested for histological examination of the SNpc using Toluidine blue staining. Data were statistically analyzed using one-way ANOVA followed by LSD post-hoc tests. The 400 mg/kgBW dose of *D. alata* extracts significantly increased dopamine levels ($p < 0.05$) compared to the negative control group. Microscopic analysis of the SNpc in mice treated with 400 mg/kgBW extract revealed preserved, dark, and solid neuronal morphology, with significantly higher scoring results ($p < 0.05$) when compared to the levodopa-treated group. These findings suggest that *D. alata* extract, particularly at a dose of 400 mg/kgBW, exhibits potential antiparkinsonian activity by elevating dopamine levels and mitigating dopaminergic neuronal damage in a haloperidol-induced PD mouse model.

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by tremor, rigidity, and bradykinesia with emerging postural instability[1]. Parkinson's disease is the second most common neurodegenerative disorder, following Alzheimer's disease. It is estimated that the prevalence and incidence of PD will increase by more than 30% in 2030[2]. PD pathology is marked by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), resulting in a decrease in the neurotransmitter dopamine[3]. The impairment of dopaminergic function is caused by the progressive degeneration of dopaminergic neurons in the SNpc that project to the striatum (nigrostriatal pathway)[4]. Several mechanisms contribute to

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this neuronal loss, including oxidative stress, which is one of the causes of decreased dopamine levels in the brain[5], along with mitochondrial dysfunction, protein aggregation, autophagy disorders, and neuroinflammation[6,7].

Administration of levodopa is one of the PD therapy strategies focusing on dopamine replacement therapy[8]. However, levodopa can cause side effects and general reactions such as nausea, vomiting, breathing disturbance, hallucinations, dyskinesia, anxiety, and others. From an economic perspective, synthetic drugs are often costly, particularly given the necessity of long-term consumption[9,10]. Therefore, the use of herbal medicines can be an alternative PD treatment that is cheaper and has a lower risk of side effects. Plants that have potential as sources of herbal medicines, as anti-Parkinsonians, are *Mucuna pruriens*[11], *Ginkgo biloba*[12], *Bacopa monnieri*[13], *Curcuma longa*[14], and *Dioscorea alata*[15]. *Dioscorea alata* or purple yam has the potential to be an anti-proliferative, anti-hyperlipidemic, and anti-oxidative agent for neurodegenerative diseases[16]. Previous research has demonstrated that *D. alata* ethanol extract can prevent motor and sensory disorders in Parkinson's model mice[15]. *Dioscorea alata* contains bioactive compounds, which include diosgenin, dioscin, dioscorin, and anthocyanin[17]. Anthocyanin compounds have the main activity as antioxidants because they have a glycosylated B-ring structure[18], which can capture free radicals, thereby preventing aging, cancer, and degenerative diseases, including Parkinson's disease[19]. Extracts rich in anthocyanins show greater neuroprotective activity than extracts containing other polyphenols, thereby preventing the death of dopaminergic cells that produce the neurotransmitter dopamine[20]. The mechanisms underlying the antiparkinsonian effects of *D. alata*, especially its role in modulating oxidative stress and dopamine synthesis, remain unclear. Despite these promising findings and the potential of *D. alata*, comprehensive studies elucidating its antiparkinsonian mechanisms, particularly concerning oxidative stress modulation and dopamine synthesis, are limited. Therefore, this study aims to determine the activity of *D. alata* extract as an antiparkinsonian agent on dopamine levels and microscopic images of the brains of Parkinson's model mice injected with haloperidol.

MATERIALS AND METHODS

Materials

Dioscorea alata were obtained from Madiun, East Java, Indonesia, and authenticated by the Laboratory of Biology, Faculty of Science and Applied Technology, Universitas Ahmad Dahlan, Yogyakarta, Indonesia (number: 438/Lab.Bio/B/X/2022). Male DDY strain mice were supplied by the Central Research and Development Laboratory of Universitas Gadjah Mada, Yogyakarta, Indonesia. Chemical reagents, including 70% ethanol, aqua pro injection (Jaya Sentosa), sodium chloride (NaCl) 0.9% (Widarta Bakti), carboxymethyl cellulose sodium/CMC-Na, and 10% formalin (Brataco), were of analytical grade. Haloperidol (OGB Dexa), levodopa (Mepro), and curcumin (Sigma-Aldrich) were used as pharmacological agents. An ELISA dopamine kit was procured from Elabscience. Compressed CO_2 gas, acetic acid, 37% HCl, and formic acid (Merck) were also utilized in this study.

Methods

Animal handling

This study utilized male DDY strain mice, aged 8-10 weeks and weighing 30-40 g, procured from the Central Research and Development Laboratory at Universitas Gadjah Mada. All experimental procedures involving animals were conducted in strict accordance with ethical guidelines and received approval from the Research Ethics Committee of Universitas Ahmad Dahlan (Approval Number: 012207095). Prior to the commencement of the study, mice underwent a 7-day acclimatization period under controlled laboratory conditions, maintained at a room temperature of 25-26°C with 50-60% humidity. A 12-hour light/dark cycle was established, and animals had *ad libitum* access to standard laboratory chow and water.

Following acclimatization, mice were randomly assigned to 7 experimental groups, with each group comprising 5 animals, as detailed in **Figure 1**. Treatment regimens were administered daily for a period of 7 consecutive days. On Day 8, all mice, with the exception of Group 1 (control), received an intraperitoneal injection of haloperidol at a dose of 2 mg/kg body weight. Three hours post-injection, blood samples were collected from the orbital vein for the subsequent analysis of dopamine levels. Immediately following blood collection, mice were humanely sacrificed, and brain tissues were harvested for the preparation of microscopic slides.

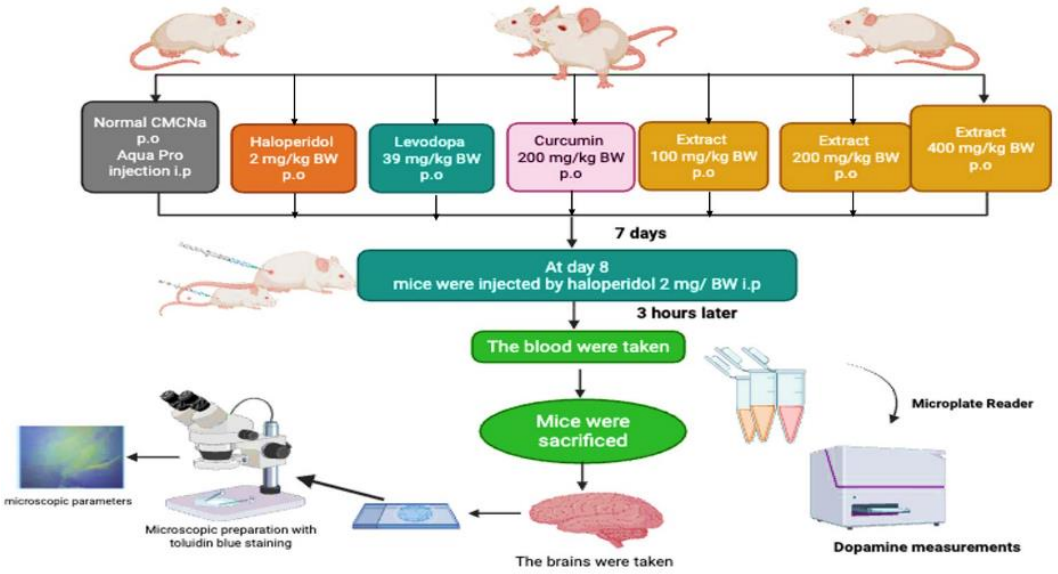

Figure 1. Schematic evaluation of *D. alata* extract toward dopamine levels and brain microscopic features in Parkinson's model mice.

Measurement of blood dopamine levels

Blood dopamine levels were quantified using a commercially available ELISA kit. Briefly, 50 µL aliquots of dopamine standards, blank controls, and prepared samples were meticulously pipetted into designated wells of a microplate. Immediately thereafter, 50 µL of Biotinylated Detection Antibody solution was added to each well, and the plate was incubated for 45 minutes at 37°C to facilitate antigen-antibody binding. Following this incubation, unbound reagents were removed by thoroughly washing each well three times with 350 µL of washing buffer, allowing each wash to stand for 1 minute before aspiration. Subsequently, 100 µL of HRP Conjugate working solution was added to each well and incubated for 30 minutes at 37°C. After another wash step, 90 µL of substrate reagent was added to each well and allowed to incubate for approximately 15 minutes at 37°C, during which color development occurred. The enzymatic reaction was then terminated by adding 50 µL of Stop Solution to each well. Finally, the optical density (OD) of each well was measured at 450 nm using a microplate reader, with results interpreted against a standard curve.

Microscopic brain observation

Following experimental procedures, mice were humanely euthanized via CO_2 inhalation and immediately subjected to dissection to extract their brain organs. Each brain was gently rinsed with 0.9% NaCl solution, weighed, and subsequently fixed in 10% neutral buffered formalin to preserve tissue integrity. For microscopic examination, brain sections were prepared and stained with Toluidine blue according to established standard histological protocols at the Anatomic Pathology Laboratory, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada. This staining technique allows for the visualization of Nissl bodies (rough endoplasmic reticulum), which are abundant in neuronal cell bodies, thereby aiding in the identification of dopaminergic neurons in the substantia nigra. Stained brain preparations were then observed under a light microscope at 400x magnification. The density of dopaminergic cells within the substantia nigra region was semi-quantitatively scored based on the following criteria adapted from previous methodologies[21]:

Score 0: Characterized by a sparse or non-solid distribution of dopaminergic cells.

Score 1: Indicates a moderately dense population of dopaminergic cells.

Score 2: Represents a very dense and abundant presence of dopaminergic cells.

Data analysis

All quantitative data, specifically the scoring results and blood dopamine levels, were subjected to statistical analysis to determine significant differences between experimental groups. A one-way ANOVA was employed to assess overall group variations. Following a statistically significant ANOVA result ($p < 0.05$), post-hoc comparisons were conducted using the Least Significant Difference (LSD) test to identify specific pairwise differences. All statistical computations were performed utilizing the IBM SPSS Statistics software, with a predetermined significance level of $p < 0.05$.

RESULTS AND DISCUSSION

As presented in **Table I**, the administration of haloperidol significantly reduced blood dopamine levels when compared to the normal control group. Conversely, treatment with levodopa and curcumin resulted in an increase in blood dopamine concentrations. Notably, the administration of *D. alata* extract at a dose of 400 mg/kg BW led to a significant increase in dopamine levels ($p < 0.05$) compared to the haloperidol-treated group, indicating a potential reversal of the haloperidol-induced reduction.

Table I. Blood dopamine levels.

Groups	Dopamine levels (pg/mL)
Normal CMC-Na	379.462 ± 58.058*
Haloperidol	330.358 ± 19.411
Levodopa	355.906 ± 9.335
Curcumin	360.973 ± 10.087
Extract 100 mg/kg BW	346.443 ± 13.842
Extract 200 mg/kg BW	373.615 ± 25.458
Extract 400 mg/kg BW	402.352 ± 44.765*

Note: *different significance with haloperidol group ($p < 0.05$)

Further investigation focused on SNpc region of the brain, characterized by its distinct dark pigmentation due to dopaminergic neurons. Microscopic images of the brain from each experimental group are presented in **Figure 2**. Analysis of these images, complemented by the scoring results in **Table II**, revealed significant morphological differences in the SNpc between the haloperidol group and the normal group ($p < 0.05$). In the normal control group, the SNpc exhibited a healthy appearance with intact dopaminergic neurons, evidenced by its characteristic dark staining. In stark contrast, the haloperidol-treated group showed a noticeable reduction in the density or number of dopaminergic cells within the SNpc, resulting in a paler, "empty" appearance. Encouragingly, treatment with levodopa, curcumin, and *D. alata* extract demonstrated a restorative effect on these dopaminergic neurons, as indicated by a visibly darker SNpc area compared to the haloperidol group, suggesting a recovery in cellular density or integrity.

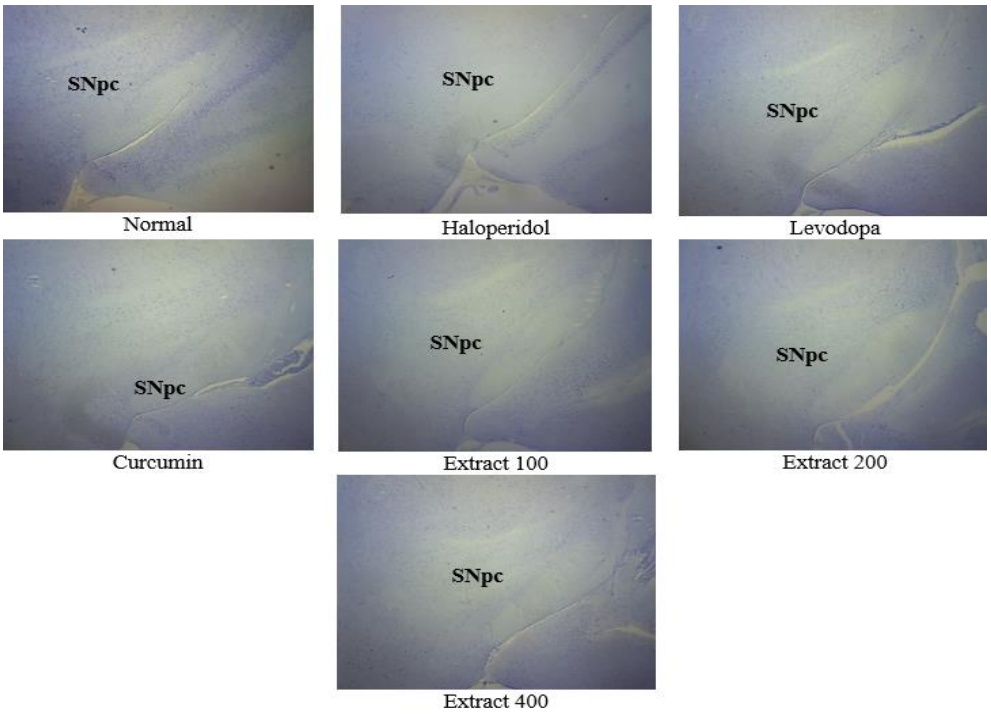

Figure 2. Brain microscopic feature of mice in the area SNpc, stained with toluidine blue at 400x magnification. In the normal group, the dopaminergic neurons in the SNpc appear healthy, indicated by a dark, dense staining. Conversely, the group treated with haloperidol shows a significant loss of these neurons, resulting in an "empty" appearance in the SNpc area. Importantly, treatment with 400 mg/kg body weight of *D. alata* extract effectively prevents this loss of dopaminergic cells, suggesting a protective effect.

Table II. Scoring results overview microscopic brain of mice.

Groups	*Scoring* (mean ± SD)
Normal CMC-Na	2.00 ± 0.00*
Haloperidol	0.20 ± 0.45
Levodopa	1.60 ± 0.55*
Curcumin	1.60 ± 0.55*
Extract 100 mg/kg BW	1.40 ± 0.89*
Extract 200 mg/kg BW	1.60 ± 0.55*
Extract 400 mg/kg BW	1.80 ± 0.45*

The observed reduction in dopamine levels and cellular loss within SNpc following haloperidol administration in this study aligns with its established neuroleptic properties. Haloperidol, an antipsychotic, primarily exerts its effects by blocking dopamine D2 receptors on postsynaptic neurons in the brain, thereby interfering with dopaminergic neurotransmission[22]. Beyond its receptor-blocking action, haloperidol is also known to induce oxidative stress in striatal cells, ultimately contributing to damage in dopaminergic neurons[23]. This cascade leads to a critical reduction in dopamine, a neurotransmitter vital for the initiation and propagation of neuromuscular coordination, particularly within the limbic and extrapyramidal systems. Consequently, dopamine deficiency manifests in characteristic symptoms such as tremors, bradykinesia, muscle stiffness, and hypersalivation[24]. These findings are further corroborated by previous research demonstrating haloperidol's capacity to induce motor and sensory disorders in murine models[25].

Conversely, the co-administration of levodopa and curcumin, as demonstrated in this study, significantly elevated dopamine levels and promoted cellular repair within the SNpc. Levodopa, a dopamine prodrug, serves as a crucial component in dopamine replacement therapy, actively facilitating the repair of damaged dopaminergic neurons[26]. Its efficacy stems from its ability to restore dopaminergic neurotransmission in the corpus striatum by enhancing dopamine synthesis in surviving neurons within the substantia nigra[27]. Upon entering the brain, levodopa is decarboxylated into dopamine by dopa decarboxylase in the substantia nigra pars compacta and subsequently stored in presynaptic neurons[28]. This stored dopamine is then released into the synaptic cleft, where it binds to postsynaptic dopamine D1 and D2 receptors[29]. Dopamine activity is ultimately terminated through reuptake into presynaptic neurons via the dopamine transporter or enzymatic metabolization by monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT)[30].

Curcumin, a naturally occurring phenolic compound, has garnered significant attention for its therapeutic potential in neurodegenerative disorders, a prospect supported by numerous *in vitro* and *in vivo* investigations[31]. Its beneficial effects are primarily attributed to its potent antioxidant, anti-inflammatory, and anti-apoptotic activities. Curcumin's ability to modulate various signal transduction pathways and inhibit the MAO-B enzyme contributes to increased dopamine levels and availability in the brain. Prior research has explicitly shown curcumin's antioxidant capacity through the restoration of dopamine, tyrosine hydroxylase (TH), and SNpc neurons in the striatum, alongside a reduction in motor and sensory disorders and neuroprotective effects in Parkinson's animal models[14]. Furthermore, curcumin's neuroprotective action, stemming from its antioxidant properties, is enhanced by its ability to traverse the blood-brain barrier, thereby increasing striatal dopamine levels in dopaminergic neurons within the SNpc[32].

The administration of *D. alata* extract at doses of 200 and 400 mg/kg BW similarly demonstrated an increase in dopamine levels and significant cellular repair in the SNpc. *Dioscorea alata* is rich in active compounds, notably anthocyanins, which are well-known natural antioxidants[33]. Specifically, pelargonidin-type anthocyanins are highly effective in scavenging hydroxyl free radicals[18]. This inhibitory mechanism involves the interruption of free radical propagation chains, where the hydroxyl groups located on the B-ring of the anthocyanin structure can readily donate electrons or hydrogen atoms to free radicals, thereby stabilizing them[7]. This observation is consistent with earlier studies demonstrating that anthocyanin-rich extracts more effectively mitigate rotenone-induced neurotoxicity in Parkinson's disease cell culture models compared to extracts rich in other polyphenols. The proposed mechanism for this neuroprotection involves the repair of mitochondrial dysfunction, specifically through the inhibition of complex I of the electron transport chain, and interference with microglial activation, both of which are critical factors in the death of dopaminergic neurons in the brain[20]. Such inhibition is crucial in preventing dopaminergic cell death, thereby contributing to increased dopamine levels.

CONCLUSION

This study provides compelling evidence that the extract of *D. alata* possesses significant antiparkinsonian potential. Specifically, administration of *D. alata* extract at a dose of 400 mg/kg BW effectively increased dopamine levels within the brain and mitigated microscopic damage to the dopaminergic neurons in SNpc region of haloperidol-induced Parkinson's disease mice. These findings suggest that *D. alata* extract may offer a novel therapeutic avenue for managing Parkinson's disease by preserving dopaminergic neuronal integrity and enhancing dopamine neurotransmission.

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Writing - review & editing: Sapto Yuliani, Dwi Utami, Laela Hayu Nurani, Mochammad Saiful Bachri

DATA AVAILABILITY

The datasets generated and analyzed during the study are available from the corresponding author upon request.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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