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The Protective Role of Honey on MPTP-induced Hippocampal Injury in Male Swiss Mice

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ABSTRACT

The agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is standard for the induction of Parkinson's disease (PD) in animal models. Cognitive dysfunction disturbs about thirty-forty percent of PD patients and can progress to dementia. Non-motor symptoms, such as hippocampal damage, contribute significantly to the deficiency in cognition observed in patients with Parkinson's disease (PD). This research work evaluated how honey performs its neuronal protection on the MPTP-induced hippocampal damage. Forty adult male Swiss mice were assigned to control, MPTP, honey, and honey + MPTP groups. MPTP was administered intraperitoneally (20 mg/kg) at 2-hour intervals, four times in one day on day 22, and honey (1.5 ml/kg) was given orally for 21 days. Histological and immunohistochemical analyses revealed significant hippocampal damage in MPTP-treated mice, including disrupted cytoarchitecture, reduced astrocytic and microglia processes, and increased ERK expression. Pretreatment with honey preserved the general hippocampal cytoarchitecture and the astrocytic and microglial processes, and modulated the activities of ERK levels, suggesting improved synaptic plasticity. These results suggest honey's potential as a functional food to help mitigate hippocampal damage and cognitive decline in PD.

Keywords: MPTP, hippocampal-damage, honey, astrocytes, microglia, Clasmatodendrosis, long-term potentiation

INTRODUCTION

The compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a known standard agent for the induction of Parkinson's disease (PD) in animal models. The hippocampus, along with the nigrostriatal system, is implicated in the symptoms of PD that are not motor activities, including dysfunctions affecting cognition and emotions. MPTP administration leads to neurochemical alterations, reducing neurogenesis and impacting neuronal processes and its density in the hippocampus[1]. These changes are linked with neurocognitive and psychiatric disorders, including dementia, and may underlie the symptoms of PD not associated with motor functions. Inhibition of the dopaminergic system by MPTP also induces architectural changes in hippocampal neurons. This aligns with the suggestion that hippocampal neural remodelling may contribute to the non-motor symptoms observed in PD[1]. However, non-motor symptoms, including gastrointestinal manifestations and deficiency in cognition, often precede motor deficits in PD. Cognitive dysfunction affects 30–40% of PD patients and can progress to dementia[2]. In unmedicated and dementia-free early-stage PD patients, atrophy has been observed in the prefrontal cortex and hippocampus[1].

Furthermore, healthy astrocytes are very instrumental to synaptogenesis which is a factor in memory formation and cognition. In a healthy hippocampal tissue, the processes of the astrocytes are well defined and forms a network or syncytium which helps reinforce the blood-brain barrier and energy production but damage due to aging, neurodegenerative disorder, oxidative stress could lead to breakage or disruption of the well-defined astrocytic syncytium. This disruption or breakage of astrocytic process is referred to as Clasmatodendrosis which results in lax blood-brain barrier, energy failure and mitochondria inhibition[3].

An important mechanism to memory and learning is long-term potentiation (LTP). It involves the potentiation of extracellular signal-regulated kinases (ERK1/2). ERK1/2 is a major factor in the regulation of synaptic proteins and promotes dendritic spine formation, positively influencing the induction and maintenance of LTP. Furthermore, this molecular pathway facilitates the expression of immediate-early genes, such as zif268 and arc, which are essential for structural modifications at the synapse[4].

Honey is a gelatinous, pasty fluid made by bees from the nectars gathers from flowers. Honey is a functional food been valued for its healing properties since prehistoric era. Honey is a phytoestrogen and with protective neuronal value, resulting from its ability to enhance brain derived neurotrophic factor (BDNF). It is also referred to as a memory booster, which may be as a result of its ability to improve neurogenesis in the hippocampus and its ability to enhance the cholinergic system. It also exhibits antioxidative and anti-inflammatory properties, which are thought to be due to the abundance of polyphenolic compounds in honey. Honey is well-tolerated by most people[5,6]. This study focuses on non-motor deficits associated with Parkinsonian neurodegeneration, particularly hippocampal damage and the resulting memory impairment in the MPTP mouse model. The research investigates the potential neuroprotective effects of honey on hippocampal neurons and cognitive function following MPTP-induced toxicity.

We hypothesize that honey, being an antioxidative and anti-inflammatory functional food, can attenuate MPTP-induced hippocampal damage, preserve synaptic plasticity, and improve cognitive performance in mice. This hypothesis is based on the existence of bioactive complexes in honey, including polyphenols and flavonoids, which may reduce oxidative stress and neuroinflammation, two major mechanisms underlying neurodegeneration in PD.

The study therefore aims to determine whether honey can protect hippocampal neurons, preserve astrocytic and microglial integrity, and regulate ERK signaling pathways, thereby maintaining cognitive function in the setting of MPTP-induced neurotoxicity.

MATERIALS AND METHODS

Experimental animals and reagents

Forty adult male Swiss mice (25-30 g) were housed at the Central Research Laboratory, University of Ilorin, with food and water *ad libitum*. They were acclimatized for 14 days preceding the experiment. The research work was approved by the University of Ilorin Ethical committee (UERC/ASN/2021/2136). MPTP hydrochloride (Catalog No: HY-15608) was obtained from MedChem Express, USA. Phosphate-buffered saline (PBS) was purchased from Sigma-Aldrich, USA. Honey (A & Shine Int'l LTD, Abuja) was acquired from Rotamedics Pharmacy, Ilorin.

Experimental design

The animals were randomly divided into four groups: Control group (n=10): received 0.2 ml of PBS orally for 21 days. MPTP group (n=10): took 20 mg/kg body weight of MPTP intraperitoneally at 2-hour intervals, four times in one day on day 22. Honey group (n=10): given 1.5ml/kg body weight of honey orally for 21 days consecutively. Preventive group (n=10): given 1.5ml/kg body weight of honey orally for 21 days, then 20 mg/kg body weight of MPTP on day 22. On day 30 (8 days post-MPTP administration), all mice were euthanized.

Histological and immunohistochemical analysis of the hippocampus

Mice were euthanized using isoflurane on day 30. One-drop method and nose cone method was employed in the administration of isoflurane. After euthanization was achieved, mice were transcardial perfused with PBS, followed by 10% neutral buffered formalin (NBF) and brain tissues were excised for histological, histochemical and immunohistochemical studies. Then, the brain tissues were fixed in NBF to prevent autolysis. After proper fixation, the coronal section of the hippocampus was exposed by cutting the entire brain tissue into two halves at the highest point and sections used were 2mm away from the two halves. The exposed brain tissues were processed for paraffin embedding. Rotary microtome, with its knife situated at 45° was used to section the paraffin block to obtain 5 microns thick of hippocampal sections.

Hippocampal slices were stained with hematoxylin and eosin (H & E) to demonstrate the cytoarchitecture of the hippocampal region. Immunohistochemical studies was done to demonstrate Ionized Calcium-Binding Adaptor Molecule 1 (IBA1), Glial Fibrillary Acidic Protein (GFAP), and extracellular signal-regulated kinases (ERK1/2) proteins. Antigen was unmasked by nurturing sections in antigen retrieval solution at 60^{o}C for 50 minutes, and then endogenous peroxidase was inhibited. The slices were then incubated in primary antibodies for Ionized Calcium-Binding Adaptor Molecule 1 (IBA1: 1:100), Glial Fibrillary Acidic Protein (GFAP: 1:100), and ERK (1:100) overnight at 10^{o}C.The slides were rinsed and incubated in the secondary antibody (goat anti-rabbit mouse) for 30 minutes. Then reactivity was revealed with DAB + hydrogen peroxide. The sections were visualized under a light microscope, and photomicrographs were captured with the aid of AmScope camera at 400x magnification (scale bar of 10μm) for H&E, GFAP and IBA-1 while ERK was captured at 40x magnification (scale bar of 50 μm)

Quantitative analysis

The photomicrographs of the immunohistochemical stained tissue sections (GFAP, IBA-1 and ERK) captured using AmScope camera was quantified using the ImmunoRatio plugin in ImageJ (NIH, Bethesda, MD, USA). Images were imported into ImageJ and

the immunoratio plugin was used to perform automated color deconvolution, by separating the diaminobenzidine (DAB)-positive staining from the hematoxylin counterstain. The percentage of positively stained nuclei was calculated as the ratio of the DAB-stained nuclear area to the total nuclear area (DAB-stained nuclei plus hematoxylin-stained nuclei). Multiple representative fields per sample were analyzed, and the mean percentage of positive nuclei was used for statistical analysis. All analyses were carried out using identical threshold settings to ensure consistency across samples.

Statistical analysis

One-way ANOVA followed by Tukey's post-hoc test were used for data analysis. Results were conveyed as mean ± standard error of the mean (SEM), with significance set at $p < 0.05$. Statistical analysis was done using GraphPad Prism version 7.0.

RESULTS

Honey protects hippocampal cytoarchitecture in MPTP induced distorted cytoarchitecture granule cells of the dentate gyrus

Histological analysis of the dentate gyrus revealed that control mice had normal, well-rounded granule cells with homogeneous cytoplasm and intact nucleoli. MPTP-treated mice exhibited numerous degenerating neurons with shrunken, irregularly shaped cells and acidophilic cytoplasm. Honey-treated mice showed predominantly healthy granule cells, and the honey + MPTP group displayed a mixture of normal and degenerating neurons (Figure 1).

Pyramidal cells of the CA3 region

In the CA3 region, control mice exhibited normal pyramidal cells with thick axon hillocks, homogeneous cytoplasm, and intact nucleoli. MPTP-treated mice had numerous degenerating neurons. Honey-treated mice showed mostly healthy pyramidal cells, and the honey + MPTP group demonstrated some normal and some degenerating cells (Figure 2).

Pyramidal cells of the CA1 region

Similar to the CA3 region, CA1 pyramidal cells in control mice appeared normal, while MPTP-treated mice had a few degenerating neurons. The honey and honey + MPTP groups showed predominantly normal pyramidal cells (Figure 3).

The preservative role of honey on hippocampal clasmatodendrosis following MPTP-induced hippocampal damage

The representative photomicrographs showing the reactive astrocytes in the Dentate gyrus of the experimental mice using Glial Fibrillary Acid Protein (GFAP) expression as shown in Figure 4A. There was abundance of normal astrocytes in the DG of the mice in the control and the honey group demonstrated by abundant astrocytic process as indicated by red arrow. The MPTP group demonstrated limited number of astrocytes most of which are not normal with broken astrocytic processes and shrunken cell bodies as indicated by black arrow. The Hon + MPTP group had a few broken astrocytes and some normal astrocytes.

The DAB/nuclear ratio (immunoratio) of GFAP expression in the hippocampal region of mice of the experimental mice as shown in Figure 4B There was a significant reduction in the immunoratio of MPTP and Honey + MPTP groups as compared to control group and a significant increase in honey group as compared to control. There was a significant increase in the immunoratio of honey as well as honey + MPTP groups as compared to MPTP only group.

Microglia in ionized calcium-binding adapter molecule-1 (IBA-1)

Figure 5A is a representative photomicrograph showing the microglia in the Dentate gyrus of the experimental mice using Ionized Calcium-Binding Adapter Molecule-1 (IBA-1) expression as shown in Figure 5A The control and Honey groups had abundant large microglia with intact process being expressed as shown by the red arrows, the MPTP group had small sized microglia with limited processes as indicated by the black arrow. The Honey + MPTP group had some large sized microglia as well as small sized microglia.

In Figure 5B, there was significant reduction in the expression of IBA-1 in honey and Honey + MPTP groups as compared to control while there was significant decrease in the expression of IBA-1 in honey group as compared to MPTP group as shown in Figure 5B.

Protective role of honey on the improvement of memory via activation of extracellular signal-regulated kinase (ERK) following MPTP-induced neurotoxicity

The representative photomicrographs showing expression of ERK in the hippocampus of the experimental mice as shown in Figure 6A. There was significantly high expression of ERK that was randomly expressed in the entire hippocampal region of mice in the control and the honey group, with the honey group having more concentrated expression especially in the dentate gyrus area. The MPTP group demonstrated minimal expression of ERK with some part of the DG area being devoid of expression. The Hon + MPTP group showed depletion of expression of ERK although its better expressed as compared to what is seen in the MPTP only group.

In Fig. 6B, there was significant increase in the immunoratio of the MPTP group as compared to the control group and a significant decrease in the ratio of honey and honey + MPTP group as compared to control. There was significant decrease in the immunoratio of honey and honey + MPTP group as compared to MPTP group.

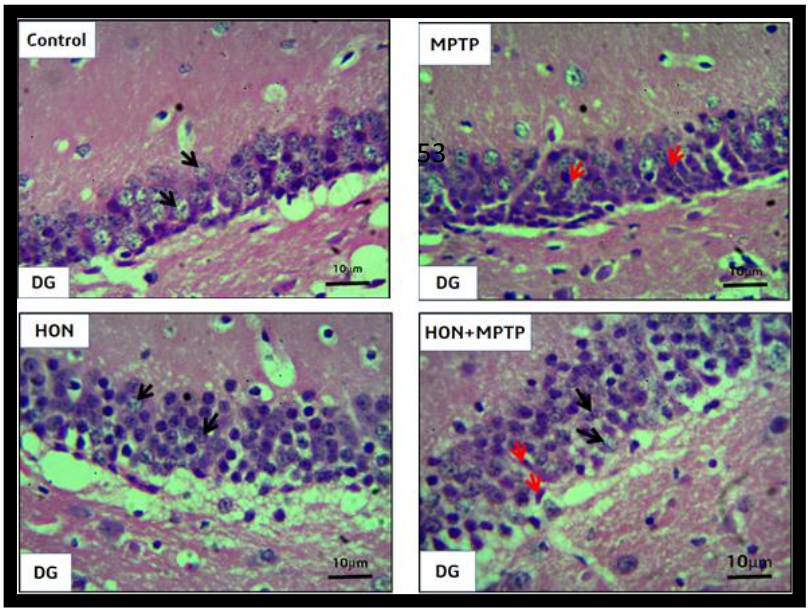

Figure 1: Cytoarchitecture of Dentate gyrus (DG) stained with (H&E). PBS group had normal, well-rounded granule cells with homogeneous cytoplasm and intact nucleoli. MPTP-treated mice exhibited numerous degenerating neurons with shrunken, irregularly shaped cells and acidophilic cytoplasm. Honey-treated mice showed predominantly healthy granule cells, and the honey + MPTP group displayed a mixture of normal and degenerating neurons. CONTROL= Phosphate Buffered Saline, MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, HON=Honey, HON+MPTP= Honey followed by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Black arrow= normal neurons, Red arrow = degenerating neurons. Magnification=x400 (Scale bar: 10 µm)

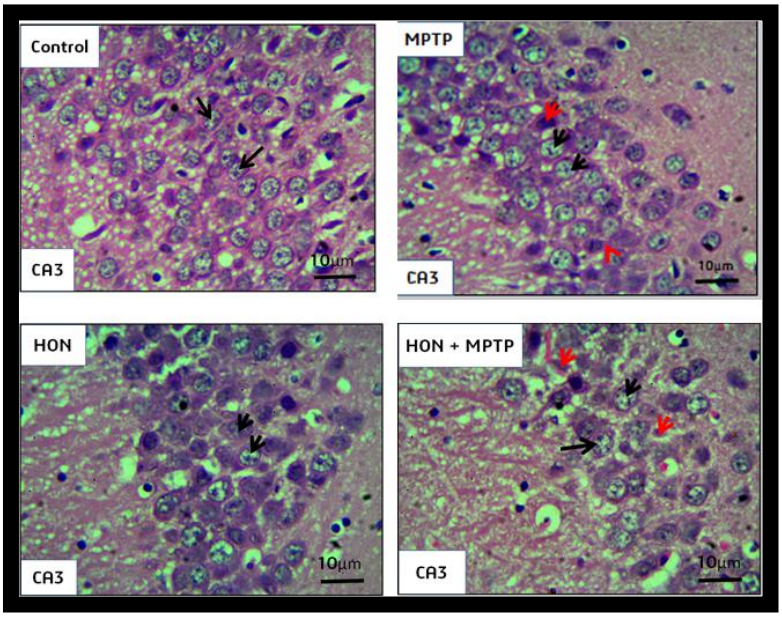

Figure 2: Cytoarchitecture of CA3 region stained with H&E. Control mice exhibited normal pyramidal cells with thick axon hillocks, homogeneous cytoplasm, and intact nucleoli. MPTP-treated mice had numerous degenerating neurons. Honey-treated mice showed mostly healthy pyramidal cells, and the honey + MPTP group demonstrated some normal and some degenerating cells. CONTROL= Phosphate Buffered Saline, MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, HON=Honey, HON+MPTP= Honey followed by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Black arrow: normal neurons; Red arrows: degenerating neuron. Magnification: x400 (Scale bar: 10 µm)

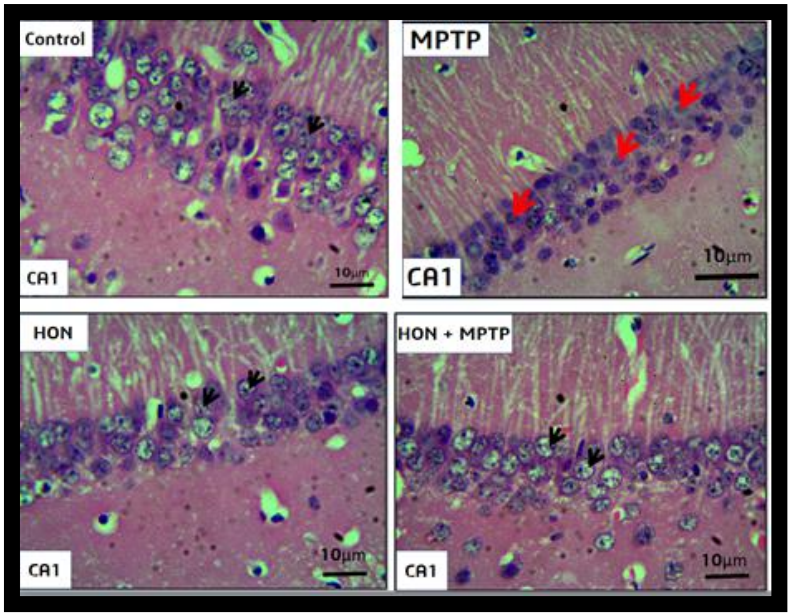

Figure 3: Cytoarchitecture of CA1 region stained with (H&E). Control mice appeared normal, while MPTP-treated mice had a few degenerating neurons. The honey and honey + MPTP groups showed predominantly normal pyramidal cells. CONTROL= Phosphate Buffered Saline, MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, HON=Honey, HON+MPTP= Honey followed by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Black arrow: normal neurons; Red arrows: degenerating neuron. Magnification: x400 (Scale bar: 10 µm)

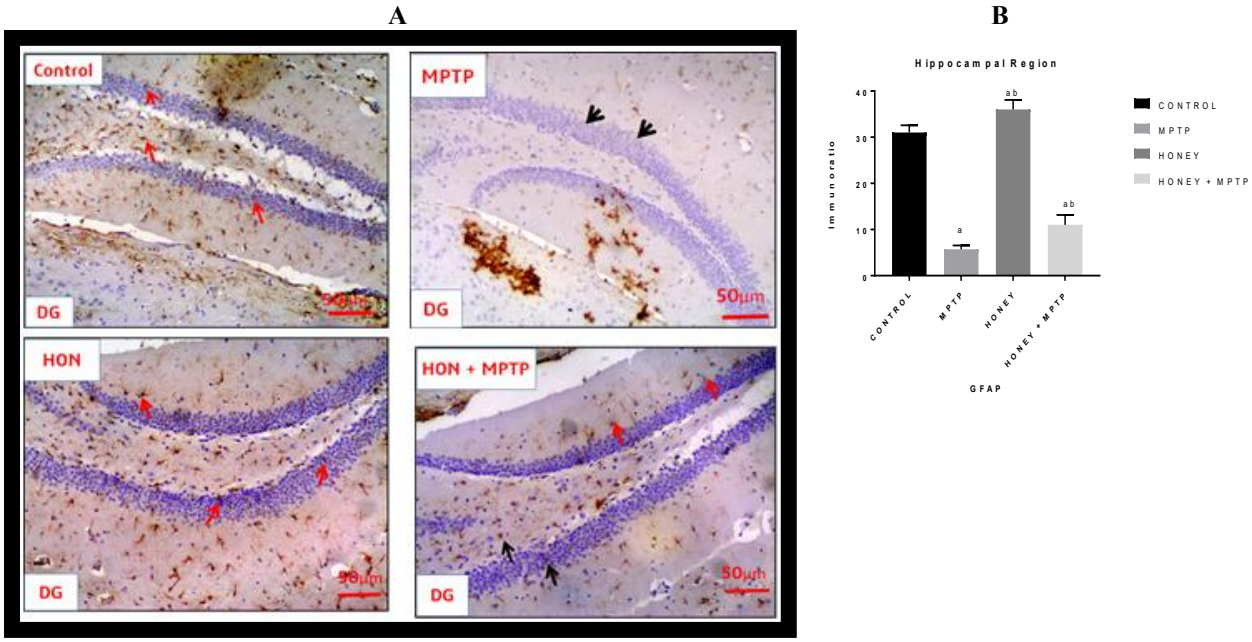

Figure 4 (A) Reactive astrocytes in the Dentate gyrus of the experimental mice using Glial Fibrillary Acid Protein (GFAP) expression. There was abundance of normal astrocytes in the DG of the mice in the control and the honey group demonstrated by abundant astrocytic process as indicated by red arrow. The MPTP group demonstrated limited number of astrocytes most of which are not normal with broken astrocytic processes as indicated by black arrow. The Hon + MPTP group had a few broken astrocytes and some normal astrocytes. **(B)** DAB/nuclear ratio (immunoratio) of GFAP expression in the hippocampal region. There was significant decrease in the immunoratio of MPTP ($^{a}p<0.05$) compared to control group, Honey+MPTP groups as compared to control group and a significant increase in honey group as compared to control. There was a significant increase in the immunoratio of honey as well as honey + MPTP groups ($^{b}p<0.05$) compared to MPTP only group. CONTROL= Phosphate Buffered Saline, MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, HON=Honey, HON+MPTP= Honey followed by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Red arrow =normal astrocytes; black arrow = fragmented astrocyte. Magnification: X 100 (Scale bar: 50 µm)

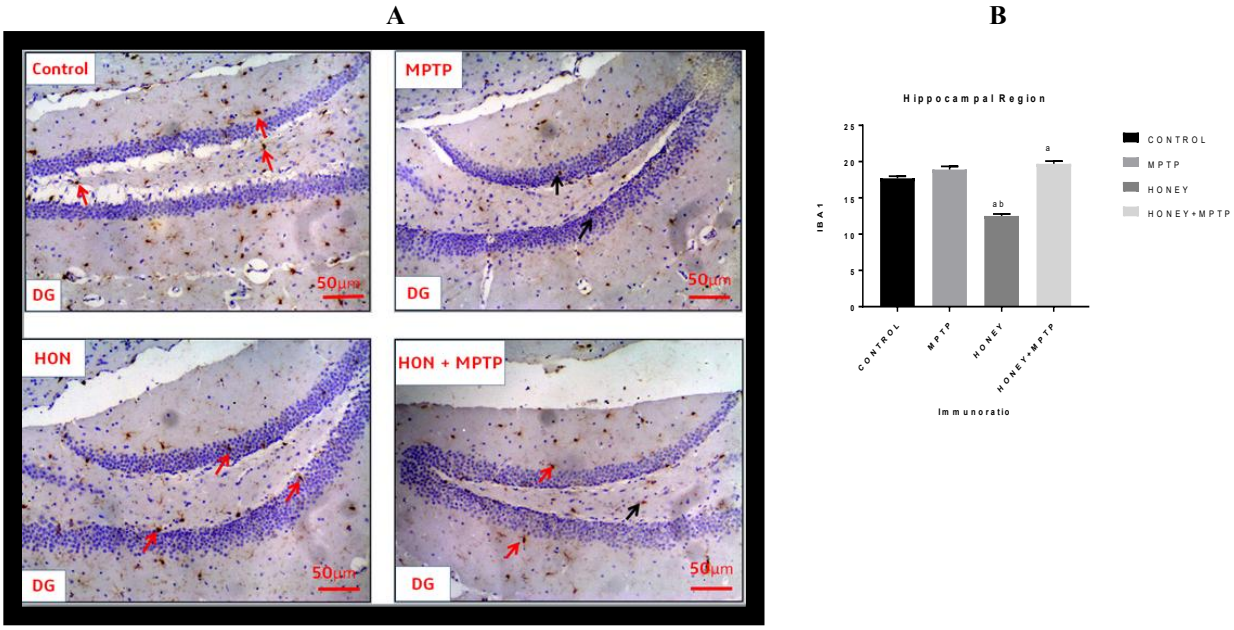

Figure 5 (A) Microglia in the Dentate gyrus of the experimental mice using Ionized Calcium-Binding Adapter Molecule-1 (IBA-1) expression as shown in the control and Honey groups had abundant large microglia with intact process being expressed as shown by the red arrows, the MPTP group had small sized microglia with limited processes as indicated by the black arrow. The Honey + MPTP group had some large sized microglia as well as small sized microglia. **(B)** There was significant reduction in the expression of IBA-1 in honey and Honey + MPTP groups ($^{a}p<0.05$) compared to control group, while there was significant decrease in the expression of IBA-1 in honey group ($^{b}p<0.05$) compared to MPTP only group. CONTROL= Phosphate Buffered Saline, MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, HON=Honey, HON+MPTP= Honey followed by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Red arrow =normal astrocytes; black arrow = fragmented astrocyte. Magnification: X 100 (Scale bar 50 µm)

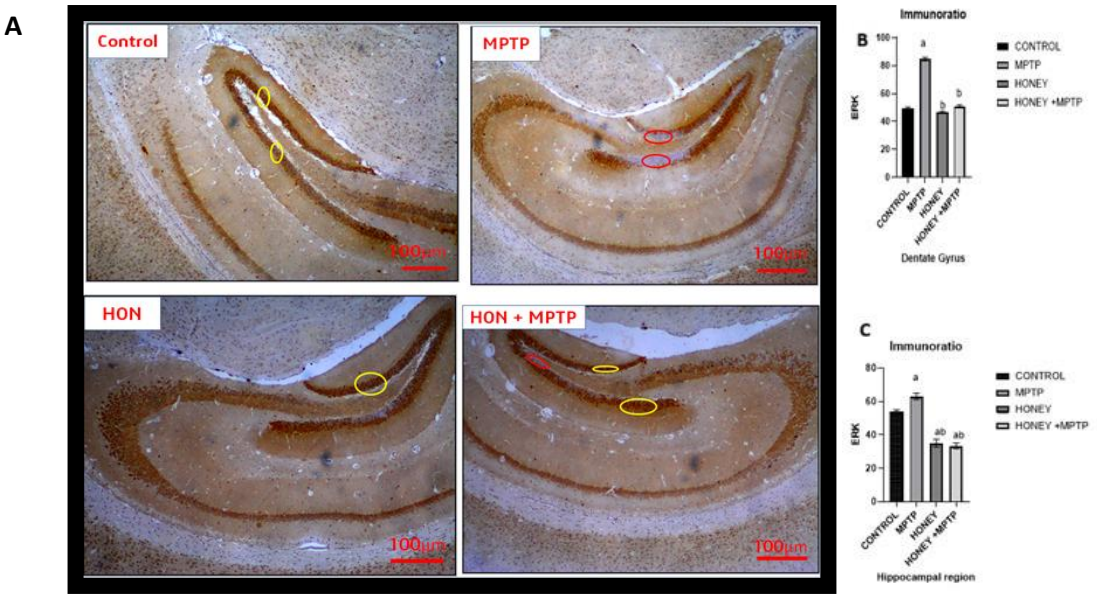

Figure 6 (A) ERK expression in the hippocampus of the experimental mice, there was significantly high expression of ERK that was randomly expressed in the entire hippocampal region of mice in the control and the honey group, with the honey group having more concentrated expression especially in the dentate gyrus area. The MPTP group demonstrated minimal expression of ERK with some part of the DG area being devoid of expression. The Hon + MPTP group shown depletion of expression of ERK although, its better expressed as compared to what is seen in the MPTP only group. **(B) & (C)** There was significant increase in the immunoratio of the MPTP group ($p<0.05$) compared to control group and a significant decrease in the ratio of honey and honey + MPTP group ($p<0.05$) compared to MPTP only group as compared to control. There was significant decrease in the immunoratio of honey and honey + MPTP group ($^{b}p<0.05$) compared to MPTP only group. CONTROL= Phosphate Buffered Saline, MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, HON=Honey, HON+MPTP= Honey followed by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Yellow oval ring = area of dense expression of ERK; Red oval ring = area of sparse expression of ERK. Magnification: x40 (Scale bar: 100 µm).

DISCUSSION

Synaptic plasticity was altered in the hippocampal region as a result of MPTP administration, suggesting an interaction between the dopaminergic (DA) system and hippocampal synaptic plasticity. Patients with early-stage PD, who are non-medicated and non-demented, often show loss of neurons in the prefrontal cortex and hippocampus[1]. Astrocyte has close associations with nerve cells and blood vessels. They play key roles in maintaining glucose metabolism, regulating glutamate and potassium levels, controlling cerebral blood flow, and secreting neurotrophic factors, like BDNF, which is essential for proper neuronal activity. These functions are crucial for cognitive processes like learning and memory, particularly through long-term synaptic potentiation (LTP)[7]. Astrocytes are vital in maintaining the blood-brain barrier, clearing surplus neurotransmitters, and supporting synapse formation. Although once thought to be homogeneous, astrocytes are now recognized as highly heterogeneous, especially in the hippocampus, where they modulate synaptic plasticity in a region-specific manner[8].

In this study, the high number of normal astrocytes observed in the control and honey-treated groups suggests normal neural activity in the hippocampus. Notably, the honey-treated group exhibited a significant increase in astrocytes, which may explain honey's well-known cognitive benefits, particularly in learning and memory. The well-defined astrocytes with its intact processes will lead to better synaptogenesis that could help enhance cognition[3]. In contrast, the MPTP-treated group showed the most minimal quantity of astrocytes, supporting findings by Weerasinghe-Mudiyanselage and colleagues, who reported hippocampal atrophy in PD patients. Honey's capacity to shield astrocytic populations in the hippocampus may be attributed to the abundance of flavonoids and phenolic compounds in it, which possess antioxidative and anti-inflammatory characteristics. These components can guard neurons from oxidative damage, enhance neuronal function, support regeneration, and modulate neuronal signaling pathways[5,9], and honey has been observed to improve memory and intelligence[10].

Neuroinflammation and microglial responses have been linked to the neurotoxicity caused by environmental agents. Microglia exhibit both neuroprotective and neurotoxic properties. In their neuroprotective role, they perform homeostatic functions by phagocytosing misfolded proteins, cellular debris, apoptotic cells, and pathological protein aggregates. However, excessive uptake of protein aggregates can impair microglial phagocytic ability, triggering neuroinflammation and, eventually, neurodegeneration. Microglia are also involved in maintaining neuronal survival and promoting neurogenesis during both prenatal and postnatal stages. Astrocytes, which have limited pathogen detection abilities due to their low expression of Toll-Like Receptors (TLRs), rely on microglia to communicate pathogen threats and induce astrocytic activation. Therefore, modulating microglial activation may offer an effective strategy for treating neurodegenerative disorders[11].

In Parkinson's disease, microglial dysfunction plays a critical role in neurodegeneration, not only in the substantia nigra but also in other brain regions like the hippocampus, which is essential for memory and cognitive functions. In this investigation, a significant decline in hippocampal microglia was noticed in MPTP-induced neurodegeneration. This reduction could result from chronic microglial activation in response to neuroinflammation, leading to microglial exhaustion or senescence, a state of wear and tear caused by prolonged inflammation and neuronal injury. This process ultimately depletes the microglial population[12,13].

Microglia are also essential for promoting and regulating neurogenesis, especially in areas like the dentate gyrus, which is critical for learning and memory[14]. Reduced neurogenesis, due to neuronal damage, may further contribute to the decline in microglia numbers. Microglia create a supportive environment for neural progenitor cells, and decreased neurogenesis leads to fewer signals for microglial recruitment and proliferation, further reducing microglial numbers[15]. This reduction creates a vicious cycle, where impaired neurogenesis exacerbates hippocampal dysfunction in PD.

However, this investigation demonstrates that pretreatment with honey effectively protected hippocampal microglia. The honey-treated group showed a marked increment in microglia compared to the MPTP-only set of experimental animals, likely due to honey's potent anti-inflammatory properties. Honey contains several flavonoids and polyphenols, such as quercetin, chrysin, and gallic acid, which can suppress the production of pro-inflammatory cytokines[16]. In MPTP-induced models, neuroinflammation driven by microglial overactivation contributes to neurodegeneration and microglial depletion. Honey has been said to cause decrease in pro-inflammatory mediators, including TNF-α, IL-1β, and IL-6, which are elevated in MPTP models[17]. Reducing these inflammatory activities likely helps create a more favorable environment for microglial survival and function in the hippocampus.

Additionally, honey has been found to regulate microglial activation by inhibiting the NF-κB pathway, which plays an essential part in microglial activation[18,19]. Royal jelly, a component of honey, has also been shown to enhance neurogenesis and synaptic plasticity, especially in neuroinflammatory conditions[20]. This neurogenic effect may create a positive feedback loop, sustaining microglial populations in the hippocampus, as an active neurogenic niche requires support from microglia.

ERK1/2 signaling is critically involved in neuronal degenerative disorders, such as, Parkinson's disease. Nitric oxide generated by glial cells stimulates neuronal degeneration via ERK1/2 potentiation, and dopamine-induced striatal neuron death has been linked to ERK1/2 activation. The PI3K/Akt and ERK1/2 signaling pathways also play a protective role in dopaminergic neurons against MPTP/MPP+-induced neurotoxicity[21].

In our study, there was a significant increment in ERK expression in the hippocampus of MPTP groups, likely due to oxidative stress. Oxidative stress and neuroinflammation often activate mitogen-activated protein kinase (MAPK) pathways such as ERK, as ERK responds to cellular injury and inflammation. Its upregulation may be a homeostatic response to counter the rise in reactive oxygen species (ROS) and to suppress the stimulation of pro-inflammatory cytokines like TNF-α and IL-1β[22-24].

Given ERK's role in synaptic plasticity, learning, and memory, the increase in ERK expression may also represent an adaptive response to the loss of dopaminergic neurons in PD, particularly in MPTP-induced models. This compensatory increase likely supports synaptic function in the hippocampus, despite ongoing neurodegenerative changes.

However, honey pretreatment modulated ERK activity, suggesting its powerful antioxidative and anti-inflammatory characteristics. Honey likely prevents excessive ROS accumulation and suppresses the production of pro-inflammatory cytokines, thereby reducing ERK overactivation as a stress response. This modulation of ERK activity could help restore balance in synaptic plasticity, improving memory and learning.

We acknowledge some limitations encountered in our study, such as the short duration of treatments in our study and the lack of behavioral assessments, these are areas our subsequent studies will improve on to further strengthen our findings.

CONCLUSION

The outcomes of this investigation demonstrate that honey attenuates MPTP-induced hippocampal damage by preserving hippocampal cytoarchitecture, maintaining astrocytic and microglial integrity, and modulating ERK signaling. These neuroprotective effects are likely mediated through the antioxidant and anti-inflammatory effects of the bioactive compounds present in honey, thereby helping to preserve synaptic plasticity and cognitive function in Parkinsonian neurodegeneration.

Conflict of interests

Authors disclose no financial or non-financial interests that are directly or indirectly related to this work submitted for publication.

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Authors contributions

R.Y and F.A wrote the main manuscript text and A.A prepared figure 4-6, A.L prepared figures 1-3, A.O, Y.O, M.S and A.D all edited the manuscript and contributed to various sections in writing. All authors reviewed the manuscript.

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