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Evaluating Neurotherapeutic Potential of Myricetin by In- Vivo Research Models

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ABSTRACT

Background: Oxidative stress, neuroinflammation, and poor neurotrophic signaling are associated with neurological diseases. Myricetin is a bioflavonoid present in berries, vegetables, and medicinal herbs, with strong anti-inflammatory, antioxidant, and neurotrophic properties in animal studies. The objective of the present in-vivo research was to assess the neuroprotective potential of myricetin on nerve growth factor (NGF) expression and neuroinflammation in chemically induced neural injury.

Methods: Thirty healthy male adult Wistar rats (180-220g, 8 weeks old) were randomly divided into five groups (n=6 per group). Group I was used as a control, with no intervention. Groups II to V were exposed to a standard propionic acid (PPA) to induce neuroinflammation. Groups III-V were induced and subsequently administered with oral myricetin of 50 mg/kg, 100 mg/kg, and 200 mg/kg for 28 days. Serum levels of NGF were measured with Enzyme-linked Immunosorbent assay (ELISA). One-way ANOVA was performed for statistical analysis using SPSS.

Results: PPA decreased NGF to 4.3 ± 0.5 pg/ml ($p < 0.001$). Myricetin restored NGF to 9.3, 7.6, and 9.8 pg/mL via 50, 100, and 200 mg/kg doses, respectively. At 200 mg/kg, C-reactive protein (CRP), tumor necrosis factor (TNF), and malondialdehyde (MDA) were decreased to 1.7 ± 0.2 mg/L, 26 ± 3 pg/mL, and 2.9 ± 0.3 nmol/mg, compared to 4.9 ± 0.4, 58 ± 4, and 6.7 ± 0.4. ($p < 0.001$).

Conclusion: Myricetin exhibits promising neurotherapeutic potential, evidenced by its ability to upregulate NGF and mitigate neuroinflammatory damage, making it a potential therapeutic option for the treatment of neurological disorders.

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Keywords: Nerve Growth Factor, Flavonoids, Rats, Wistar, Neurodegenerative Diseases
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INTRODUCTION

Neurological disorders, including Alzheimer's disease, ischemic stroke, epilepsy, and diabetic neuropathy, are increasingly associated with chronic neuroinflammation, oxidative stress, and disrupted neurotrophic signaling pathways [1]. These conditions are becoming common globally, with few effective neurotherapeutic treatment options [2]. Myricetin is a natural flavonoid that has gained recognition as a potent anti-inflammatory, antioxidant, and neurotrophic agent in preclinical animal and cell models [3].

In rodent cerebral ischemia, Myricetin decreased infarct area, improved neurological outcome, and stimulated Nrf2 signaling to counteract oxidative and apoptotic cellular injury [4]. Myricetin in lipopolysaccharide-induced neuroinflammation models inhibits microglial activation, suppresses MAPK/JNK phosphorylation, and downregulates pro-inflammatory mediators, including Tumor necrosis factor (TNF-α), IL-1-β, and COX-2. Myricetin inhibits STAT1-mediated M1 microglial polarization during hypoxia[5]. In the senescence-accelerated mouse model, myricetin in the diet enhanced cognitive behavior and boosted cerebral nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) expression through phosphorylation of cAMP response element-binding protein (CREB) [6]. Myricetin reduced reactive oxygen species, advanced glycation end products, and improved nerve conduction and Na^+/K^+-ATPase activity by activating Nrf2/HO-1 in diabetic neuropathy models [7].

Although myricetin shows promise in neuroinflammatory rat models and inflammatory biomarkers, no in-vivo study has completely assessed the impact of myricetin on serum NGF levels and inflammatory biomarkers [8]. This is particularly necessary since NGF supports the survival and synaptic plasticity of neurons during neural injury [9,10]. The results of this study may assist in the development of plant-based neuroprotective interventions and present a mechanistic understanding of neuroregeneration induced by flavonoids.

The purpose of this study was to determine the changes in serum NGF levels after treatment with Myricetin at graded doses. This study also assessed the ability of myricetin to reduce inflammatory and oxidative stress markers in a neuroinflammation model.

METHODS

The in-vitro collaborative research analysis (EC/037/03/24) conducted mainly at IMCH Tandu Khana and SH Lahore from February 2024 to August 2024 to determine the neurotherapeutic effects of Myricetin on serum NGF and inflammatory markers in a rat model of a chemically induced neuroinflammatory disease.

Animals were kept under standard conditions (22 ± 2 °C, 12-hour light/dark cycle, 55-60% humidity) with access to diet and water. Thirty healthy adult male Wistar rats were recruited through consecutive sampling and randomly assigned to the five groups (n=6 per group): Group I (control), Group II (PPA-induced), and Groups III-V (propionic acid (PPA)-induced + Myricetin at 50, 100, and 200 mg/kg, respectively). The sample size was determined using OpenEpi version 3.0.0 (released 2013, Atlanta, GA, USA) based on an effect size of 1.2, power of 80%, and alpha of 0.05 [11].

The inclusion criteria were male Wistar rats, aged 8 weeks, healthy, with a normal weight range, no neurological or systemic disorders, and active behavior during acclimatization. The exclusion criteria were rats showing symptoms of infection, congenital deformities, pre-existing neurological disorder, those experiencing considerable weight loss (>10%), or neurologically related behavioral abnormality during the primary assessment. PPA (250 mg/kg) intraperitoneal injection was used for neuroinflammation induction, and treatment groups received myricetin for 28 days. Blood samples were obtained after treatment to conduct biochemical tests. The concentration of NGF was determined by rat-specific Enzyme-linked-immunosorbent assay (ELISA) kits. TNF-α, C-reactive protein (CRP), and malondialdehyde (MDA) were measured by conventional immunoassays.

SPSS version 26.0 (released 2019, IBM Corp., Armonk, NY) was used to analyze data. Intergroup comparisons were performed using 1 way ANOVA. P-value < 0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics (n = 30)

Variable	Group I(Control)	Group II(Induced)	Group III(Myr-50)	Group IV(Myr-100)	Group V(Myr-200)	Test Value	p-value
Age (weeks)	8	8	8	8	8	F = 0.91	0.48
Weight (g)	200 ± 5	198 ± 6	199 ± 4	201 ± 5	202 ± 4	F = 1.12	0.36
Baseline NGF (pg/mL)	11.8 ± 0.6	11.7 ± 0.5	11.6 ± 0.5	11.9 ± 0.4	11.7 ± 0.6	F = 0.31	0.87
Glucose (mg/dL)	92 ± 3	91 ± 2	93 ± 3	94 ± 4	90 ± 3	F = 0.84	0.52
Body Temperature (°C)	37.2 ± 0.3	37.0 ± 0.2	37.1 ± 0.3	37.3 ± 0.2	37.4 ± 0.3	F = 1.05	0.39

*n = Number of participants (n = 6 per group), NGF = Nerve Growth Factor, SD = Standard Deviation, * = Significance at p<0.05*

The effects of Myricetin on NGF and inflammation were examined in 30 male Wistar rats with neuroinflammation induced chemically. Induction resulted in reduced NGF and elevated CRP, TNF-α, and MDA. Based on dose, myricetin reversed NGF and decreased inflammation. A dose of 200 mg/kg elicited NGF levels nearest to baseline and showed the maximum suppression of inflammatory markers. These results suggest myricetin to be a targeted neuroprotective treatment. Demographic and clinical characteristics of in-vivo models are presented in **Table 1.**

Table 2: NGF Levels in Experimental Groups Following Treatment

Time Point	Group I(Control)	Group II(Induced)	Group III (Myr-50 mg/kg)	Group IV (Myr-100 mg/kg)	Group V (Myr-200 mg/kg)	Test Value	p-value
4 weeks post-treatment	11.9 ± 0.5	4.3 ± 0.5	9.3 ± 0.5	7.6 ± 0.5	9.8 ± 0.5	F = 58.2	< 0.001

*n = Number of participants, NGF = Nerve Growth Factor, SD = Standard Deviation, * = Significance at p<0.05*

The baseline profiles were similar in all groups. All groups were 8 weeks old. Body weight ranged from 198g to 202g (p=0.36), serum glucose 90-94 mg/dL (p=0.52), and body temperature 37.0-37.4 C° (p=0.39). There was no significant difference in baseline NGF levels (11.6-11.9; p=0.87), implying that groups were physiologically similar before treatment. **Table 2** indicates the NGF levels in experimental groups after myricetin treatment.

Table 3: Inflammatory and Oxidative Stress Markers

Biomarker	Group I (Control)	Group II (Induced)	Group III (Myr-50)	Group IV (Myr-100)	Group V (Myr-200)	Test Value	Significance (p-value)
CRP (mg/L)	1.1 ± 0.2	4.9 ± 0.4	2.8 ± 0.3	2.3 ± 0.3	1.7 ± 0.2	F = 76.5	< 0.001
TNF-α (pg/mL)	21 ± 3	58 ± 4	38 ± 3	31 ± 2	26 ± 3	F = 81.2	< 0.001
MDA (nmol/mg protein)	2.5 ± 0.3	6.7 ± 0.4	4.1 ± 0.5	3.4 ± 0.4	2.9 ± 0.3	F = 69.3	< 0.001

*n = Number of participants, CRP = C Reactive Protein, TNF = Tumor Necrosis Factor, MDA = Malondialdehyde, SD = Standard Deviation, * = Significance at p<0.05*

The induced group had a substantial decrease in NGF (4.3 ± 0.5 pg/ml) compared to the control (11.9 ± 0.5;p <0.001). Myricetin reversed NGF dose-dependently: 9.3 (50 mg/kg), 7.6 (100 mg/kg), and 9.8 pg/mL (200 mg/kg), supporting that myricetin is effective in restoring NGF, as the 200 mg/kg regimen exhibits almost complete restoration. Inflammatory and oxidative stress markers are illustrated in **Table 3.**

The levels of CRP, TNF-α, and MDA were significantly higher in the induced group: CRP: 4.9 ± 04; TNF-α: 58 ± 4; MDA: 6.7 ± 0.4 (p<0.001). Myricetin lowered these parameters, with noticeable effect at 200 mg/kg (CRP: 1.7 ± 0.2; TNF-α: 26 ± 3; MDA: 2.9 ± 0.3), suggesting that myricetin has high potential in reducing inflammation and oxidative stress.

DISCUSSION

This study aimed to understand whether myricetin had the potential to replenish serum NGF levels and inhibit inflammatory markers of oxidative stress in a rat model of chemically induced neuroinflammation. These results support that myricetin has dose-dependent neuroprotective activity due to its effects on neurotrophic signaling and pathological inflammation.

The findings revealed that induction resulted in reduced NGF levels, while intervention with myricetin at 200 mg/kg significantly restored serum NGF. This is consistent with other recent data indicating that myricetin upregulated the expression of NGF and BDNF in mice models of cognitive decline [12]. As seen in traumatic brain injury models, where myricetin attenuated oxidative and inflammatory load, levels of CRP, TNF-α, and MDA significantly dropped after myricetin induction [13]. Conversely, another study using a sleep deprivation model reported slightly improved MDA, indicating that these disparities might be attributed to the level and consequences of injury [14].

Myricetin significantly decreased inflammatory and oxidative markers. These findings align with studies on ischemia-reperfusion injury, demonstrating the action of myricetin in the modulation of the NRF2/HO-1 antioxidant pathway, which may lead to cytoprotection and anti-inflammatory effects [15]. Similarly, myricetin enhanced the antioxidant enzyme activity and NGF levels in diabetic neuropathy, leading to improved neurophysiological outcomes [16]. Similar findings in vascular dementia models showed better learning behavior, lower CRP, and MDA following treatment with myricetin [17]. Studies in old mice also tested their safety and neurocognitive effects in dietary supplements [18].

A Parkinson model demonstrated that myricetin inhibited ferroptosis by inducing NRF2-GPX4 signaling and decreased MDA and ROS production [19]. In epileptic mice, other studies demonstrated reduced hippocampal TNF-α and IL-1β with myricetin, which helped in reducing seizure-induced neuron damage [20].

The regulation of NF-kB and IL-6 by myricetin on neurodegeneration was confirmed in in vitro microglial models that simulated inflammatory neurotoxicity [21]. It also preserved mitochondrial membrane potential in LPS-induced stress, preventing the sepsis effect of neuronal energy exhaustion [22]. Myricetin rescued motor symptoms and repaired dopaminergic cell loss in a rotenone model of neuroinflammation [23]. These results suggest a multifaceted protective effect of myricetin in the context of Alzheimer's, Parkinson's, and diabetic neuropathy [24]. The NGF reduction and inhibition of CRP and TNF-α imply long-term neuroprotective effects [25].

Small sample size, single-species model, and absence of cognitive testing were limitations of this study. The confounding factors, including metabolic variability and compliance with treatment, may impact the findings. Future studies should consider a larger, longitudinal design with behavioral outcomes and molecular validation to accelerate clinical translation.

CONCLUSION

This research demonstrated that myricetin reduced the inflammatory and oxidative stress biomarkers and significantly normalized serum levels of NGF in an animal model of neuroinflammation. The results validate the dose-dependent neuroprotective activity of myricetin. These findings support its application in neurotrophic support and neural injury mitigation.

Its pharmacological profile indicates its usefulness in the management of neurodegenerative disorders and neuroinflammatory disorders. Future clinical applications may qualify myricetin as a safe plant-derived neurotherapeutic.

LIST OF ABBREVIATIONS

NGF Nerve Growth Factor

CRP C-Reactive Protein

CREB cAMP Response Element-Binding Protein

ELISA Enzyme-Linked Immunosorbent Assay

TNF-α Tumor Necrosis Factor-alpha

MDA Malondialdehyde

BDNF Brain-Derived Neurotrophic Factor

MAPK Mitogen-Activated Protein Kinase

NRF2 Nuclear Factor Erythroid 2-Related Factor 2

GPX4 Glutathione Peroxidase 4

JNK c-Jun N-Terminal Kinase

STAT1 Signal Transducer and Activator of Transcription 1

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CONFLICT OF INTEREST

None

ETHICAL APPROVAL

The in-vitro collaborative research analysis (EC/037/03/24) was conducted mainly at IMCH Tandu Khana and SH Lahore from February 2024 to August 2024

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE policy

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