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# Evaluating Neurotherapeutic Potential of Naringenin by True Experiments: Insights into In-Vivo Psychiatry Care Models

***Abdul Ghafoor[1], Sana Kashif[2], Syed Muhammad Shahkar Ali[3], Samreen Memon[4], ShaheerSuhail Memon[4], Asim Mehmood[5], Pirya Nangdev[4]***

*[1]Department of Medicine, Bolan Medical College, Bolan University of Medical and Health Sciences, Quetta,[2]Department of Anatomy, Chandka Medical College/Shaheed Mohtarma Benazir Bhutto Medical University, Larkana, Sindh, [3]Department of Psychiatry and Behavioural Sciences, Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan, [4]Department of Anatomy, Liaquat University of Medical & Health Sciences, Jamshoro,[5]Department of Anatomy, Suleman Roshan Medical College, Tando Adam, Pakistan.*

**ABSTRACT**

**Background:** The brain function and development are impaired when psychiatric disorders cause neuroinflammation and neurotrophic dysregulation. This study aimed to evaluate the Naringenin's neurotherapeutic potential utilizing controlled in vivo trials, with an emphasis on its function in controlling neuroinflammation and restoring neurotrophic balance in a psychiatric care model.

**Methods:** The in vivo experimental research took place during four months, from April 2021 to August 2021, utilizing 20 healthy male rats, aged eight weeks. Experiments were performed on animals at the Animal House, and biochemical analyses were carried out at SMDC Lahore and LUMHS Jamshoro. The subjects were divided into five groups: Group I (control) and Groups II–V, which received 250 mg/kg/day of propionic acid (PPA) to induce neuroinflammation that resembled psychiatric disorders. Naringenin was administered to Groups III–V at escalating doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg after PPA was induced for four weeks. The ELISA testing system measured Nerve Growth Factor (NGF) serum concentrations, and the data were analyzed with one-way ANOVA followed by Tukey post hoc comparisons between all samples. Data analysis was conducted using SPSS Version 21.

**Results:** The Naringenin treatment resulted in stepwise elevation in NGF levels across various doses, and the 200 mg/kg dosage delivered nearly normal levels of NGF. The NGF measurements (pg/mL) were as follows: Group I – 11.5 ± 0.5, Group II – 4.0 ± 0.5, Group III – 9.2 ± 0.5, Group IV – 7.6 ± 0.5, and Group V – 9.7 ± 0.5. The therapeutic function of Naringenin to counteract neurotrophic deficits caused by inflammation finds support from these observed improvements.

**Conclusion:** The in vivo psychiatric care models reveal the neurotherapeutic potential of naringenin, because it fights neuroinflammation and restores NGF levels to normal.

**Keywords:** Naringenin, Neuroinflammation, NGF, Psychiatric Disorders, Psychiatry, Propionic Acid.

***Corresponding Author:***
**Dr. Pirya Nangdev,**
Department of Anatomy,
Liaquat University of Medical & Health Sciences,
Jamshoro, Pakistan.
Email: piryaanatomy.lumhs11@gmail.com
ORCID: https://orcid.org/0009-0000-2912-2763
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## INTRODUCTION

The worldwide frequency of psychiatric disorders continues to mount, while producing lasting brain inflammation, abnormal signal patterns, and decreased Nerve Growth Factor (NGF) concentrations [1]. The disorders result in major disabilities that disrupt emotional control, mental capacity, and life well-being [2]. The existing pharmacological treatment methods encounter multiple limitations, including unwanted side effects, inadequate effectiveness, and minimal disease-changing potential [3]. The recent interest in psychiatric care strategies prompts investigations to discover natural compounds with combined neuroprotective and anti-inflammatory properties [4,5].

The promising compound for research is Naringenin which exists naturally as a flavonoid. It is mostly present in grapefruits and oranges [6]. Several preclinical experiments prove that Naringenin functions as an anti-inflammatory agent, while providing antioxidant defenses and protective effects on nervous tissue [7]. Naringenin influences signaling pathways to control brain functions through manipulation of neurotrophic factor levels, as well as regulating oxidative stress pathways and cytokine systems [8,9]. The research has particularly focused on understanding if naringenin can improve NGF levels, because they sustain neuronal growth, differentiation and survival processes [8]. Studies have identified NGF dysregulation as a risk factor for multiple psychiatric conditions, such as depression, schizophrenia, and stress-related cognitive deterioration [10,11].

In this study, the experiment utilized an in vivo psychiatric care model with controlled conditions to determine how Naringenin affects neurotherapeutic effects in rodents that received neuroinflammatory treatment with propionic acid (PPA).

This study examined how Naringenin administration influenced NGF serum levels, aiming to evaluate its ability to reduce neuroinflammation and stimulate neural connections. The findings delivered substantive knowledge about Naringenin's ability to serve as a medicinal plant remedy for psychiatric treatments.

## METHODS

This in vivo experimental study (Ref: EC/0785/22/) was conducted from April 2021 to August 2021, in compliance with institutional animal care and ethical guidelines. The research team conducted animal experiments following ethical protocols, that received approval from separate Animal Ethics Committees. SMDC Lahore and LUMHS Jamshoro Sindh served as locations for animal housing and biochemical analysis while the experiments took place at the Animal House.

The study employed twenty male Wistar rats; each eight weeks old with body weights of 180–220 grams. The animals were housed under standard laboratory conditions: a temperature of 22±2°C, humidity between 40–60%, and a 12-hour light/dark cycle. Rats maintained continuous unsupervised access to standard chow and drinking water throughout the experimental period. Protocols for sterilization and regular cleaning routines-maintained hygiene standards and environmental norms.

The animals were randomly divided into five groups (n=4 per group): Group I (Control): It served as controls by receiving no PPA or Naringenin treatment while Group II underwent PPA-induced neuroinflammation without treatment. Group III–V received PPA with oral Naringenin dosages at 50 mg/kg, 100 mg/kg, and 200 mg/kg respectively. Groups II–V developed neuroinflammation similar to psychiatric disorders after receiving intraperitoneal Propionic Acid (PPA) doses of 250 mg/kg/day for five consecutive days of administration. PPA required dilution solutions made with sterile normal saline. The freshly prepared Naringenin solutions were provided to treatment groups as daily oral doses throughout a four-week continuous treatment course.

Anesthetic-aided cardiac puncture allowed researchers to obtain blood samples after completion of the study. After centrifugation the serum was obtained then placed at −20°C for later analysis. The research group measured Nerve Growth Factor (NGF) using enzyme-linked immunosorbent assay (ELISA) methods based on the manufacturer guidelines with serum samples. An automated ELISA reader assessed optical density. Data analysis was conducted using SPSS Version 21.

The data presentation showed results expressed with a standard deviation (SD) value added to each mean average. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test considered group means to determine statistical significance. A p-value of less than 0.05 was considered statistically significant in this study.

## RESULTS

**Table 1: Environmental and Care Parameters for Experimentation**

| Parameter | Setting / Value |
|---|---|
| Animal strain & gender | Male Wistar rats |
| Acclimatization | 7 days |
| Temperature | 22 ± 2 °C |
| Humidity | 40–60% |
| Light/Dark cycle | 12-hour (07:00–19:00) |
| Cage type & bedding | Polycarbonate shoebox; corn cob, changed bi-weekly |
| Food & water access | Ad libitum standard chow and filtered water |
| Ethical approval (Ref.) | EC/0785/22 |

All twenty male Wistar rats were kept at the same standard laboratory conditions, as shown in **Table 1**, for seven days and provided ample food and water at all times. This study confirmed the successful development of the neuroinflammatory model by checking NGF levels in the subjects' serum using ELISA. Upon regular observation, there were no unusual findings in their clinical state. The baseline characteristics of the animals in each group did not differ significantly ($p > 0.05$).

Nerve Growth Factor (NGF) serum concentrations were shown in **Figure 1** and **Table 2** across different testing groups. Animals whose condition was induced by Propionic Acid (PPA) experienced substantial reductions in Nerve Growth Factor (NGF) levels relative to the control group. Group II demonstrated a substantial decrease in Nerve Growth Factor levels which showed neuroinflammation patterns linked to psychiatric disorders.

Among Groups III–V, the administration of Naringenin produced a dose-dependent improvement in NGF recovery, where Group V receiving 200 mg/kg Naringenin showed maximum NGF restoration. The data showed that Naringenin proved effective in reducing PPA-induced neuroinflammatory damage by achieving NGF values that approached control group levels.

Statistical analysis using $p < 0.05$ revealed the therapeutic impact of Naringenin treatment on NGF concentrations between PPA-treated animals in Group II and Naringenin-treated groups (Groups III–V). Survival analysis of participants in Group V showed that Naringenin at 200 mg/kg protected the nervous system against damage.

**Table 2: Quantitative Analysis of Naringenin's Effect on NGF Levels**

| Groups (Parameter) | I (Control) | II (PPA) | III (NAR-50) | IV (NAR-100) | V (NAR-200) | Statistics(p-value) |
|---|---|---|---|---|---|---|
| **NGF Levels (pg/mL)** | 11.5 ± 0.5 | 4.0 ± 0.5 | 9.2 ± 0.5 | 7.6 ± 0.5 | 9.7 ± 0.5 | $p < 0.05$ |

The determination of NGF levels in serum samples utilized ELISA tests. Naringenin administration at different doses produced varying degrees of NGF enhancement in Groups III–V relative to Group II (PPA-treated/routine), which demonstrated decreased NGF levels. Experimental rats in Group V that received 200 mg/kg Naringenin exhibited NGF levels that neared the baseline control levels.

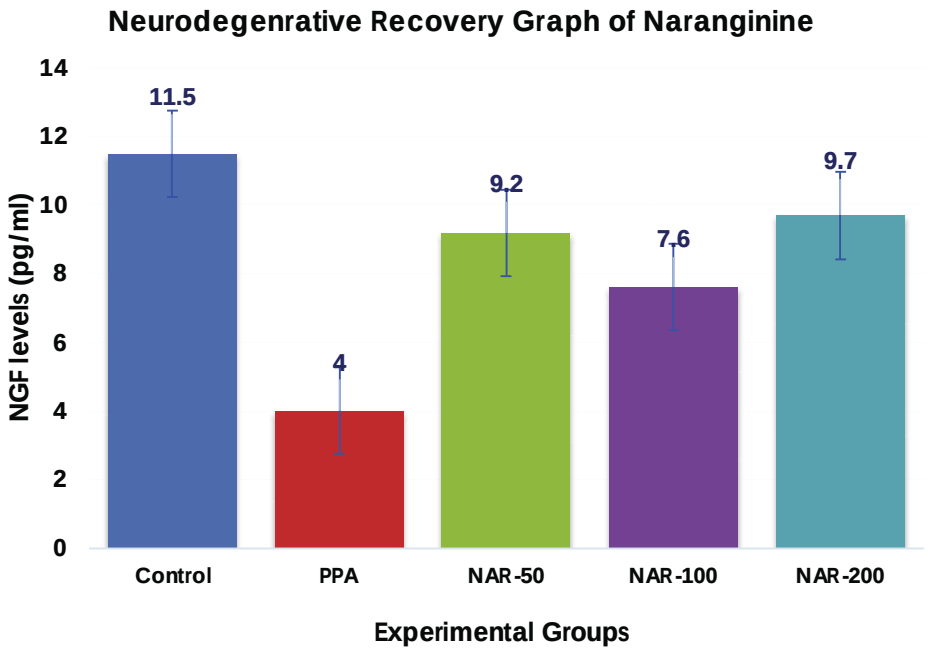


**Figure 1: Comparative Analysis of Serum NGF Levels Across Experimental Groups**

Groups: I (Control): Non-induced control group, II (PPA): Propionic acid-induced group, III (NAR-50): Naringenin 50 mg/kg, IV (NAR-100): Naringenin 100 mg/kg, V (NAR-200): Naringenin 200 mg/kg.

A rising trend among serum Nerve Growth Factor (NGF) levels displays direct relationship to Naringenin dosage levels showing its protective effects against PPA-induced neuroinflammation. Results from Group V showed the greatest rise which confirms Naringenin could serve as a therapeutic option to treat neuroinflammatory psychiatric disorders.

**DISCUSSION**

Research showed that psychiatric disorders demonstrate underlying neuroinflammation and defects in neurotrophic development. Experimental models developed from propionic acid (PPA) exposure serve as essential tools in neurotherapeutic research, as PPA decreases levels of NGF alongside other neurotrophic factors. Neuroprotective properties of Naringenin, a citric acid-derived flavonoid, were investigated by assessing its influence on NGF expression in PPA-elicited neuroinflammatory rats.

The neuroprotective effects noted in this study are in agreement with earlier research that emphasized the compound's potential to modulate neuroinflammation and maintain neuronal health [12,13]. For example, flavonoids such as Naringenin have been found to stimulate important neuroprotective signaling pathways, including the PI3K/Akt and MAPK pathways, which are important for the promotion of neuronal survival and reduction of inflammatory damage [14]. Moreover, existing literature has recognized Naringenin's strong antioxidative activity that helps in alleviating oxidative stress—a critical component in psychiatric disorder pathophysiology [15]. Such findings are also supported by the present research, whereby Naringenin treatment caused noteworthy increases in NGF levels in line with neurotrophic recovery in other models of neuroinflammation [16,17]. These findings further highlight the therapeutic potential of Naringenin as a natural compound that can deal with neuroinflammation and neurotrophic deficits, making it a promising prospect for the creation of new, plant-derived therapeutic approaches in psychiatry [18,19].

Recent research found that naringenin actively reduces inflammation by protecting cells from oxidative damage and adjusting the NF-κB pathway for neuroinflammation control [20,21]. The potential therapeutic value of Naringenin as a natural psychiatric treatment materializes from its mechanism to clean free radicals and suppress pro-inflammatory cytokines and enhance neurotrophic factor production [22]. The Naringenin-treated groups of PPA subjects demonstrated increased NGF levels, which exceeded untreated PPA levels and reached

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statistical significance ($p < 0.05$). Researchers have established that naringenin strengthens neuroinflammation repair through its ability to maintain neurons and guide neural differentiation and synaptic operations [23].

The dose-dependent enhancement in NGF levels in all Naringenin-treated groups is in line with these results, further supporting the compound as a therapeutic candidate in treating psychiatric disorders characterized by neuroinflammation [24]. Previous research also pointed out that flavonoids such as Naringenin provide promising alternatives to traditional treatments and proposed that plant-derived neurotherapeutics may complement or even surpass existing pharmacological treatments [25].

Further investigation will be needed to apply these encouraging results to wider clinical healthcare settings. The study of brain function, together with social behaviour tests, will help verify the actual functional benefits caused by NGF biochemical improvements. Neuroprotective benefits of Naringenin should be validated through biomarker assessments for antioxidants, as well as neurotrophic evaluations by tracking MDA, GSH and SOD measurements. Research must analyse the long-term safety of Naringenin exposure on the nervous system, as well as its effectiveness for psychiatric ailments that result in significant neurological damage. Research needs to measure BDNF levels, as this will help reveal the combined neurological benefits of Naringenin treatment for brain flexibility and overall health.

## CONCLUSION

The study demonstrated that the administration of Naringenin leads to therapeutic recovery of NGF levels in PPA-treated neuroinflammatory environments. Laboratory tests showed that an injection of Naringenin at 200 mg/kg returned NGF protein levels to normal ranges, which indicates that this compound could become a therapeutic option for neurotrophic deficit caused by inflammation. Plant-derived compounds such as Naringenin show potential as additional treatment methods for psychiatric disorders, based on increasing research findings. The therapeutic benefits and clinical applications of Naringenin need additional research focused on behavioural results and markers of oxidative stress for validation.

## LIST OF ABBREVIATIONS

**NGF:** Nerve Growth Factor
**SD:** Standard Deviation
**ANOVA:** One-way Analysis of Variance
**PPA:** Propionic Acid

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## CONFLICT OF INTEREST

None

## ETHICAL APPROVAL

This in vivo experimental study certificate (Ref: EC/0785/22/) was obtained in compliance with animal care and ethical guidelines from separate Animal Ethics Committees by SMDC Lahore and LUMHS Jamshoro, Sindh.

## AUTHORS' CONTRIBUTIONS

All other Authors contributed equally as per IMCJE. All authors agreed to be accountable for all aspects of the research.

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