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Neuroprotective Properties of Naringenin Against 5-Fluorouracil Chemotherapy in an Adult Rat Model

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Abstract: Fluorouracil (5-FU), a widely used chemotherapeutic agent, is known to induce oxidative stress and neurotoxicity in addition to its anticancer effects. The aim of our study is to determine the protective effect of naringenin (NAR) with antioxidant capacity against the undesirable effects that 5-FU used against cancer may have on the brain. Twenty-eight adult male Sprague–Dawley rats were randomly assigned to four groups (n = 7 each): control, NAR, 5-FU, and 5-FU + NAR. 150 mg/kg 5-FU was administered intraperitoneally to the 5-FU and 5-FU + NAR groups. 100 mg/kg NAR was administered to the NAR and 5-FU + NAR groups via a gavage catheter. Biochemical analyses performed on brain tissues taken from the animals at the end of the experiment showed that 5-FU increased the levels of brain oxidative stress markers. It was found that glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) levels decreased and malondialdehyde (MDA) levels increased in brain tissue due to the effect of 5-FU. It was also confirmed that the situation was normalized as a result of the combined application of 5-FU and NAR. Immunohistochemical studies showed that 5-FU increased the expression of caspase 3 and TNF-α in the brain, while NAR, which has antioxidant, antiapoptotic and anti-inflammatory effects, largely inhibited their increase. These findings suggest that NAR may serve as a promising adjunct therapeutic agent to mitigate neurotoxicity associated with 5-FU chemotherapy.

1. Introduction

Chemotherapy is one of the leading methods used in modern medicine to combat cancer. In addition, it is known that chemotherapy drugs cause oxidative stress in animals and humans (Il'yasova et al., 2011). These drugs have also been found to increase lipid peroxidation and upregulate levels of malondialdehyde (MDA) in the hippocampus (Ashok and Sheeladevi, 2014). Therefore, as a result of an increase in MDA levels, cognitive impairment and neuronal loss can develop in the brain. One of the most common problem encountered in chemotherapy is the good balancing of damage to tumor cells and healthy tissues. The negative side effects encountered in this treatment also make it difficult for patients to comply with the treatment and follow-up to the treatment (Han et al., 2008).

One of the medications used for treatment in this regard is 5-fluorouracil (5-FU) (Mihlon, et al., 2010). 5-FU is an antimetabolite used in the treatment of many cancers, including prostate, colorectal (bowel), and breast cancer. It has also been confirmed that this chemotherapeutic drug passively crosses the blood brain barrier and damages cell proliferation processes (Formica et al., 2006). In addition, 5-FU performs its anticancer activity by inhibiting the thymidylate synthase enzyme. 5-FU's inhibition of this enzyme also causes DNA damage (ElBeltagy et al., 2012). The incorporation of metabolites of 5-FU into RNA causes disruption and damage to RNA functions. Studies provide data indicating that 5-FU negatively affects cell proliferation and cell survival in the rat brain. As a result, it has been confirmed that this situation can cause a decrease in immature neurons and cognitive impairment (ElBeltagy et al., 2010). Previous studies have demonstrated that 5-FU increases the expression of TNF-α and caspase-3, which are markers of inflammation and apoptosis, respectively, in the cerebellum, cerebrum and hippocampus (Zhang et al., 2019; Zhou et al., 2023; Raafata et al., 2023). 5-FU also causes a formation called chemobrain in which cognitive changes occur (Mustafa et al., 2008). It has also been reported that 5-FU triggers oxidative stress, hippocampal neurodegeneration, neuroinflammation and lipid peroxidation by increasing harmful oxygen radicals. Moreover, 5-FU reduces the expression of markers of immature neurons and the antioxidant defense system in rat brain (Welbat et al., 2018).

In patients receiving cancer treatment, reducing the side effects that occur and providing alternatives that support the treatment can increase the chance of success. Supportive herbal products are used to enable these patients to live a better quality of life, reduce the unwanted effects of chemotherapy, achieve a stronger immune system, and minimize the spread of cancer. In this regard, the use of herbal medicines together with drugs used in cancer treatment is increasing. Flavonoids, an antioxidant abundant in human food sources, are frequently used in the treatment of chronic diseases (Chen et al., 2007; Azirak et al., 2019). Naringenin (NAR) is a natural flavanone constituent isolated from citrus fruits, grapes, cherries, bergamot, tomatoes, and plants. The biological activities of NAR include antioxidant, anti-inflammatory, antitumor, anti-apoptotic and neuroprotective properties (Mir and Tiku, 2015). In previous studies, various benefits of NAR used for therapeutic purposes in neurodegenerative diseases such as Parkinson's disease, neuroinflammation, neurotoxicity have been proven (Krishna Chandran et al., 2019; Azirak et al., 2025). It was also found in these studies that the blood brain barrier could not prevent the passage of NAR (Youdim et al., 2003). NAR can provide both an increase in cognitive functions and protection against neurodegeneration due to its antioxidant properties (Ghofrani et al., 2015). NAR exhibits neuroprotective effects against oxidative stress and prevents neuronal death. NAR achieves these beneficial effects through its antioxidant capacity and regulating effect on neuronal survival (Spencer, 2008).

In this study, the neuroprotective effects of NAR against the adverse effects of 5-FU in a rat model were investigated biochemically and immunohistochemically.

2. Material and Methods

2.1. Chemicals

5-FU, which we used in the current study, was ordered from Actavis (Little Island, Cork, Ireland) and NAR from Madaus (Madaus, Istanbul, Turkey). Other chemicals we needed were purchased from Sigma Kimya A.Ş.

2.2. Experimental applications

In our applications, 28 Sprague-Dawley type male rats weighing 210-255 g and 8-9 weeks old were obtained from Adıyaman University Research Center. The experimental study was carried out after receiving ethics committee approval (2024/021). The rats were given fresh drinking water every day and cage cleaning was performed regularly. Additionally, the shelters were set to an environment where the temperature was 21 ± 2°C, the humidity was 50 ± 5%, and the lighting was 12 hours light and 12 hours dark. Standard pellet feed was used ad libitum to feed the subjects. Rats were randomly divided into 4 equal groups according to the inducing and protective agents to be given. All experimental procedures were conducted in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978) and ARRIVE Guidelines.

1. Control group (n = 7): These rats were not given any medication.

2. Experimental group (5-FU group, n = 7): In the experiment, a single dose of 5-FU (150 mg/kg) was administered i.p. on day 6 (Arafah et al., 2022).

3. Experimental group (NAR group, n = 7): NAR was orally administered to these rats after being dissolved in 100 mg/kg distilled water for 7 days (Wali et al., 2020).

4. Experimental group (5-FU + NAR group, n = 7): 5-FU and NAR were administered at the same routes and doses as the previous groups.

Rats were sacrificed on day 7 after intramuscular injection of ketamine (30 mg/kg i.m.) and xylazine (5 mg/kg i.m.) and an intracardiac blood sample was taken using a syringe to determine brain enzyme activity. Serum samples were separated by centrifugation at 5,000 x g for 15 min and the serum was stored at -80ºC for biochemical analysis. Brain tissues were excised and weighed. The brain was divided into two parts. One part was stored at -80ºC until biochemical analysis was performed. The other part was fixed in 10% neutral formalin for histopathological evaluation.

2.3. Oxidative stress biomarkers

Brain homogenization was performed using a homogenizer (Turrax T 25, Wilmington, USA). Homogenates (0.5-1.0 g tissue) were obtained by centrifuging the samples at 10,000 × g for 15 min at 4°C. Glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) and MDA were determined using a spectrophotometer (UNICO Instruments C., Dayton, USA). Protein density analysis was performed using the method of Lowry et al. (1951) (Lowry et al., 1951). MDA was evaluated using the Draper and Hadley (1990) method. The tissues were reacted with thiobarbituric acid (95°C, pH 3 and 15 min) and a pink pigment was obtained. The parameter evaluation process was calculated on a device (UNICO Instruments C., Dayton, USA) with maximum absorption at 532 nm (Draper and Hadley, 1990). GSH was assessed by the method of Ellman (1959). 5'-dithiobis 2-nitrobenzoic acid was added to the prepared sample and a yellow-green color was formed as a result of the reaction between this chemical and glutathione. The measurement was made with a spectrophotometer (410 nm absorbance) (Ellman, 1959). SOD was measured by the method of Marklund and Marklund (1974). The mechanism is inhibition of autoxidation of pyrogallol. The measurement was made in a

spectrometer (180 s at 440 nm) and determined as U/mg Hb (Marklund and Marklund, 1974). CAT was measured by the method of Aebi (1984). Analysis; 10% homogenates were centrifuged (15 min, 4°C and 8,500 × g) in 0.9% NaCl and hydrolysis of hydrogen peroxide was performed in phosphate buffer (pH 7.0). The measurement was determined as nmol/mg protein in a spectrometer (240 nm absorbance) (Aebi, 1984).

2.4. Histological analysis

After anesthesia was performed and the brain was removed, it was left to fix in 10% neural formalin solution for one day. After fixation, the tissues were washed in tap water overnight, dehydrated by passing through a graded alcohol series, and polished by passing through a xylol series. The tissues were then infiltrated in liquid paraffin and embedded in paraffin. After this stage, the tissue blocks obtained were cut with a microtome at 5 µm thickness and placed on polylysine-coated slides.

2.5. Immunohistochemistry

Tissue sections deparaffinised by passing through xylene and alcohol series were subjected to Microwave-stimulated antigen retrieval step as detailed in previous publication (Gur and Timurkaan, 2012). After this process, tissue sections were incubated with 3% (in methanol) H_2O_2 for 5 minutes to block endogenous peroxidase. Polyclonal primary antibodies used in the study, anti-caspase-3 (AF6311, lot 73g3336) and anti-TNF-α (AF7014, lot 2h43451), were diluted 1/100 and 1/200 with PBS, respectively. Then, tissue sections were incubated with diluted primary antibodies in a humid chamber for 16-20 hours. Tissue sections used as negative control were incubated with PBS instead of primary antibody. After incubation, tissue sections that went through the steps detailed in previous study (Gur and Aktas, 2020; Gur, 2022) were examined and photographed with an Olympus Bx-52 photomicroscope.

2.6. Statistical analysis

Data were calculated as mean ± standard error (SEM). The Shapiro-Wilk test was used in the normality assessment process. Parametric and non-parametric data were obtained in biochemical parameters. ANOVA and Tukey HSD paired comparison methods were used when comparing groups with homogeneous variance. The Welch test was used for groups with heterogeneous variances. The processes of the Kruskal Wallis test were adhered to in evaluating non-parametric data. $P \leq 0.05$ value was taken as basis for statistical significance.

3. Results

3.1. Oxidative stress analyses

MDA increased in the 5-FU group compared to the control ($p < 0.01$). Antioxidants GSH ($p < 0.02$), SOD ($p < 0.03$) and CAT ($p < 0.01$) decreased in 5-FU compared to the control. Treatment of 5-FU in combination with NAR shows significant outcomes compared to 5-FU alone. It was observed that NAR application (5-FU + NAR) normalized all the deteriorated values in 5-FU by preventing oxidative stress (Table 1).

Table 1. Brain tissue oxidative stress biomarkers

Brain tissue oxidative stress biomarkers	Control	NAR	5-FU	5-FU + NAR
SOD (U/mg protein)	5.01 ± 0.09^{b}	6.69 ± 0.34	$3.08 \pm 0.29^{a,c}$	4.85 ± 0.14^{b}
CAT (k/g protein)	2.33 ± 0.40^{b}	3.58 ± 0.25	$1.04 \pm 0.32^{a,c}$	2.01 ± 0.31^{b}
GSH (µmol/g)	0.304 ± 0.23^{b}	0.475 ± 0.41	$0.105 \pm 0.16^{a,c}$	0.320 ± 0.30^{b}
MDA (nmol/g tissue)	2.05 ± 0.20^{b}	3.14 ± 0.09	$1.46 \pm 0.22^{a,c}$	2.40 ± 0.05^{b}

Data are means ± SEM, n = 7.
a: Significant from Control; b: Significant from 5-FU; c: Significant from 5-FU + NAR.
Abbreviations: 5-FU: 5-Fluorouracil; NAR: naringenin; SOD: superoxide dismutase; CAT: catalase; GSH: glutathione; MDA: malondialdehyde.

3.2. Immunohistochemistry

When the brain and cerebellum tissues of the control and NAR group rats were examined, it was determined that these tissues were TNF-α-negative. In the brain tissues of the FU group rats, it was observed that some of the pyramidal and other neurons were TNF-α-positively stained, while others were TNF-α-negative. TNF-α-positive and negatively stained neurons were found in the molecular layer of the cerebellum tissue. In the examinations, it was seen that most of the Purkinje cells and type II ganglion cells were TNF-α-positive. Although TNF-α expression in the brain and cerebellum tissues of the 5-FU + NAR group rats decreased compared to the FU group. TNF-α was evaluated as positive in some of the Purkinje cells and other neurons (Figure 1.). Although caspase-3-positive immunoreaction was formed in all examined groups, positive staining was observed the most in the FU group. It was observed that most of the pyramidal and other neurons in the brain tissue of the FU group rats were caspase-3-positive. However, caspase-3-positive immunoreaction in cerebellar tissue was only observed in Purkinje cells. Some of the Purkinje cells of the rats in this group were caspase-3-positive, while the others were negative. Although caspase-3 expression in the brain and cerebellar tissues of the rats in the 5-FU + NAR group was decreased compared to the FU group, the proportion of caspase-3-positive Purkinje cells and other neurons was higher than in the control and NAR groups (Figure 1.).

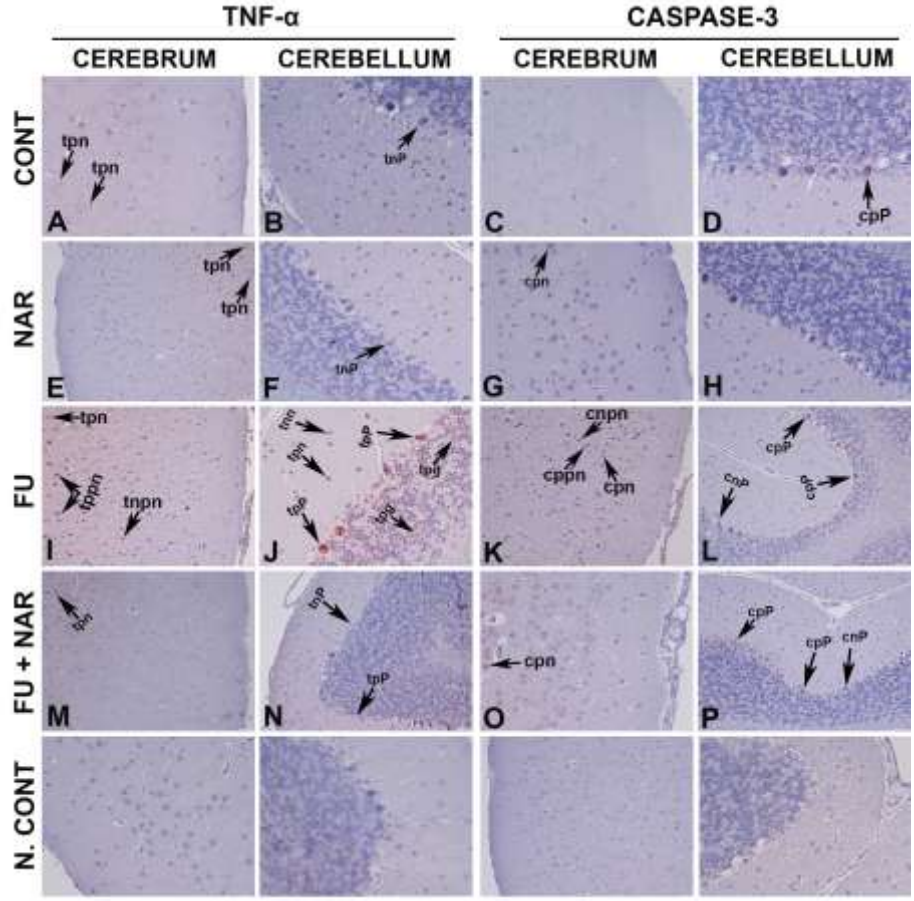

Figure 1. TNF-α and CAS-3 positive cells in brain tissue sections of control, NAR, FU and 5-FU + NAR groups. tpn, TNF-α-positive neuron; tnn, TNF-α-negative neuron; tppn, TNF-α-positive pyramidal neuron; tnpn, TNF-α-negative pyramidal neuron; tnP, TNF-α-negative Purkinje cell; tpP, TNF-α-positive Purkinje cells; tpg, TNF-α-positive Golgi type II cell; cpn, CAS-3-positive neuron; cppn, caspase-3-positive pyramidal neuron; cnpn, CAS-3-negative pyramidal neuron; cpP, caspase-3-positive Purkinje cells; cnP, CAS-3-negative Purkinje cells (E, I, K, L, M, N, P ×200; A, B, C, D, F, G, H, J, O ×400).

4. Discussion

5-FU neurotoxicity remains poorly understood, with limited mechanistic or prospective clinical trial data available to define risk factors or effective management strategies. The use of chemotherapeutic drugs for therapeutic purposes is extremely common in clinical areas (Iraz et al., 2015; Bilgiç et al., 2022; Aktaş et al., 2024a; Aktaş et al., 2025). 5-FU, in addition to being an anti-tumor drug, also has neurodegenerative, neuroinflammatory, cytostatic and immunosuppressive effects. Despite several advantages, the clinical application of 5-FU was limited due to the development of drug resistance after chemotherapy. Previous studies have confirmed that 5-FU induces apoptosis and suppresses proliferation of cells in many neurogenic regions of the brain (Dietrich et al., 2006). In patients receiving 5-FU treatment, reducing side effects and providing alternatives that support the treatment can increase the chance of success. In addition, supportive herbal products can be used to help these patients live a better quality of life, reduce unwanted effects, and gain a stronger immune system (Bilgic et al., 2021; Aktaş et al., 2024b). In this context, the use of herbal compounds is increasing along with 5-FU treatment (Sadek et al., 2018; Zeweil et al., 2020). It is known that the natural compound NAR is among the most suitable alternatives in this regard. In our study, we assumed that the application of 5-FU together with NAR for preventing brain damage could both enhance the effect of NAR and prevent the damage caused by 5-FU. Therefore, NAR was used to eliminate or minimize the side effects of the chemotherapy drug 5-FU.

Chemotherapeutic applications generally cause oxidative stress, leading to increased oxidative damage in lipids and DNA (Uzkeser et al., 2012; Gür and Bilgiç, 2022; Bilgiç et al., 2023; Gür et al., 2025). It is known that the main source of damage caused by 5-FU in the brain is oxidative stress. In the literature on this subject, they confirm that 5-FU increases the formation of free oxygen radicals. At the same time, this chemotherapeutic drug causes lipid peroxidation, leading to an increase in MDA (Zhang et al., 2019; Bilgiç and Aktaş, 2022). As is known, there is a balance in the production and destruction of free oxygen radicals in order to sustain life in living organisms. In our study, it is seen that 5-FU effectively activates oxidative stress in the brain. This situation is confirmed by the decrease in GSH level, CAT and SOD activities and the increase in MDA level in the 5-FU group. In the present study, it was determined that there was a significant increase in SOD, CAT and GSH levels in animals treated with 5-FU + NAR compared to the 5-FU group. These findings proved that NAR could cause an increase in antioxidant enzyme levels that play an active role in clearing oxygen radicals in the brain after 5-FU application. Similarly, many studies have reported that NAR acts as a free radical scavenger through its antioxidant properties (Mansour et al., 2023). It can also be interpreted that NAR indirectly reduces oxidative stress by stimulating antioxidant enzymes. Therefore, these results show that NAR may reduce neuronal damage due to 5-FU application by suppressing oxidative stress.

In our study, TNF-α and caspase 3 expression, a markers of imflamattion and apoptosis in brain tissues, was absent in the control group, while intense immunostaining was observed in the 5-FU group. In this case, the increase in TNF-α and caspase-3 activity in normal brain tissues and the induction of apoptosis can be attributed to the 5-FU treatment. These findings overlap with the findings of previous studies and confirm the effects of 5-FU on increasing TNF-α and caspase-3 expressions and thus apoptosis in the central nervous system (Zhang et al., 2019; Zhou et al., 2023; Aktaş and Bilgiç, 2025a,b). In our study, it can be thought that 5-FU caused tissue damage by triggering oxidative damage and initiated inflammatory and apoptotic processes (Zhou et al., 2023; Raafata et al., 2023). In conclusion, our findings show that oxidative stress induced by 5-FU can initiate a series of harmful reactions, causing cell death. Therefore, the presence of weak TNF-α and caspase-3 immunostaining in the NAR-treated group can be interpreted as NAR treatment inhibiting apoptosis by preventing the

increase in TNF-α and caspase-3 levels in normal brain tissue affected by 5-FU. Depending on all these data obtained, it can be said that NAR treatment in our study reduces apoptosis and oxidative stress in accordance with previous studies (Zhou et al., 2023). The data we obtained are also compatible with the literature on this subject. In our study, the significant improvements in histopathological changes in the 5-FU + NAR group confirm that NAR application is effective. In addition, studies on this subject confirm that NAR provides significant improvement in neurotoxicity (Zhou et al., 2023; Raafata et al., 2023). In light of all these findings, it can be stated that NAR has a neuroprotective effect against 5-FU-induced brain damage. In line with the data of our study, it has been proven biochemically and histopathologically that the combination of 5-FU and NAR reduces the neurotoxicity caused by 5-FU. However, for the clinical application of NAR and 5-FU together in cancer treatment, their antitumor efficacy and toxicity need to be confirmed by numerous clinical studies.

5. Conclusion

In our study, 5-FU increased TNF-α expression and oxidative stress in the brain, which ultimately caused cellular damage and apoptosis. It can be interpreted that NAR is neuroprotective against oxidative stress thanks to its different properties, especially antioxidant. NAR largely prevented the negative effects of 5-FU in the brain with its anti-apoptotic, antioxidant, immunomodulatory and anti-inflammatory effects. Therefore, it has been demonstrated that NAR is potentially protective against 5-FU-induced neurotoxic effect. As a result, these two drugs show that they can be an effective combination in cancer treatment. We also believe that the results of this study may shed light on determining the treatment outcomes of 5-FU in the clinic.

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Authorship Contribution Statement

Sedat Bilgiç: Writing – review & editing, Validation, Supervision, Project administration, Methodology. İbrahim Aktaş: Resources, Methodology, Investigation, Funding acquisition, Data curation. Ahmad Yahyazadeh: Validation, Software, Methodology.

Conflict of Interest

All authors confirm that they have no interests to declare.

Declaration

We have not used any AI tools or technologies to prepare this manuscript.

Ethics Statement

The procedures were carried out according to the protocol (Protocol 2024/021) received from the ethics committee of the Adıyaman University Research Center, Adıyaman, Türkiye.

Data Availability Statements

The data supporting this study's findings are available upon request from the corresponding author.

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