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Antioxidant and anti-apoptotic roles of sesame oil and N acetylcysteine against gentamicin-induced nephrotoxicity in rats

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ABSTRACT

The goal of the present study was to evaluate the antioxidant and anti-apoptotic roles of sesame oil (SO) and N acetylcysteine (NAC) against gentamicin (GM) induced nephrotoxicity. This study was carried out on 36 male Wistar rats divided into six equal groups: control (saline, once daily, PO); SO, group (5 ml of SO/kg, once daily, PO); NAC group (150 mg of NAC/kg, once daily, PO); GM group (80 mg of GM/kg, IP). The SO+GM and NAC+GM groups received SO, NAC as mentioned. Saline, SO, and NAC were administered for 30 days, while GM was given one hour after SO and NAC administration in the last 9 days of the experiment. Levels of urea, creatinine, and uric acid were significantly increased in GM-treated groups when compared to the control. The concentration of malondialdehyde (MDA) in the kidney tissues of the GM-treated groups was notably substantially higher than in the control group. Superoxide dismutase (SOD) and reduced glutathione (GSH) levels in renal tissues were significantly lower in the GM-treated groups compared to the control group. Furthermore, the microscopic kidney lesions showed a difference between the groups that received GM and the control groups. Additionally, GM increased the expression of Tumor Necrosis Factor α (TNF-α), Bax, and decreased the expression of Bcl2. When compared with the effect of SO, NAC had a better effect on controlling GM damage in the kidneys. Controlling GM-induced oxidative stress, in particular using SO and NAC, plays a crucial role in kidney protection.

1. INTRODUCTION

Gentamicin (GM) induced nephrotoxicity involves several mechanisms, including inflammation, nitric oxide (NO) propagationd decreased renal blood flow (Christo et al. 2011), lipid peroxidation (Rangan et al. 2009), and lower activity of kidney antioxidant enzymes such as superoxide dismutase (SOD) and glutathione (GSH) (Abdelrahman et al. 2018). Furthermore, experimental data indicated that nephrotoxicity is closely related to the stimulation of proapoptotic proteins (Ansari et al. 2016).

Sesame (*Sesamum indicum*) has nutritional and medicinal and benefits (Majdalawieh and Mansour, 2019). It is a rich source of lignans and phytoestrogens, thus it is added to human food for its numerous health benefits (Mohamed and Awatif 1998). Sesamin, sesamol, sesaminol, and sesamolin are Sesamin lignans that have anti-inflammatory and antioxidant effects (Wu et al. 2019). Along with its free radical scavenging activity, sesame oil possessed some functions as lowering lipid peroxidation and iron chelating (Sarma et al. 2019). It has also been found to have anti-aging, anti-atherosclerosis, and anti-hypertension properties, which are due to the potent antioxidative effects of phenolic constituents (Khan et al. 2016). One of the most active and strongest components of sesame oil is seasonal, contributing to its therapeutic benefits (Majdalawieh and Mansour, 2019). Sesamol possesses antioxidant, antimutagenic, anti-inflammatory, chemopreventive, anti-hepatotoxic, and antiaging properties (Siriwarin and Weerapreeyakul, 2016). The high free radical-scavenging potential of SO could be attributed to many antioxidant components or the inhibition of ROS generation due to the presence of phenolic compounds and used to lower lipid peroxidation (Espin et al. 2000).

N-acetyl cysteine (NAC) is a glutathione precursor with a thiol group that acts as an anti-inflammatory and antioxidant (Tras et al. 2021). NAC was used for treatment of some poisons and paracetamol and was recognized as safe (Fallah et al. 2018). Furthermore, it restored the oxidant-antioxidant balance by increasing the amount of cellular GSH, preventing lipid peroxidation, and ROS scavenging (Mantawy et al., 2020). A previous study has shown that NAC has hepatorenal protective properties against a variety of xenobiotics (Heidari et al., 2016). Due to the high antioxidant effects of NAC, it's used in many disorders related to the creation of harmful free radicals (Owumi et al. 2021).

The goal of this study was an evaluation of the antioxidant and anti-apoptotic roles of So and NAC against renal damage

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induced by GM through serum biochemical analysis, histopathological and immunohistochemical examination.

2. MATERIAL AND METHODS

2.1. Chemicals:

GM (Garamycin 80®; gentamicin sulfate 80 mg/2 ml vial, was obtained from Memphis Co, Cairo, Egypt). SO (was purchased from El-Captain Co for extracting natural oils, herbs, and cosmetics; El-Obour City, Cairo, Egypt). NAC (was obtained from SEDICO, 6 October City, Egypt). The analytical kits (Bio-diagnostics Co, Giza, Egypt).

2.2. Rats and design:

Thirty-six Wister Albino male rats weighing 195 ± 25 g (were obtained from Animal House, Fac Vet Med, Benha University, Egypt). Rats were maintained at 25 °C, subjected to a 12:12 h light / dark cycle, and given water ad libitum and commercial pellet freely and left for 7 days before the study. These animals were randomly separated into six groups of six rats each, as shown: The control group (5 ml saline/kg once daily, PO); SO, group (5 ml of SO/kg once daily, PO; Abdel-Daim et al. 2016); NAC group (150 mg of NAC/kg once daily, PO; Elsayed et al. 2021); GM group (80 mg of GM/kg for 9 days, IP; Abdeen et al. 2021). The SO + GM and NAC + GM groups received SO, NAC as mentioned above. The saline, SO, and NAC were administered for 30 days, while GM treatment was given one hour after SO and NAC administration in the last 9 days of the experiment. Ethical Committee of the Fac. Vet. Med, Benha University approved the study (BUFVTM 01-07-21).

2.3. Sampling:

One day after the previous treatment, rats were anesthetized with isoflurane. For serum separation, blood samples were obtained from the retro-orbital plexus (centrifugation at 1200 g for 15 min). Serum was stored at −20°C for biochemical analysis of urea, creatinine, and uric acid.

Kidneys were removed, rinsed with 0.9% NaCl in distilled water, and perfused with ice-cold 50 mmol/L sodium phosphate-buffered saline (100 mmol/L Na_2HPO_4/NaH_2PO_4, pH 7.4) containing 0.1 mmol/L EDTA. The tissue samples were homogenized on ice (Electrical Homogenizer) using 1g tissue and 5 ml phosphate buffer (pH 7.4). The homogenates were centrifuged for 20 min at 1200 x g for supernatant separation. Supernatants were used for the detection of oxidative stress biomarkers. The measured oxidative stress biomarkers were malondialdehyde (MDA), reduced glutathione (GSH), and superoxide dismutase (SOD).

The remaining kidney tissues were preserved for 72 hours in 10% neutral buffered formalin for histological analysis. Following that, the samples were washed with tap water before being immersed in ethyl alcohol serial ascending dilutions. The specimens were cleared in xylol then immersed in paraffin and cut into 4 µm thick sections. These sections were stained with hematoxylin and eosin according to the method described by Bancroft and Gamble (2008) and examined microscopically for histological investigation.

For immunohistochemistry, Bax, Bcl-2 and TNFα Paraffin-embedded tissue sections of 3 µm thickness were rehydrated in xylene and then rehydrated by utilizing graded ethanol solutions. Slides were then inactivated with 5% bovine serum albumin (BSA) in Tris-buffered saline (TBS) for 2 h. After that, sections were immunostained with primary antibodies. The slides were rinsed by TBS, the sections were incubated with goat anti-rabbit secondary antibody. Sections were washed with TBS and incubated in a solution of diaminobenzidine (0.02%) containing 0.01% H_2O_2 for 10 min. Counterstaining was conducted by utilizing hematoxylin, and the slides were investigated under a light microscope.

2.4. Statistical analysis:

Data are displayed as mean ± SE. Statistical analysis was performed using the statistical software package SPSS for Windows (Version 21.0; SPSS Inc., Chicago, IL, USA) using one-way ANOVA followed by Duncan's post hoc test for multiple group comparisons. Statistical significance was estimated at P value < 0.05.

3. RESULTS

The results of serum biochemical analysis revealed that GM had a marked influence on kidney function indices. GM exerted a considerable increase in serum creatinine, urea, and uric acid levels. Treatment with SO and NAC significantly declined the serum levels of creatinine, urea, and uric acid when compared to the GM group (Table 1). In addition, NAC had a better protective effect against GM-induced renal injury.

GM treatment caused oxidative damage in the renal tissue evidenced by a considerable rise in MDA levels, decreased SOD activity, and GSH levels. Treatment with SO and NAC caused marked mitigation of increased MDA levels and decreased SOD activity, and GSH levels (Table 1). NAC substantially improved oxidative damage in renal tissues caused by GM compared to the SO treatments with GM.

The microscopic examination of the kidney of the control, SO, and NAC groups revealed normal histological architectures of the cortex and medulla (Figure 1, A-B-C). While the examined renal tissues of the GM treated group revealed; congestion of the blood vessels, odema, degeneration and coagulative necrosis in the renal tubule epithelium (Figure1D). The treatment with SO improved the microscopic picture of the examined kidneys, although the edema and the blood vessels congestion persist (Figure1E). Also, treatment with NAC made progressive improvement in comparison to the GM group, the number of congested blood vessels was little in comparison to SO group and the edema disappeared (Figure1E).

The BAX is pro-apoptotic member of BCL-2. Immunostaining of the kidneys of rats in control group revealed moderate immunopositive reaction in a few tubular cells (Figure 2A), while it was very faint to negative immunoreaction in SO group (Figure 2B) and moderately positive in the NAC group (Figure 2C). The immunoreaction for BAX was negative in the GM group (Figure 2D), moderate positive immunoreaction in GM+SO group (Figure 2E) and moderate to strong immunoreaction in GM+NAC group (Figure 2F).

The BCL-2 immunostaining (Anti-apoptotic protein) of the kidney of rats in control group showed the moderate immunopositive reaction in the renal tubules (Figure 3A), negative immunoreaction in SO group (Figure 3B), and the NAC group (Figure 3C). The immunoreaction for BCL-2 was decreased in the GM group (Figure 3D) and positive immunoreaction in GM+SO group (Figure 3E). While it was returned to be lower immunoreaction in the GM+NAC group except sole cells of some renal tubules (Figure 3F).

The TNF-α immunostaining was moderate immunopositive reaction in few tubular cells of the kidneys of rats in control group (Figure 4A), while it was very faint to negative

immunoreaction in a few cells of the kidneys of rats in SO group (Figure 4B), and the NAC group (Figure 4C). The immunoreaction for TNF-α was negative in the GM group (Figure 4D). It was faint positive immunoreaction in GM+SO group (Figure 4E) and negative immunoreaction in GM+NAC group (Figure 4F).

Table1 Effects of SO, NAC, CP on serum biochemical parameters and antioxidant parameters in renal tissues (n=6).

parameters	Control	SO	NAC	GM	SO+GM	NAC+GM
Creatinine (mg/dL)	0.62± 0.02^{d}	0.63± 0.02^{d}	0.57± 0.02^{d}	1.73± 0.05^{a}	1.32± 0.04^{b}	0.85± 0.03^{c}
Urea (mg/dL)	20.83± 0.95^{a}	21.39± 0.91^{d}	18.29± 0.85^{d}	76.32± 2.67^{a}	55.91± 1.98^{b}	32.44± 1.27^{c}
Uric acid (mg/dL)	1.95±0.06^{d}	1.99± 0.05^{d}	1.79± 0.06^{d}	5.47± 0.17^{d}	4.17± 0.13^{b}	2.69± 0.08^{c}
MDA (nmol/g)	128.44± 3.97^{d}	130.77± 3.93^{d}	117.90± 3.54^{d}	231.20± 7.15^{a}	196.15± 5.58^{b}	153.26± 4.60^{c}
SOD (U/g)	6.68± 0.21^{a}	6.80± 0.20^{a}	6.46± 0.15^{a}	4.77± 0.14^{c}	5.52± 0.17^{b}	5.34± 0.16^{b}
GSH (mg/g)	28.77± 0.89^{a}	29.29± 0.88^{a}	28.08± 0.79^{a}	20.55± 0.64^{c}	23.76± 0.71^{b}	23.02± 0.69^{b}

Data are expressed as the mean ± SE (n = 6). Different superscript letters in the same row indicate statistical significance at $P \leq 0.05$.
Malondialdehyde (MDA); superoxide dismutase (SOD); reduced glutathione (GSH).

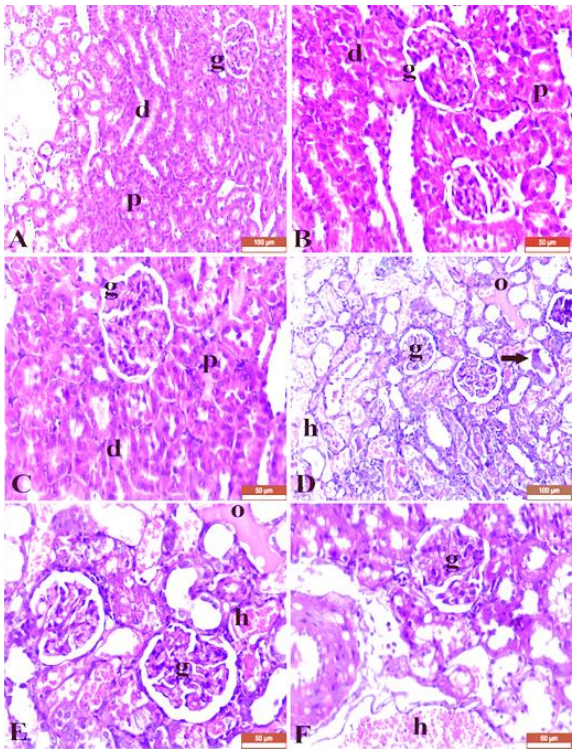

Figure 1 Photomicrograph of the kidney of the control, SO and NAC groups showing renal glomeruli (g), proximal convoluted tubules (p), and distal convoluted tubules (d) (Figure A-B-C). The kidney of rats intoxicated with GMs howing congestion of the blood vessels (h), edema (o), and coagulative necrosis the renal tubules epithelium (arrow) (Figure D). The addition of SO made few improvements in the histopathological changes, although the edema (o) and the blood vessels congestion still persist (h) (Figure E). The addition of NAC showed congested blood vessels (h) (Figure F). H&E stain.

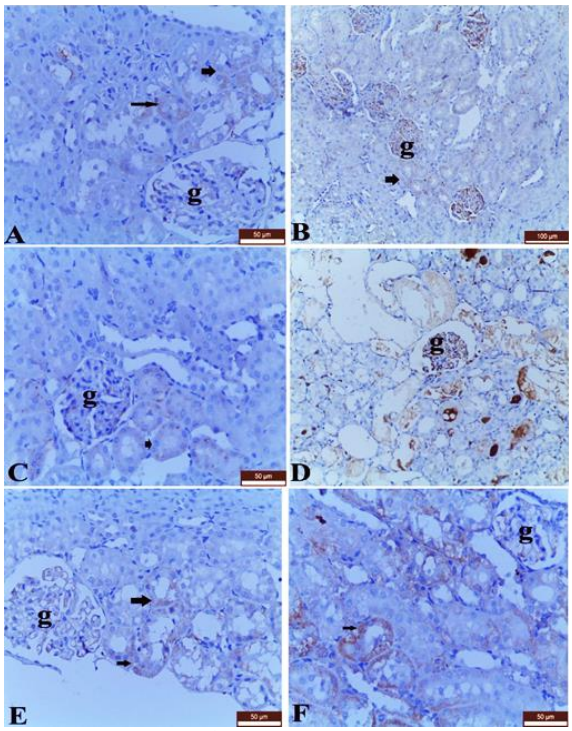

Figure 2 Photomicrograph of the kidney BAX immunostaining (proapoptotic gene) showing moderate immunopositive reaction in few tubular cells (arrow) in control group (Figure A), while it was very faint to negative immunoreaction in SO group (arrow) (Figure B), moderately positive in the NAC group (arrow) (Figure C), negative in the GM group (Figure D), moderate positive immunoreaction in GM+SO group (arrow) (Figure E) and moderate to strong immunoreaction in GM+NAC group (arrow) (Figure F). BAX immunostains.

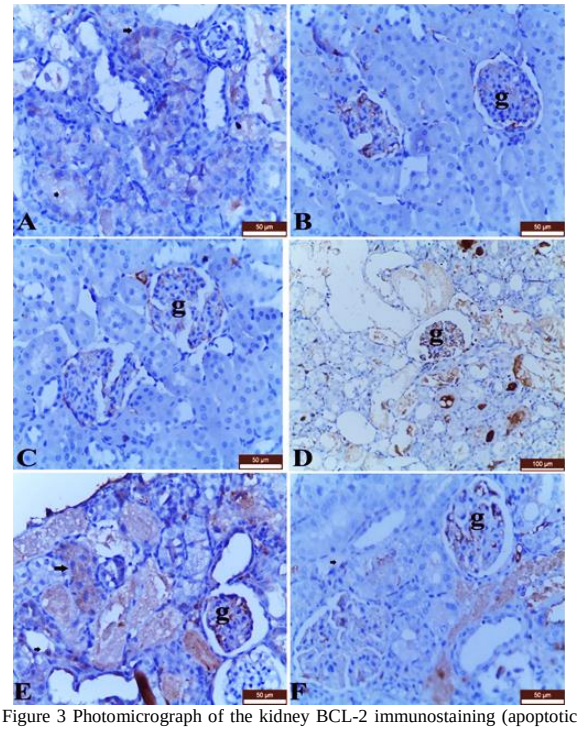

Figure 3 Photomicrograph of the kidney BCL-2 immunostaining (apoptotic gene) showing moderate immunopositive reacting in the renal tubules (arrow) of rats in control group (Figure A), negative immunoreaction in SO group (Figure B), and the NAC group (Figure C), negative in the GM group (Figure D), positive immunoreaction in GM+SO group (arrow) (Figure 3E) and negative immunoreaction in the GM+NAC group except sole cells in some renal tubules (arrow) (Figure F). BCL-2 immunostains.

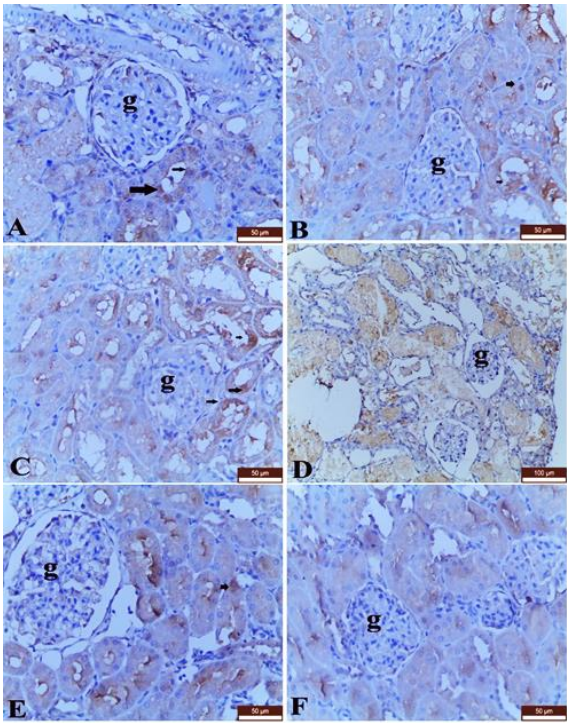

Figure 4 Photomicrograph of the kidney TNF-α immunostaining showing immunopositive reaction in few tubular cells (arrow) in control group (Figure A), very faint to negative immune reaction in few cells of SO group (Figure B) (arrow), and NAC group (arrow) (Figure C). The immunoreaction for TNF-α in the GM group (Figure D), faint positive immunoreaction in GM+SO group (arrow) (Figure E) and negative immunoreaction in GM+NAC group (Figure F). TNF-α immunostains.

4. DISCUSSION

The current investigation revealed that SO and NAC can protect rats from GM-induced nephrotoxicity. Treatment with SO and NAC markedly alleviated GM-induced changes in renal biomarkers, histology, and immunohistochemistry.

Serum creatinine, urea, and uric acid levels that are elevated can cause renal impairment (Pai et al. 2012; Elsayed et al. 2014). Also, increased levels of creatinine in serum inhibited glomerular filtration (Vaidya et al. 2008), while a high level of BUN indicates renal failure (Arora et al. 2010). Accumulation of GM in epithelial cells of the kidney exerted cell death through free radical generation, lowered blood flow to the kidney, and induced inflammation (Sharma et al. 2021).

The severity of GM-induced nephrotoxicity is promoted by oxidative stress (Abdeen et al. 2021; Atsamo et al. 2021). GM elicited a rise in MDA, a decline in SOD activity, and GSH content (Atsamo et al. 2021; Elkomy et al. 2019). This study confirmed the significance of oxidative stress in nephrotoxicity evoked by GM. These points are connected between nephrotoxicity, oxidative stress, lipid peroxidation, and kidney damage (Abouzed et al. 2021). These studies discovered a relationship between GM-induced nephrotoxicity and poor GSH activity in the renal cortex, which could contribute to oxidative damage due to impaired antioxidant defenses. SOD inactivation would thus render it incapable of defending against the elevated ROS levels caused by GM (Abouzed et al. 2021). GM accumulates in the renal tubules, lowering antioxidant defenses, and causing tubular necrosis, glomerular congestion, and kidney failure (Abdel-Raheem et al. 2009).

SO, and NAC treatment caused reversal of oxidative parameters, proving the antioxidant action of SO and NAC. SO significantly protect against renal injury induced by GM (Hsu et al. 2010). SO, ability to protect against GM-induced renal impairment is dependent on its ability to inhibit renal oxidative stress. The reduction of renal hydroxyl radical production by SO may also play a role in its antioxidative-based protection against GM-induced nephrotoxicity (Hsu et al. 2010). SO may reduce the development of hydroxyl radicals by limiting the creation of superoxide anion and NO. SO includes a wide range of components, including antioxidant vitamins, glycerol esters of various fatty acids, and lignans such as sesamol (Hsu et al. 2007), which is a potent antioxidant (Wan et al. 2015). Sesamol protects against LPSand iron (Hsu et al. 2007) because of its powerful antioxidative properties.

During oxidative stress, SO suppressed cellular ROS formation (Wollin and Jones 2003). SO, supplementation decreased serum renal injury biomarkers and increased the amounts of antioxidant enzymes in the kidney. Nonfat antioxidants such as tocopherol, sesamolin, sesamin, and sesamol are fundamental for SO's antioxidant and protective abilities (Wan et al. 2015). Our results confirmed the use of SO as a daily food supplement for reducing oxidative stress (Abdel-Daim et al. 2016). SO normalizes changes in antioxidant activity by LPO (Soliman et al. 2015).

On the other hand, NAC protects the kidney against nephrotoxicity (Abdel-Wahab et al. 2017; Rababa'h et al. 2018; Elsayed et al. 2021). NAC protects the kidneys by maintaining cell membrane integrity, consequently decreasing enzyme leakage through membranes, and displaying renal protective effects (Joshi et al. 2014).

NAC is an antioxidant that has the strongest reactions with hydroxyl radicals and hypochloric acid, but not with hydrogen peroxide or superoxide radicals (Arakawa and Ito, 2007). It may also have an indirect antioxidant effect by increasing GSH production and supplying GSH for GSH-Px-catalyzed activities (Saricaoglu et al. 2005). NAC is a precursor of glutathione, a very effective free antioxidant found in cells. Also, Elsayed et al. (2021) recorded that NAC has a free radical scavenging activity and antioxidant action. Histopathologically, the renal tissues of the GM group showed congestion of the blood vessels, edema, degenerative changes, and coagulative necrosis in the renal tubule epithelium, and similar findings were reported in a previous study (Abdeen et al. 2021).

The proteins Bax and Bcl-2 play important roles, with Bax acting as a pro-apoptotic factor and Bcl-2 acting as an anti-apoptotic factor. Furthermore, TNF-α activation causes oxidative stress and renal inflammation (Abouzed et al. 2021). In this study, GM upregulated Bax and TNF-α, and downregulated Bcl-2 expression. Similar findings confirmed the same effects of GM administration (Abouzed et al. 2021). SO, and/or NAC addition with GM restored Bax, Bcl-2 and TNF-α towards control group.

5. CONCLUSION

GM induced oxidative damage to the kidney, which was triggered by increases in the renal function biomarker in serum as well as disruptions in the oxidant/antioxidant system. However, co-treatment with SO or NAC mitigated the negative effects of GM, most likely by increasing cellular antioxidant defense. Comparing with the effect of SO, NAC had a better potential effect against GM-induced renal damage in rats.

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