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ORIGINAL ARTICLE

Anti-Inflammatory Effect of Acetylcysteine and Royal Jelly against Fluoxetine-Induced Hepatotoxicity in Rats

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ABSTRACT

Background: Hepatic toxicity of antipsychotic drugs needs to be protected by hepatoprotective medications. This study evaluated the anti-inflammatory effect of N-acetylcysteine (NAC) and Royal jelly against hepatotoxicity of fluoxetine in rats.

Methods: Thirty adult female rats were divided into five equal groups of 6 rats. Group A was considered negative control. Group B were rats administered orally by fluoxetine (10 mg\kg) to induce hepatotoxicity. Group C were animals pre-treated with oral NAC (200 mg\kg) and then fluoxetine (10 mg\kg). Group D was pre-treated with Royal jelly (150 mg\kg) following the use of fluoxetine (10 mg\kg). Group E was pre-treated with oral Royal jelly and NAC following fluoxetine utilization. After completion of 28 days of treatment, the rats were euthanized and a blood sample was collected and evaluated for inflammatory cytokines of tumor necrotizing factor alpha (TNF-α), interleukin-10 (IL10) and oxidative stress biomarkers of malondialdehyde (MDA) and glutathione (GSH) by ELISA.

Results: Fluoxetine induced hepatotoxicity and an increase in inflammatory cytokines such as TNF-α. Royal jelly and NAC showed significant anti-inflammatory and antioxidant effects by reduction in inflammatory cytokines and oxidative parameters.

Conclusion: Both NAC and Royall jelly were shown to have antioxidant and anti-inflammatory activities, even NAC impact was more than Royal jelly against hepato toxicity induced by fluoxetine.

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Introduction

Fluoxetine {N-methyl_3 _Phenyl_3_[4_ (trifluoromethyl) phenoxy] propan_1_amine} is chemically the most commonly prescribed drug for depression and other neuro-psychotic disorders (1). It is commonly used because of its greater flexibility (2) as it is particularly lipophilic and strongly linked to plasma proteins, enabling the medication in its active form, nor-fluoxetine, to be transported to the brain. It was shown that around 94 percent of fluoxetine is linked to plasma proteins (3). Fluoxetine undergoes metabolism via the hepatocytes, mainly isoenzymes that are part of the cytochrome P450 metabolic system, particularly CYP2D6 (4); while its chronic use can result in hepatic toxicity (5). It was shown that fluoxetine

and norfluoxetine can cause hepatotoxicity and oxidative stress in rats (6). Hepatic ischemia, necrosis, cholestasis, steatosis, inflammation, and hepatomegaly have been observed with different dosages of fluoxetine (7).

N-Acetylcysteine (NAC) is a medicine approved by the FDA and classified by the World Health Organization (WHO) as an essential substance, commonly used for the management of an overdose of acetaminophen (paracetamol) and, subsequently, as a mucolytic treatment in respiratory illnesses (8). The major function of NAC is linked to its anti-inflammatory and antioxidant effects, which aid in the preservation of an intra-cellular redox inequality. Therefore, its therapeutic potential involves a variety of disorders that are related to oxidative stress, including their etiology and progress. Not only NAC functions as a powerful cell bio-protector, but its pharmacokinetic properties which are related to safety, bioavailability, absorption with its low cost are the reasons for the growing interest in its beneficial effects (9). Conversely, the prevalent belief that NAC's antioxidative properties result from its capacity to serve as a cysteine (Cys) source, hence it can promote the production of glutathione (GSH) in the body (10).

Royal jelly is a natural product of hypopharyngeal glands of working bees and is a special and remarkable food source for bee queen larval nourishment. Because they have a few negative consequences, natural products are employed as therapeutic agents to treat a variety of disorders. Royal jelly influences development, physical growth, and cell proliferation. It is a mixture of proteins, lipids, sugar, vitamins, vital amino acids, and water (11, 12). Royal jelly exhibits anti-inflammatory and anti-oxidant impacts in addition to immunomodulatory and antitumor effects (13-15). Moreover, Royal jelly has exhibited antimicrobial, antiallergic and anti-hypercholesterolemic effects (16, 17). Many studies illustrated that NAC and Royal jelly can have hepatoprotective impact against carbon tetrachloride induced hepatic toxicity (18, 19). As Royal jelly and NAC protective effects on hepatic toxicity induced by fluoxetine in rats has not been thoroughly investigated, the present study aimed to compare the antioxidant and anti-inflammatory effects of NAC and Royal jelly against hepatotoxicity induced by fluoxetine in rats.

Materials and Methods

The medications, materials, and chemical compound applied in the research involve fluoxetine capsules from Actavis Company, N-Acetylcysteine capsule from America Medic and Science (AMS). Royal jelly capsule from Basic Nutrition in UK. Distilled Water (D\W) from Pioneer, Iraq. Formaldehyde solution from SDFC Limited, India. Normal saline 0.9% (N\S) from Pioneer, Iraq. Totally, 30 healthy female rats between 10 and 12 weeks old and 180-250 g in weight were used in the study. They brought from College of Veterinary Medicine, University of Basrah, Basrah, Iraq. They were randomly housed in poly-propylene cages containing saw-dust in the animal house of College of Pharmacy, University of Basrah, Basrah, Iraq. Firstly, they were adapted to their environment in their cages by setting the optimum room temperature about 21±4°C, light/dark photoperiods of 12 L-12 D for two weeks avoiding unnecessary stresses. Rats were fed with a commercial pellet diet and water *ad libitum* through the experimental period.

The rats were divided into five equal groups of 6 rats. Group A was considered negative normal controls that were given orally distilled water, without any type of drugs for 28 days. Group B was the positive control rats administered orally only by fluoxetine (10 mg/kg/day) dissolved in distilled water (20). Group C received the NAC pretreatment dose orally (200 mg\kg\day) dissolved in distilled water (21) and after 60 minutes, the rats were administrated orally by fluoxetine (10 mg/kg/day) dissolved in distilled water. Group D were the animals pretreated orally by Royal jelly (150 mg/kg/day) dissolved in distilled water (22) and then; after 60 minutes, the rats were given fluoxetine (10 mg/kg/day) orally dissolved in distilled water. Group E were pre-treated by orally Royal jelly (150 mg/kg/day) and then after 60 minutes received NAC (200 mg\kg\day) orally and finally fluoxetine (10 mg/kg/day) was given orally. So the time between each dose in treated groups was 60 minutes before inductions. After the last dose, the rats were fasted for 24 h and then euthanized by chloroform, dissected, and blood samples were collected. The blood samples were later centrifuged at 3000 rpm for 5 minutes and the serum was collected and saved for further evaluation regarding inflammatory cytokines, oxidative stress biomarkers utilizing ELISA. Statistical analysis was conducted using SPSS software (Version 25, Chicago, IL, USA). The data were presented as [mean±standard error (SE)]. One way ANOVA evaluated any variations between the test groups. Differences with a p value <0.05 were considered statistically significant.

Results

The fluoxetine receiving group exhibited a non-significant statistically change in serum level of proinflammatory cytokine TNF-α when

compared to negative control group (133.43±4.12 and 112.20±11.21) (mean±SE), respectively. Royal jelly group (D), and NAC treated group (C) exhibited a non-significant change too in comparison to fluoxetine receiving group (134.23±12.98, 108.44±6.08 and 133.43±4.12) (mean±SE), respectively. The combination treated group that received both Royal jelly and NAC exhibited a significant increase in serum level of TNF-α when compared to fluoxetine receiving group (154.54±6.67 and133.43±4.12) (mean±SE), respectively (Figure 1).

Regarding serum IL-10 level, in fluoxetine receiving group, a significant decrease was noticed when compared to the control group (13.98±0.62 and18.19±0.88) (mean±SE), respectively. The Royal jelly treated group illustrated a non-significant change in IL-10 level in comparison to fluoxetine receiving group (15.82±0.37 and 13.98±0.62) (mean±SE), respectively. The combination (E) and NAC treated group (C) displayed a significant increase in serum IL-10 level when compared to fluoxetine treated group (17.63±0.42, 16.52±0.94 and 13.98±0.62) (mean±SE), respectively (Figure 2, Table 1).

Fluoxetine receiving group (B) depicted a significant increase in MDA serum level when

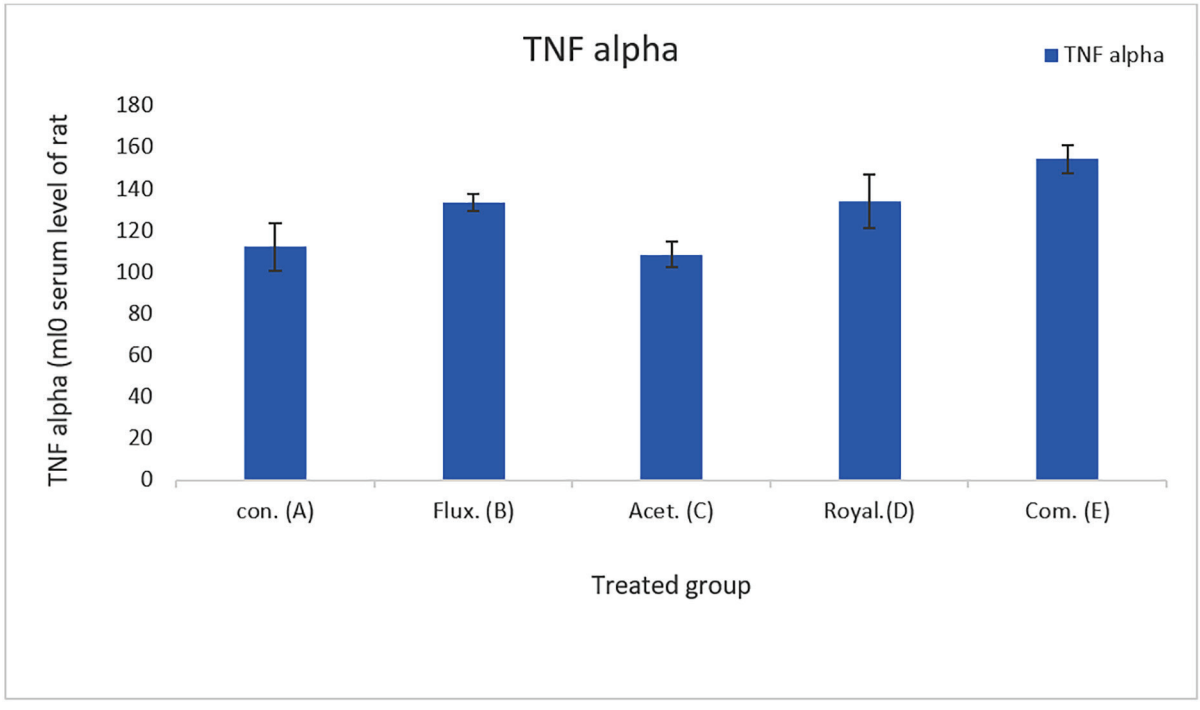

Figure 1: Serum level of tumor necrotizing factor alpha (TNF-α) in treated groups.

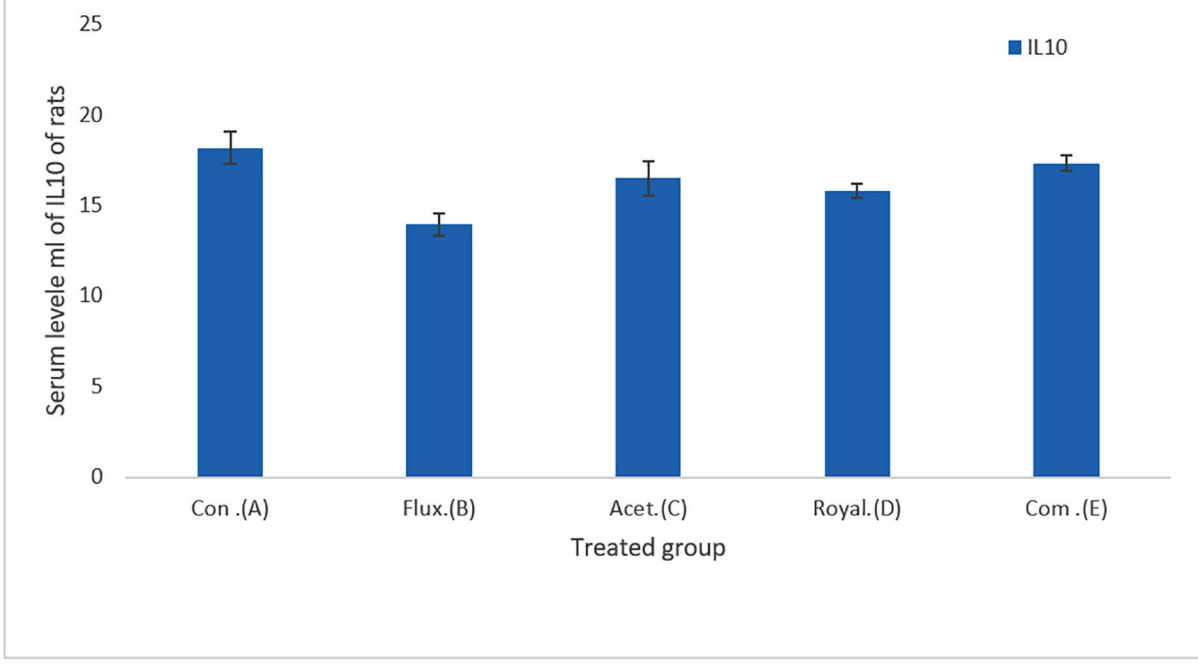

Figure 2: Serum level of interleukin-10 (IL-10) in treated groups.

Table 1: Serum level of malondialdehyde (MDA), glutathione (GSH), tumor necrotizing alpha (TNF-α), and interleukin-10 (IL-10) in all groups.

Group	MDA serum level (mean±SE)	GSH serum level (mean±SE)	TNF alpha serum level (mean±SE)	IL-10 serum level (mean±SE)
Negative control (A)	100.81±7.05#	254.63±17.06#	112.20±11.21	18.19±0.88#
Fluoxetine (B)	133.52±11.18*	149.36±9.50*	133.43±4.12	13.98±0.62*
NAC (C)	92.94±2.96#	186.76±28.27	108.44±6.08	16.52±0.94#
Royal jelly (D)	98.50±3.51#	219.23±16.20	134.23±12.98	15.82±0.37*
Combination (Royal jelly+NAC) (E)	100.28±5.42#	314.42±60.19#	154.54±6.67*	17.63±0.42#

The values are presented as mean±standard error. *Significant differences (p<0.05) when compared to negative control, while the symbol # referred to significant differences (p<0.05) when compared to fluoxetine group. NAC: N-Acetylcysteine.

compared to the control group (133.52±11.18 and 100.81±7.05) (mean±SE), respectively. The Royal jelly, NAC and also combination treated groups showed a significant decrease in MDA serum level in comparison to fluoxetine receiving group (98.50±3.51, 92.94±2.96, 100.28±5.42 and 133.52±11.18) (mean±SE), respectively (Figure 3). Fluoxetine receiving group revealed a significant reduction in GSH serum level when compared to the control group (149.36±9.50 and 254.63±17.06) (mean±SE), respectively. Both Royal jelly and NAC treated groups exhibited a non-significant change in glutathione (GSH) serum level in comparison to fluoxetine receiving group (219.23±16.20, 186.76±28.27 and 149.36±9.50) (mean±SE), respectively. The combination treated group denoted to a significant increase in GSH serum level when compared to fluoxetine receiving group (314.42±60.19 and 149.36±9.50) (mean±SE), respectively (Figure 4).

Discussion

Drugs are transformed into physiologically inert forms and removed from the body, mostly through the hepatic metabolism, so hepatic toxicity has been intimately linked to the production of drug metabolites which are highly reactive (23). Fluoxetine is the most commonly prescribed drug for depression. Nor-fluoxetine as the most active form of fluoxetine with hepatic metabolism has an extended half-life and excreted via urine (24). Some studies revealed continued use of fluoxetine is associated with hepatic toxicity and chronic liver illness due to inflammation and oxidative stress (25, 26).

In this study, the induction of hepatic toxicity by orally administration of fluoxetine (10 mg\kg) could increase the oxidative stress and inflammation in liver tissue. MDA as an indicator of the lipid peroxidation (27) is a reference for the degree of cell destruction (28). In our study, there was an increase in serum

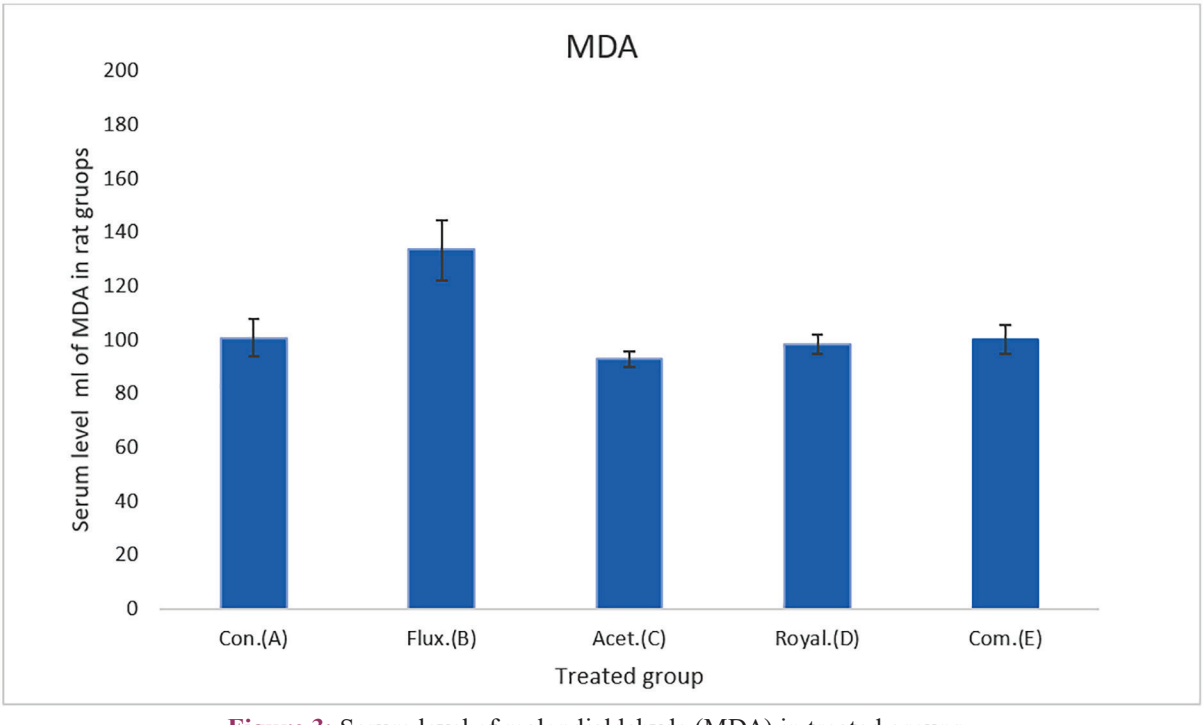

Figure 3: Serum level of malondialdehyde (MDA) in treated groups.

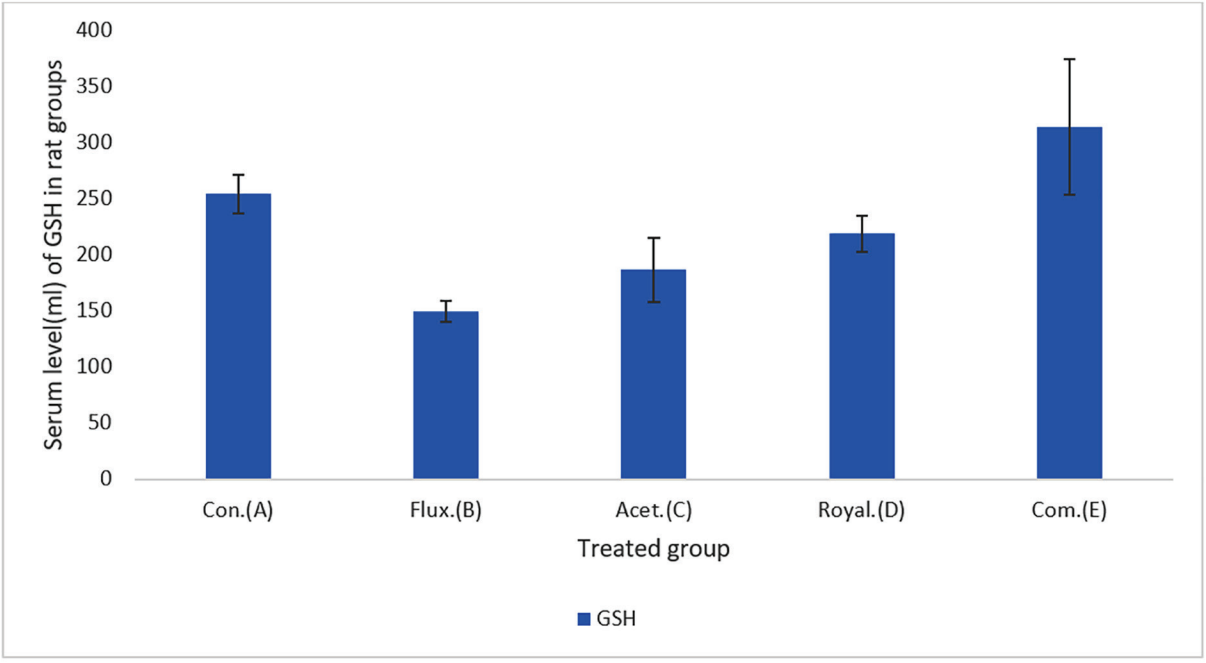

Figure 4: Serum level of glutathione (GSH) in treated groups.

level of MDA in fluoxetine treated group. That was coupled with a significant reduction in GSH serum level as a crucial antioxidant defense mechanism indicating the impairment of the antioxidant defense system that made the liver more suitable for toxicity. Our finding is in agreement with a previous study indicating that drugs or their metabolites can produce oxidative stress, which builds up free radical and causes mitochondrial malfunction, which can directly induce hepatotoxicity (29, 30).

There are findings that described hepatotoxicity resulting from production of free radicals that enhanced by fluoxetine (31). The frequency of liver illnesses is rising and protective or preventative medicines are urgently needed. In our study, the results showed significant hepatoprotective influence of NAC against fluoxetine-induced hepatotoxicity by reducing oxidative stress and maintenance of the equilibrium between oxidant and anti-oxidant system. Our findings are in agreement with findings on animals revealing that NAC possessed a strong protective ability against oxidative stress and inflammation (31).

Royal jelly is regarded as a significant source of natural antioxidants that are capable of overcoming the adverse effects of oxidative damage, which is thought to be the root cause of several diseases (32). Our findings revealed the significant scavenging free radical capacity of Royal jelly and its hepatic protective ability against fluoxetine-induced hepatotoxicity that agree with a previous study denoting to a hepatoprotective agent before cisplatin injection and an antioxidant activity, radical scavenging and antiapoptotic properties against cisplatin hepatotoxicity (33).

We demonstrated an increase but non-significant in TNF-α serum level and a significant reduction in IL-10 serum level of rats receiving fluoxetine when compared to control group. Also, we showed the anti-inflammatory impact of NAC treated rats against fluoxetine-induced hepatic toxicity by a significant reduction in TNF-α and increase in IL-10 serum level. These findings are in agreement with the study implying that NAC could prevent lipopolysaccharide hepatotoxicity by lowering the release of inflammatory cytokines, raising antioxidant capacity (34). Active immune cells such as T cells, B cells, and macrophages were shown to create the pleiotropic cytokine of IL-10 endogenously which primarily promotes the control of several anti-inflammatory mechanisms (35, 36).

Royal jelly did not illustrate a significant anti-inflammatory effect against fluoxetine-induced hepatotoxicity and no significant change in proinflammatory cytokines of TNF-α and IL-10 against fluoxetine-induced hepatotoxicity. It may be due to low dose of Royal jelly used in our study. This finding agrees with some recent studies revealing the Royal jelly anti-inflammatory impact in a dose dependent mechanism (37, 38). Royal jelly was shown to prevent inflammatory cytokines belonging to fatty acids in royal jelly namely Sebacic acid (SeA), 10 Hydroxedacanoic acid of 10HDA and 10HDAA; while they exhibited significant dose dependent impacts on IL-10 level. The sebacic acid

was demonstrated to have the ability to suppress TNF-α production too (39).

This study was also in agreement with a recent study evaluating the Royal jelly protecting impact against UV radiation on the skin in different doses (2.5, 5%,10%). The results showed an increase in royal jelly cream led to a significant reduction in TNF-α level. Moreover, the maximum dosage could cause a reduction in Nf-kB (transcription factor) expression and an improvement in nuclear-related factor (Nrf2) expression level too (40anti-inflammatory properties were shown in vitro. Nanoparticles, including nano-silver (NS). The combination treated group of our study resulted in a significant modulation in MDA and GSH serum levels. Also, IL-10 impact against fluoxetine-induced hepatotoxicity was noticed together with a significant increase in TNF-α expression when compared to control group. These findings suggest that there may be adverse effects rather than synergistic effects resulting from combination use of Royal jelly and NAC.

Conclusion

Fluoxetine treatment was demonstrated to induce hepatotoxicity and a significant change in inflammatory cytokines and oxidative stress serum biomarkers. However, pre-treatment with NAC or Royal jelly could protect liver against fluoxetine-induced hepatic toxicity. Royal jelly and NAC had antioxidant impacts against fluoxetine-induced hepatic toxicity too via a significant reduction in oxidative. In our study, NAC had a more potent hepatoprotective activity against fluoxetine-induced hepatotoxicity when compared to Royal jelly because increase in pro-inflammatory cytokines were linked with the degree of damage in various models of hepatotoxicity. Therefore, inhibiting the effects of these cytokines by NAC and Royal jelly can enhance liver function.

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Authors' Contribution

The authors confirm their contribution to the paper as follows: Study concept and design: MAKI and MNA. Data collection: AHN; results analysis and interpretation: MAKI, MNA and AHN. Manuscript planning: MAKI, MNA and AHN. All authors contact the results and confirmed the final version of manuscript.

Conflict of Interest

The authors state no discrepancy of conflict of interest related to this article.

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