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Paraquat-induced Oxidative Stress, Immune Response and The Protective and Therapeutic Role of Nicotinamide Mononucleotide in Rats

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I. Abstract

Paraquat, a widely used herbicide, is known for its high toxicity due to its ability to react with and damage cell components by generating oxygen-free radicals, leading to an immune imbalance. Conversely, elevating levels of NMN (nicotinamide mononucleotide), a precursor to NAD+, can enhance oxidative and thus immune balance. This study aimed to evaluate the effect of oxidative paraquat as well as the protective and therapeutic role of nicotinamide mononucleotide in some immunological and oxidative stress markers in rats. Fifty female rats were randomly divided into five groups of ten rats each: a control group, one group received a dosage of paraquat; another received a dose of either nicotinamide mononucleotide or paraquat followed by nicotinamide mononucleotide (therapeutic effect); the last group received a dose of nicotinamide mononucleotide followed by paraquat (protective effect). Blood samples were collected after the treatment period ended, and tests were performed for several immunological and biochemical markers. After analyzing the data using ANOVA one way and Tukey's post hoc test for multiple comparisons. The results showed that paraquat exposure led to an elevate indicators of both oxidative stress, increased MDA(p<0.001) and decreased catalase enzyme(p<0.001), and the inflammatory immune response, TNF-α (p<0.001) and IL-1β(p<0.0001). A decrease in interleukin-137(p<0.0001), complement, C3(p<0.0001) and C4(p<0.001), and T cells, CD8 and CD4, (p<0.001) was also observed. In contrast, the antioxidant NMN reversed this effect by reducing oxidative stress and contributing to a decrease in the inflammatory response. The therapeutic group showed a significant improvement compared to the control group, but the effect was more pronounced in the protective group in most of the studied indicators. These results suggest that paraquat induces an immunological impairment associated with oxidative stress and nicotinamide mononucleotide; it has an effective ability to reduce its harmful impact and restore immune homeostasis, especially when given protectively.

Key word : *Immunological, Nicotinamide mononucleotide, Oxidative stress, Paraquat, Rats.*

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II. Introduction

The use of chemicals such as herbicides in the environment has become a growing concern due to the serious damage these compounds can cause, which may super pass any intended benefits. This includes impacting the health of living organisms, both humans and animals, The minimum lethal dose has been determined to be 30 mg/kg and accumulating in soil and plants, especially in areas not subject to strict regulations governing their use. Particularly in developing countries, where users are primarily exposed to substances orally and through skin contact, Paraquat is considered one of the most toxic of these pesticides it causes cellular damage through various mechanisms including oxidative stress, paraquat is a commonly used due to its rapid action and high non-selective efficacy, and is therefore used to control weeds. It works by forming free radicals, which causes oxidative stress in plants, leading to the destruction of photosynthesis and consequently plant damage[1-4]. According to a study conducted on male rats, it was found that paraquat causes a change in several biological indicators. It causes an elevation in oxidative stress indicators in male rats [5,6]. It also disrupts the immune system, leading to an increase in inflammatory factors such as cytokines. A study conducted at the University of Michigan found that exposure to paraquat in laboratories led to a decrease in T cells and a decrease in their production of cytokines such as INF-γ, resulting in a weakened immune response necessary to reduce the progression of damage. Another study showed that paraquat increased the expression of inflammatory genes such as TNF-α and IL-1β in phagocytic cells and led to the suppression of innate immunity[7,8]. Numerous studies have been conducted evaluate a potential therapeutic agents that reduces the toxicity of paraquat, and it has been found that antioxidants play an active role in mitigating its harmful effects[9,10]. Elevated NAD+ levels can significantly contribute to reducing cellular and metabolic degradation, thereby mitigating physiological conditions such as diabetes, liver cirrhosis, and neuropathies by alleviating oxidative stress through the provision of biosynthetic precursors. Given the important role that NAD^+ plays in cellular metabolism, nicotinamide mononucleotide, a source of NAD^+ precursors, has emerged as a potential treatment that contributes to reducing cellular and immune deteriorations [11-13]. Many studies have also pointed to the role of NMN in cell regeneration and immune response enhancement, as this relationship between NAD+ levels and immune cell activity is evident. Immune cells, including T cells, B cells, and natural killer cells, require substantial metabolic energy to function effectively, research models have shown notable results in how NMN influences immune cell populations. which enhanced T cell proliferation and natural killer cell activity in subjects supplemented with NMN. These suggest where NMN have a potential mechanism can support the body's ability to generate and maintain a healthy, responsive immune system. [14,15]. A study conducted on pigs showed that NMN

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contributes to reducing metabolic disturbances that cause stress and disrupt placental mitochondrial function. Each pig receiving 0.2 grams of NMN daily resulted in reduced intrauterine fetal growth retardation and increased placental levels, thereby reducing oxidative stress and programmed cell death[16]. Despite the effective role of nicotinamide mononucleotide (NMN) and its protective and therapeutic properties through enhancing NAD^+ levels, and despite paraquat's high toxicity, studies addressing its role in mitigating paraquat's harmful effects remain limited, particularly in animal models. Therefore, this study was focused on evaluating the protective and therapeutic effect of NMN against the oxidative stress and immune system dysfunction caused by paraquat exposure.

III. Materials and methods

Experimental animals

Fifty albino female rats (3 months old) weighing between 180 to 200 mg, obtained from the animal house of Tikrit University/College of Veterinary Medicine, 10 rats per cage in a room with a regulated temperature (25°C) and were kept on a 12-hour light/dark cycle with food and water provided continuously. the animals were left for adaptation least 1 week before the procedure.

Experimental design and grouping of animals

Paraquat was given at a dose of 20 mg/kg/day intraperitoneally. The components were appropriately diluted, and rats were injected with 0.250 ml daily, while NMN was administered orally by dissolving 500 mg of NMN in 5 mL of distilled water and dosing 1 ML /day. Rats were divided to five group, ten rats per cage, group I, II, III, IV and V. group I as a control group, group II had received paraquat daily for month at the dose described above (paraquat was provided by Olivia company), group III had received NMN, as mentioned above, for month (NMN was obtained by Nustricost company, USA), group IV were had a paraquat firstly with the same dose above for month and then had NMN also with the same previously dose for month after that, to demonstrate the therapeutic effect of the NMN, the last group (V) had NMN firstly daily for month and then injected with paraquat daily for month, to demonstrate its protective effect, the method describe in [17,18] with some modifications.

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Evaluation of immunological and oxidative stress marker

Rats blood was collecting after ending the treatment period , as shown in figure 1, for subsequently analysis conduction by using commercial kits obtained from Sunlong Biotch Co., LTD : catalase (CAT) enzyme (catalog No. AK0612), the level of malondialdehyde (MDA) (catalog No. AK0662), Tumor necrosis factor alpha (TNF-α) (catalog No. SLD004Hu), Interleukin-1beta(IL-1β) (catalog No. SL040Ra), Interleukin 37 (IL37) (catalog No. SL1974Ra), cluster of differentiation 8 and 4 (CD8, CD4) (catalog No. SL0170Ra , catalog No. SL1201Ra), and Complement 3 and 4 (C3, C4) (catalog No. SL0187Ra , catalog No. SL1490Ra), were measured. The assays were performed according to the manufacturer's instructions.

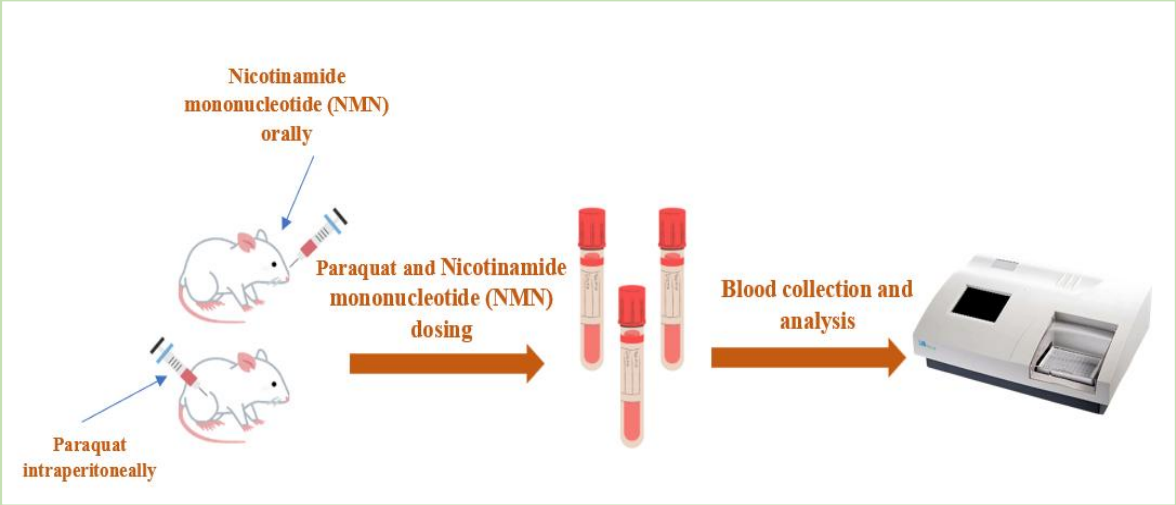

Figure 1 Experimental procedure revealing animals administration, blood sampling and conducting analysis

Statistical analysis

Data were analyzed by using SPSS. mean and standard deviation are calculated. one-way ANOVA followed by Tukey's post hoc test were used to compare the effect of treatment across the groups. A significant P value was defined as < 0.05.

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IV. Results and discussion

Evaluation of TNF-α response under paraquat and Nicotinamide mononucleotide (NMN) effect

Figure 2 shows that the treatment with paraquat and NMN has a significant effect according to the ANOVA test ($p < 0.001$). This effect was pronounced in the protective group compared to the therapeutic group according to Tukey's test

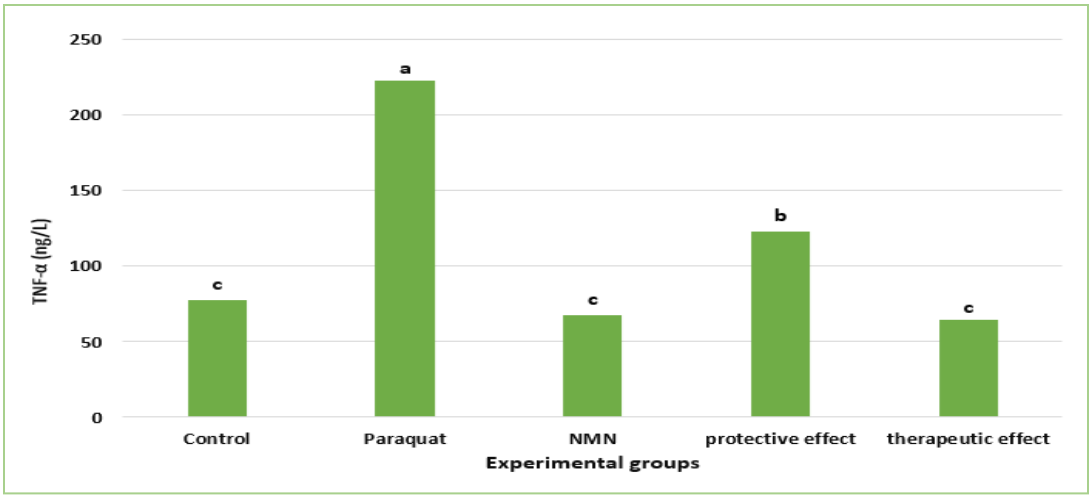

Figure2 TNF-α levels under paraquat and nicotinamide mononucleotide (NMN) treatment in rats' group. At a significance level of $p<0.05$.

The results demonstrate significant differences between the groups at a significance level of 0.05. The paraquat group recorded the highest significant increase in TNF-α levels as display in Figure 2, while NMN group showed the highest significant decrease compared to the control group. Both treated groups (protective and therapeutic effect) recorded a decline in TNF-α levels towed to the control group value. The increased concentration in the paraquat group may attributed to elevated oxidative stress, which leads to the gradual activation of pathways inflammatory pathway. Elevated levels of oxidative stress resulting from the effects of paraquat activate the NF-κB inflammatory pathway, stimulating cytokine production, particularly TNF-α. This finding is consistent with previous studies that showed elevated levels of NF-κB and TNF-α in the lung tissue of paraquat-treated mice, along with widespread direct inflammatory tissue damage, The increased concentration in the paraquat group may attributed to elevated oxidative stress, which leads to the gradual activation of pathways inflammatory pathway. Several studies reported that TNF-α, an inflammatory cytokine, produced in large quantities during inflammation. It is considered one of the early immune signals that stimulate the production of other cytokines to activate the inflammatory response. The return of its levels to a decrease upon exposure to NMN indicates the substance's effectiveness in reducing the high activity of

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the immune system and its protective effect was more pronounced. The exposure to paraquat activate the NF-κB inflammatory pathway, stimulating cytokine production, particularly TNF-α. This finding is consistent with previous studies that showed elevated levels of NF-κB and TNF-α in the lung tissue of paraquat-treated. The decrease is attributed to NMN's role in combating free radicals and reducing the activation of inflammatory pathways. Conversely, several studies have pointed to the role of NMN in reducing inflammation by augmenting NAD^+ levels and thus reducing or inhibiting TNF-α levels[1,19-21].

Evaluation of IL-1β response under paraquat and Nicotinamide mononucleotide (NMN) effect

As seen in the figure below, the ANOVA test revealed statistically significant values arising from the impacts of paraquat and NMN treatments(p<0.0001). When comparing the groups, Tukey's analysis revealed that paraquat significantly increased IL-1β levels while NMN significantly decreased them, with NMN's preventive effect greater than its therapeutic effect.

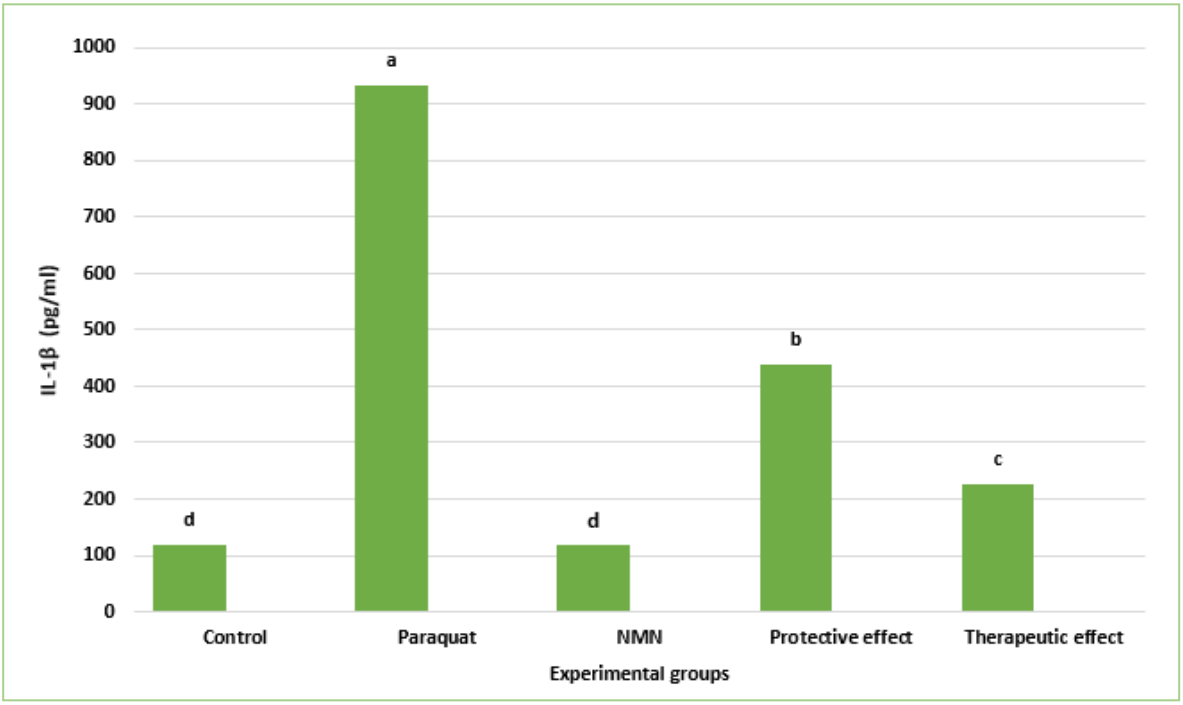

Figure 3 IL-1β levels under paraquat and nicotinamide mononucleotide (NMN) treatment in rats' group. At a significance level of p<0.05.

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As shown in Figure 3 the analyzing data of IL-1β, it is an indicator that rises as a result of stimulating the inflammatory response, reinforce the effect of the two substances used in the treatment . These results reflect the role of paraquat as a strong oxidizing agent, which in turn leads to the activation of the NLRP3 (inflammasome) complex. This is essential for the maturation and secretion of IL-1β, as free radicals (ROS) convert it from its inactive to its active form. The mechanism is reversed at the NMN group, which supports the substance's role as an antioxidant by maintaining mitochondrial efficiency and reducing the effects of free radicals through participation in intracellular oxidation-reduction reactions. This, in turn, reduces IL-1β production in both the treatment and prevention groups, indicating the role of the antioxidant NMN in reducing the inflammatory response and restoring it to normal levels. This consistence with many previous studies[22-25].

Evaluation of IL-37 response under paraquat and Nicotinamide mononucleotide (NMN) effect

As shown in Figure 4, paraquat cause decreasing in IL-37 in rats whereas NMN returns its level near the normal range, despite the mean of protective effect being higher than the therapeutic effect, but there is no significant difference between them according to Tukey test (p<0.0001)

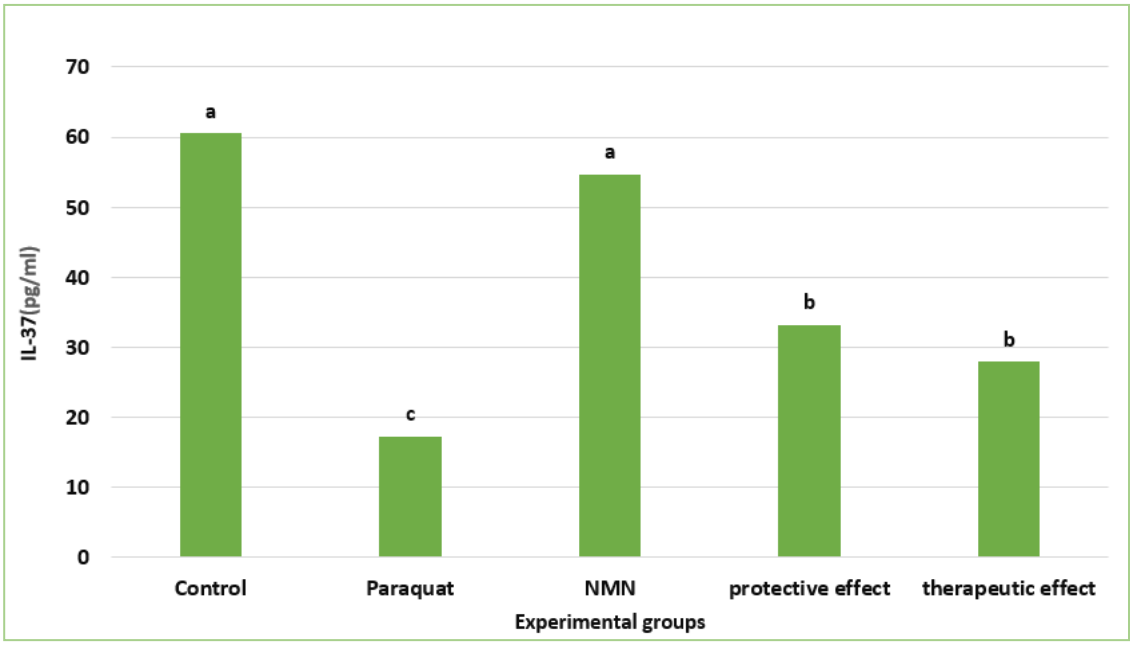

Figure 4 IL-37 levels under paraquat and nicotinamide mononucleotide (NMN) treatment in rats' group. At a significance level of p<0.05.

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In contrast to the previous indicators as above Figure reveals, a decline in IL-37 levels was observed in the paraquat-treated group. IL-37 is considered an anti-inflammatory and suppressor of inflammation. This significant decline could be due to the high levels of free radicals generated by paraquat treatment, which lead to high oxidative stress that weakens anti-inflammatory pathways, especially IL-37, are may be insufficient to counteract it and this agreement with many previous studies. However, in the NMN, therapeutic and protective an increase was observed, indicating the effective role of NMN in reducing NF-κB activity by enhancing NAD^+ levels and restoring cellular and immune homeostasis, despite the scarcity of direct studies on IL-37 and NMN. Thus, the overall trend of this cytokine acting as an anti-inflammatory agent, low IL-37 levels to increased inflammation in situations of oxidative stress. Numerous studies indicate that an excessive production of TNF-α and IL-1β amplifies the immune response, leading to tissue damage that affects physiological functions. In contrast, this interleukin, IL-37, attempts to create an immune balance to limit the immune response. Overall, this study supports the notion that anti-inflammatory cytokines increase with interventions that reduce oxidative stress. This is clearly demonstrated by the protective effect of NMN, which contributes to the restoration of immune homeostasis, as illustrated in Figure 4. [22, 26-28].

Evaluation of MDA response under paraquat and Nicotinamide mononucleotide (NMN) effect

As Figure 5 displays, MDA levels were elevated under the paraquat influence, which is evidence of cellular membrane damage. In contrast, NMN reduces MDA levels, with a statistically significant value (p<0.001) based on the ANOVA test, despite a noticeable effect in therapeutic and protective groups, but there are no significant differences between them according to Tukey analysis.

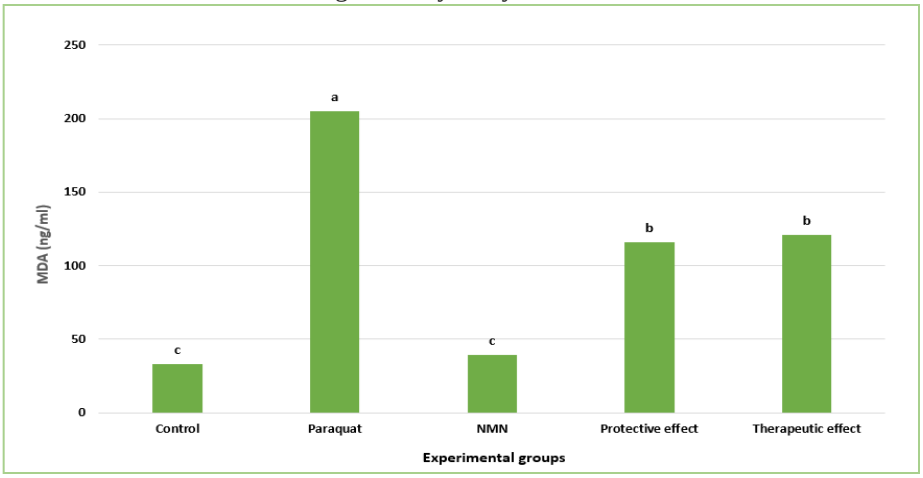

Figure 5 MDA levels under paraquat and nicotinamide mononucleotide (NMN) treatment in rats' group. At a significance level of p<0.05.

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Figure 5 illustrates a significant increase (p<0.05) in MDA levels was observed in the paraquat group, whereas it decreased in the NMN group. This is attributed to paraquat's high oxidative capacity upon entering the cell, where it reacts with cell components. Generating oxygen free radicals that are subsequently converted into hydrogen peroxide, which ultimately leads to the formation of a highly reactive hydroxide radical that reacts with the unsaturated fatty acids of cell membranes, resulting in the formation of MDA as a product of oxidation. Exposure to paraquat stimulates the immune system and signals the presence of damage. Macrophages M1 then release free radicals (ROS), which cause lipid peroxidation and produce MDA as a marker of damage. MDA binds to proteins to produce epitopes, which activate immune cells by triggering the NF-κB pathway, thus increasing the secretion of immune cytokines that amplify the inflammatory response. The decrease in the NMN group might be attributed to the substance's ability to reduce the effect or generation of free radicals by immune cells. It was also observed There is no difference between the therapeutic and protective group, which may be attributed to the fact that oxidative stress parameters are rapidly responsive to antioxidant resulting in exert similar effect, several studies have indicated that exposure to NMN promotes repair of damage caused by an overactive immune response by activating the SIRT1 pathway thereby enabling NMN to create a balanced and protected cellular environment [20, 29-32].

Evaluation of catalase enzyme response under paraquat and Nicotinamide mononucleotide (NMN) effect

There is a noticeable effect of NMN in increasing catalase levels in rats, as shown in Figure 6, and thereby enhancing the antioxidant defense system; on the other hand, the paraquat group shows a sharp decline. The therapeutic and protective group shows a similar significance despite their differences in mean values (p<0.001).

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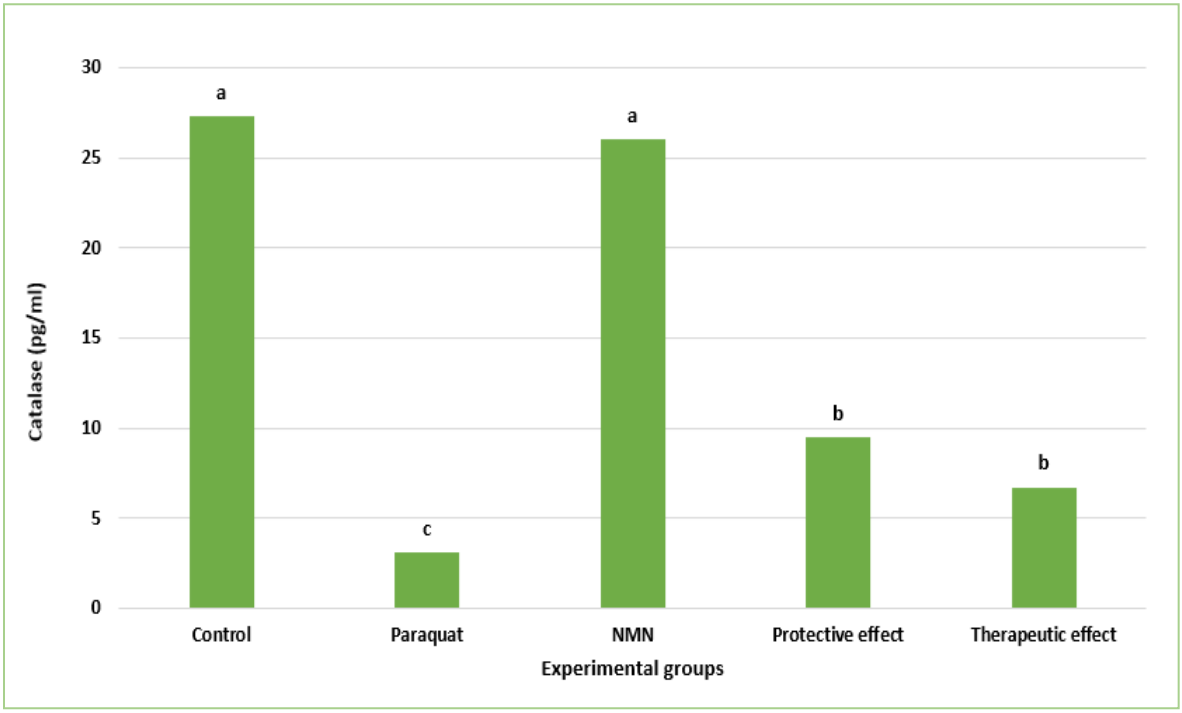

Figure 6 Catalase enzyme levels under paraquat and nicotinamide mononucleotide (NMN) treatment in rats' group. At a significance level of $p<0.05$.

The decline in catalase under the influence of paraquat is due to its high potential for generating free radicals and oxidizing proteins. Catalase works to break down hydrogen peroxide into water, but high concentrations of free radicals deplete the cell's defense mechanisms against oxidative stress, as shown in Figure 6. In contrast, catalase levels rise in the NMN group, which is work as a precursor to NAD+, which is necessary in the function of the SIRT1 pathway, where the latter is necessary to activate the transcription factor Nrf2, which in turn stimulates the production of antioxidant enzymes, including catalase which works by regulating the immune response by maintaining moderate levels of hydrogen peroxide within immune cells, macrophages, and neutrophils, sufficient to activate the response without excess, thus protecting healthy cells from uncontrolled inflammation or cell death, it can also be observed that mean of the protective effect of NMN is also higher than its therapeutic effect, This may be due to NMN's role in providing sufficient levels of NAD+, thus giving cells protection and the ability to resist damage before it occurs and this findings in agreement with previous study[33- 36].

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Evaluation of C3 and C4 response under paraquat and Nicotinamide mononucleotide (NMN) effect

As shown in Figures 7 and 8, a substantial effect in complement levels was observed. A noticeable decline in C3 and C4 in the paraquat group, on the other hand, treatment with NMN returns their levels to the normal levels compared with the control group, with a more pronounced effect in the C3 level in the protective group.

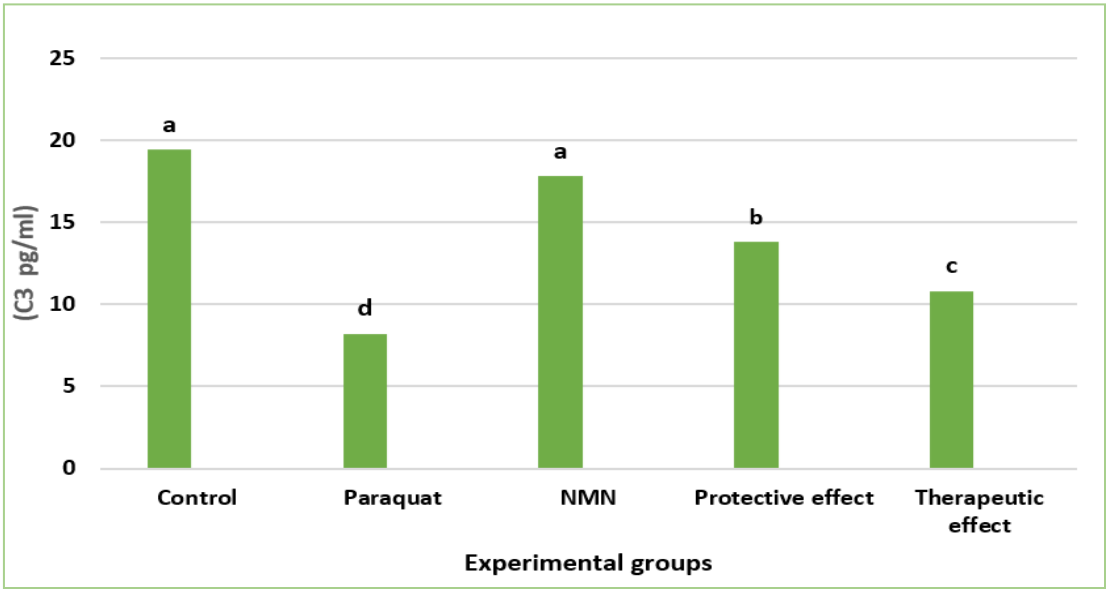

Figure 7 C3 levels under paraquat and nicotinamide mononucleotide (NMN) treatment in rats' group. At a significance level of p<0.05.

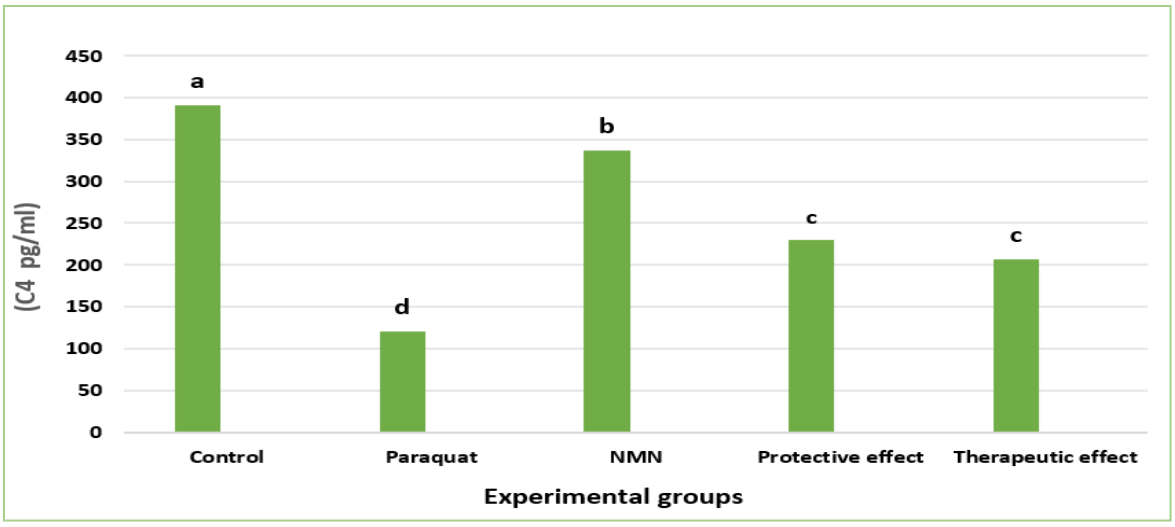

Figure 8 C4 levels under paraquat and nicotinamide mononucleotide (NMN) treatment in rats' group. At a significance level of *p*<0.05.

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The marked decrease under the influence of paraquat in C3 and C4 is due to the consumption of complement C3 and C4 compared to the control group, as display in above Figures. This results from damage to proteins and cell membranes due to oxidative stress, which leads to activation of the complement system, particularly the alternative pathway, and consequently its consumption as it binds to damaged cells to label and remove them. However, the NMN, the protective and therapeutic group, complements levels rise again, indicating the effectiveness of NMN as an antioxidant in restoring immune balance and reducing of cellular damage, thus reducing the activation of inflammatory pathways, which allows support for liver functions in the synthesis of complement proteins and this consistent with previous study[37-39].

Evaluation of CD4 and CD8 response under paraquat and Nicotinamide mononucleotide (NMN) effect

As shown in the figure below, CD4 and CD8 levels decrease under the influence of the highly oxidizing agent paraquat, then rebound upon treatment with NMN. ANOVA showed a highly significant effect (p> 0.001), and Tukey's analysis indicated that the protective group had a significant effect on restoring CD4 and CD8 levels.

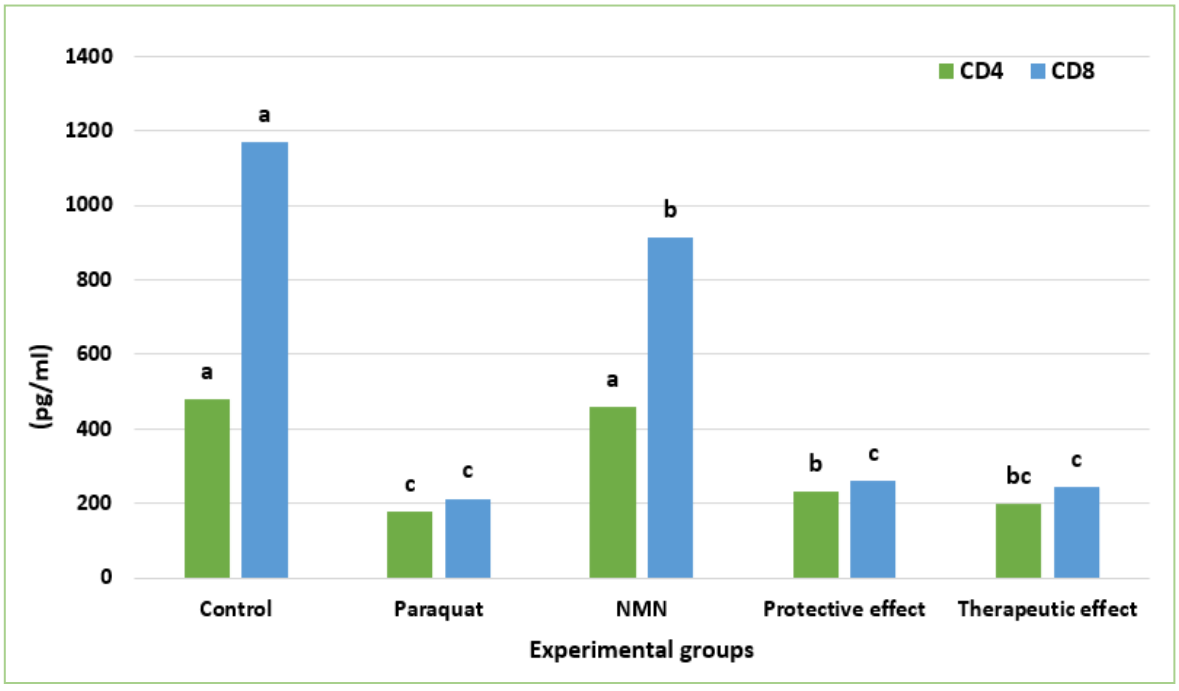

Figure 9 CD4 and CD8 levels under paraquat and nicotinamide mononucleotide (NMN) treatment in rats' group. At a significance level of p<0.05.

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The results demonstrate, as shown in Figure 9, a sharp decrease in both CD4 and CD8 in the paraquat group, low levels of CD4 and CD8 cause an immune dysregulation that might leads to an uncontrolled increase in the production of inflammatory cytokines. A previous study indicated that chronic exposure to paraquat led to a 37% decrease in CD4 cells and an increase in inflammatory cells in the blood and spleen. in contrast to a marked elevation in the NMN group compared to the control group. CD4 and CD8 levels also increase in both the therapeutic and protection groups. Large numbers of oxygen-free radicals produced from paraquat exposure, affecting cell functions, particularly those of mitochondria, which leads to the induction of apoptosis in T cells, especially CD4 cells, and inhibits their proliferation. This may be attributed to NMN's ability to promote T cell proliferation by reducing oxidative stress and boosting NAD+ levels, thereby protecting mitochondria and producing the energy necessary for their survival and proliferation. These findings are consistent with previous studies [10, 40-43].

V. Conclusion

This study demonstrates that paraquat induces a strong immune response, causing a harmful cellular damage resulting from oxidative stress, while nicotinamide mononucleotide restores immune balance by reducing or preventing the effect of generated free radicals. It was also shown that the protective effect was superior to the therapeutic effect in several indicators, which is attributed to the exhaustion of cells due to oxidative stress, whereas the protective effect gets cells ready beforehand to deal with the damage These results support the importance of protective treatment to reduce the effects of oxidative stress on the immune system.

Ethics certification

The Scientific Research Ethics Certificate was obtained from the Committee at University of Anbar.

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