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Nicotinamide Mononucleotide Attenuates Paraquat -Induced Thyroid, Renal and Hepatic Dysfunction in a Rat Mode

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Abstract

Exposure to paraquat interfere with serious metabolic processes, initiating structural injury to various organs, including the liver, kidney and thyroid. The main attention of this study was to evaluate the impacts of NMN contrary to paraquat toxicity in albino rats. Fifty female albino rats were splitting into 5 collections: Control group. Paraquat group, in which rats were intra-peritoneal injected with paraquat pesticide at a concentration of 0.25 ml daily for 30 days. NMN group, in which rats administrated NMN at a dose of 1 ml orally via stomach tube for 30 days. Protective group, in which rats were treated with NMN for 30 days and then with the paraquat for another 30 days. Therapeutic group in which rats were treated with the paraquat for 30 days and then with NMN for another 30 days. Paraquat exposure lowered T4, T3, total protein while increasing TSH, ALT, AST, total bilirubin, urea, creatinine. The activities of antioxidants enzymes, including SOD and GPx were reduced following paraquat administration. Nevertheless, NMN treatment reduced all paraquat stimulated injuries in the liver, kidney and thyroid of rats due to its ability for enhancing NAD+ levels.

Key Words: Paraquat, Nicotinamide mononucleotide NMN, Liver, Kidney, Thyroid hormones

الملخص

ان التعرض لمبيد الباراكوات يتداخل مع العمليات الأيضية ويحدث تغيرات تركيبية لمختلف الأعضاء، بما في ذلك الكبد والكلى والغدة الدرقية. ان الهدف الاساسي لهذه الدراسة هو تقييم تأثير **NMN** ضد سمية الباراكوات في الجرذان البيضاء. تم تقسيم خمسين جرذاً أبيض (اناث) إلى 5 مجموعات: المجموعة الضابطة. مجموعة الباراكوات، حيث تم حقن الجرذان داخل الصفاق بمبيد الباراكوات بمقدار 0.25 مل يومياً لمدة 30 يوماً. مجموعة **NMN**، حيث تم إعطاء الجرذان **NMN** بجرعة 1 مل عن طريق الفم عبر أنبوب المعدة لمدة 30 يوماً. المجموعة الوقائية، حيث تم علاج الجرذان بـ **NMN** لمدة 30 يوماً ثم بالباراكوات لمدة 30 يوماً أخرى. المجموعة العلاجية، حيث تم علاج الجرذان بالباراكوات لمدة 30 يوماً ثم بـ **NMN** لمدة 30 يوماً أخرى. أدى التعرض للباراكوات إلى انخفاض **T4** و**T3** والبروتين الكلي مع زيادة **TSH** و**ALT** و**AST** والبيليروبين الكلي واليوريا والكرياتينين. وقد انخفضت فعالية الإنزيمات المضادة للأكسدة، بما في ذلك **SOD** و **GPx** . قلل علاج **NMN** من جميع التأثيرات التي يسببها الباراكوات في الكبد والكلى والغدة الدرقية للجرذان ويعزى ذلك الى قدرته على زيادة مستويات **NAD**+..

الكلمات المفتاحية : الباراكوات، أحادي نوكليوتيد النيكوتيناميد (NMN)، الكبد، الكلى، هرمونات الغدة الدرقية.

Introduction:

Xenobiotic are foreign chemicals or toxins that may accumulate in the body poising a serious risk to human health, among these xenobiotic are pesticides which are widely used in the agriculture to reduce the insects attack which led to the losses in crop production and to reduce human diseases caused by vector insects [1]. Paraquat is a pesticide usually used in the control of harmful weeds in agricultural aspects globally, this quaternary nitrogen compound (1,1′-dimethyl-4,4′-bipyridinium di-chloride) is extremely active causing numerous cases of acute toxicity and death [2].

Paraquat is one of the greatest commonly applied herbicides in the biosphere, in spite of its great human poisonousness and the devastating confirmation of its great morbidity and mortality [3]. It is categorized as class II (moderately toxic) via the World Health Organization WHO [4]

Paraquat poisoning is a major public health issue all over the world because of its high lethality, its pathophysiology categorized by a complicated series of biochemical as well as cellular actions results in multi-organ failure including mitochondrial damage, lipid peroxidation and oxidative stress, excessive

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inflammatory reactions, and stimulation of apoptotic paths, with an obvious weakness for the lungs, kidneys, as well as the liver [5,6].

The kidney is the chief organ Accountable for paraquat elimination, the accumulation of this compound in the renal tubular cells, can trigger series of reduction and oxidation reactions, creating reactive oxygen species, finally injuring the proximal tubules [7]. Earlier studies illustrate that paraquat intoxication caused acute liver injury known by persistent raise of liver aminotransferases and histopathological alterations [8, 9, 10].

According to animal model exposed to paraquat prompts oxidative stress in hepatic cells, causing great increase in the up-regulation of genes expression and the levels of liver enzymes finally, induce apoptosis, in addition to mitochondrial disturbances [9]. Many pesticides have been described to act as endocrine disrupting chemicals which may affect thyroid gland via numerous ways, comprising disturbance of the hypothalamus–pituitary–thyroid axis, reserving of sodium-iodine symporters, interfere with TSH receptors, , reserve of the thyroid peroxidase enzyme, modification of the binding sites of transport proteins, reduced cellular uptake of thyroid hormone, modification the transcription of thyroid hormone receptors and inhibition of deiodinase enzymes [11, 12, 13].

Exposure to paraquat in both humans and animals has been noted to change the serum concentrations of thyroid hormones comprising thyroxine, thyronine, as well as thyroid stimulating hormone [14]. Contact with paraquat in rats raised the expression of the thyroid hormone transporters including organic anion-transporting polypeptide 1C1 (Oatp1c1) and monocarboxylate transporter 8 (Mct8) as well as the thyroid receptor alpha (TRα), proposing a probable endocrine disturbance [15].

Nicotinamide mononucleotide NMN is a naturally compound derivative of vitamin B3 that acts as a main precursor to Nicotinamide Adenine Dinucleotide NAD+, many studies showed that Nicotinamide NMN is a potent Nicotinamide adenine dinucleotide NAD+ enhancer, NAD+, is an essential coenzyme for numerous enzymes classes, it is necessary for life [16]. Nicotinamide mononucleotide NAD+ is a coenzyme present in every alive cells that acts a serious part in several biological routes, comprising energy metabolism as well as cellular signaling, it is chiefly identified for its part in redox reactions plus energy production [17].

Worldwide, among 250,000 to 370,000 fatalities results from pesticide toxicity are stated yearly, and further than 90% of acute paraquat situations cause by intentional consumption [18]. According to the serious health effects of this pesticide on vital organs in the body including liver, kidneys, and thyroid gland, and according to the beneficial health effects of NMN on the body, the aim of this research is to study the protective and therapeutic effect of NMN against this pesticide in a rat model.

Materials and Methods:

Chemicals

Paraquat (purity: 98 %) and NMN (purity ≥ 99 %) were obtained from Sigma-Aldrich (Germany).

Animals:

The study included 50 female albino rats, each weighing 180-200 grams. The rats were housed at the Animal Household of College of Veterinary Medicine in Tikrit University under typical situations: heat 23–27 ◦C, moisture at 45 ±5 % and Supplied with unlimited contact to diet and water. The animals were divided into five groups (10 in each group). The first group was not treated with any substance and was considered the control group. The second group was intra-peritoneal injected with paraquat pesticide at a concentration of 0.25 ml daily for 30 days and was considered the paraquat group. The third group was administrated NMN at a dose of 1 ml orally via stomach tube for 30 days and was considered the NMN group. The fourth group was treated with NMN for 30 days and then with the paraquat for another 30 days and was considered the protective group. The fifth group was deled with the paraquat for 30 days and then with NMN for another 30 days and was considered the therapeutic group.

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Blood sample collection:

At the termination of the experiment period all rats were anesthetized using (ketamine 100 mg/ kg plus xylazine 50 mg/kg, i.m.). Blood sample was taking using heart puncture method, the blood clot for 20 minute and centrifuged on 3000 rpm for 10 minute, serum samples were collected and kept in -20℃ in the refrigerator till used.

Physiological Parameters Analysis.

Liver function tests were estimated via kinetic technique by commercially obtainable kits, randox (france), determination of ALT and AST were estimated by (colorimetric procedure). Bilirubin was estimated via DPD- technique; total protein level was carried out by linear chemicals S.L. (Joaquim costa 18 2ª planta. 08390 Montgat, Barcelona, Spain). Kidney function tests were done using a multi chemical fully automated chemistry analyzer by various chemical kit, determination of urea concentration was carried out via enzymatic (urease) kinetic technique, creatinine was estimated by jaffe kinetic technique.

The levels of thyroid hormones and antioxidant enzymes were assessed via enzyme-linked immunosorbent assay (ELISA). measurment of TSH, T4,T3 concentration was carried out using an ELISA kit gained from LDN Labour Diagnostica Nord GmbH and Co.KG, a company based in Germany. The levels of SOD and GPx were quantified by anenzyme-linked immunosorbent assay (ELISA) kit (Monobind Inc., Lake Forest, USA).

Statistics:

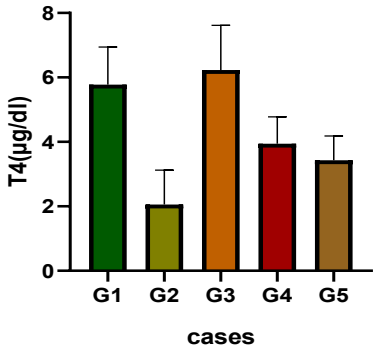
Information were presented as Mean ± SD. One-way ANOVA plus Tukey's test was used. A value of $p < 0.001$ was considered as a measure of significance.

Results:

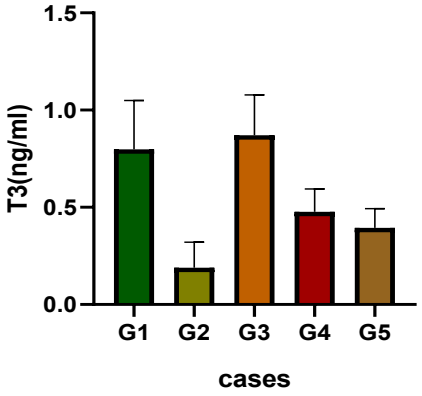
Impact of NMN on Thyroid Hormones

Paraquat supplementation stimulated a considerable ($p < 0.001$) lessening in the levels of T3, T4, with a considerable elevation in the level

of TSH in comparison to all other groups, while NMN administration considerably ($p < 0.001$) increase T3, T4 and caused a significant decrease in TSH level Figure 1 (A,B & C).



(A)



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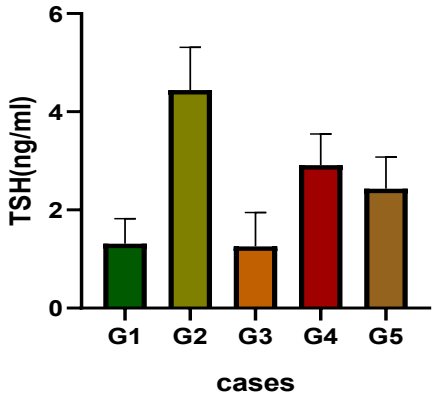
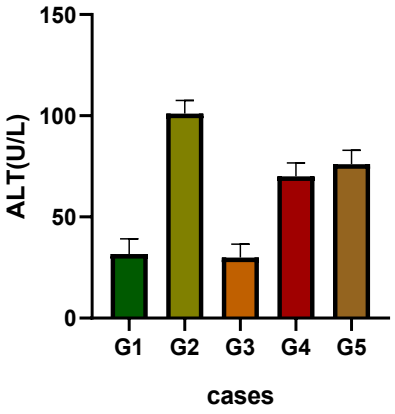


(C)

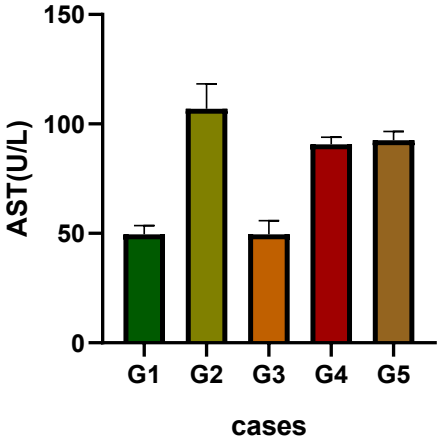
Fig. 1. Protective and therapeutic impact of NMN upon A) T4 B) T3 and C) TSH. Blocks are exposed on the base of mean ± SD. Dissimilar colures on blocks illustrating significant disparity. (G1: Control , G2: Paraquat , G3: NMN , G4: Protective, G5: Therapeutics)

Impact of NMN on Liver Function Tests

Paraquat supplementation caused a considerable ($p < 0.001$) lessening in the level of total protein with a considerable elevation in the Total bilirubin and liver enzymes AST, ALT levels while NMN administration considerably ($p < 0.001$) increase total protein level and caused a significant decrease in total protein and liver enzymes. Figure 2 (A,B,C &D).



(A)



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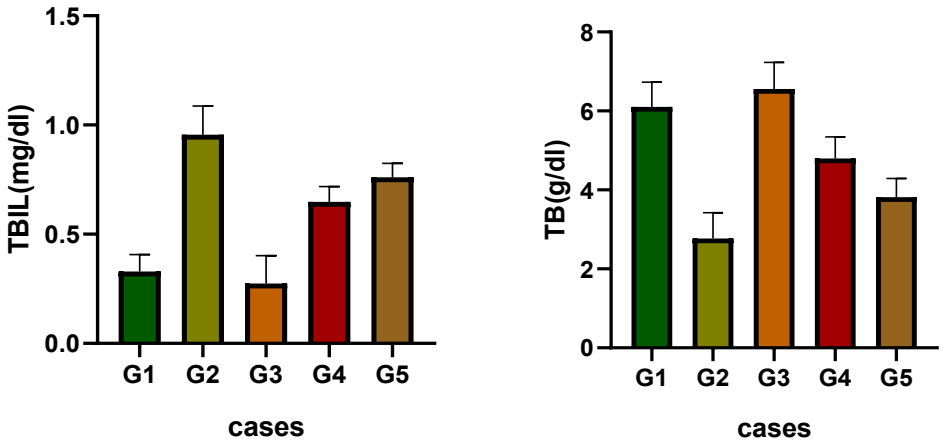
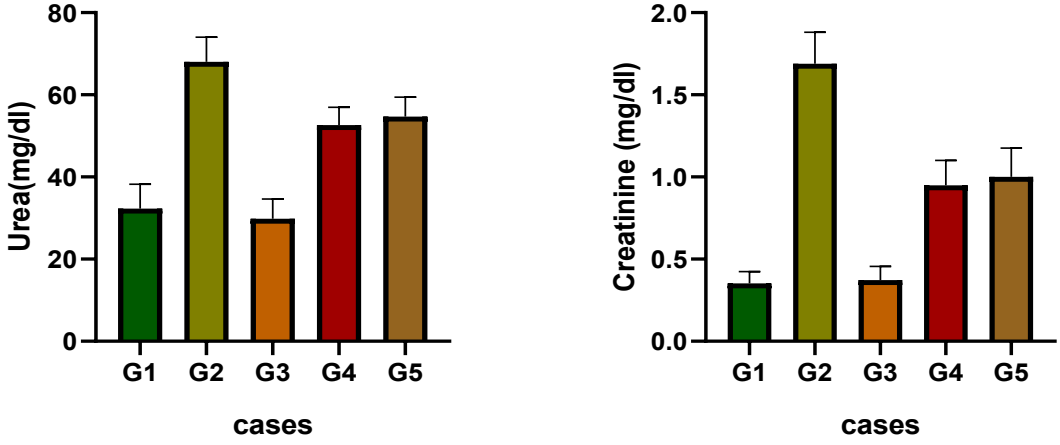


(C) (D)

Fig. 2. Protective and therapeutic impact of NMN upon A) ALT B) AST C) Total bilirubin and D) Total protein. Blocks are exposed on the bae of mean ± SD. Dissimilar colures on blocks illustrating significant disparity. (G1: Control , G2: Paraquat , G3: NMN , G4: Protective, G5: Therapeutics)

Impact of NMN on Kidney Function Tests

Paraquat supplementation prompted a considerable ($p < 0.001$) elevation in urea and creatinine levels while NMN administration considerably ($p < 0.001$) decrease total their levels. Figure 3 (A &B).



(A) (B)

Fig. 3. Protective and therapeutic impact of NMN upon A) Urea B) Creatinine Blocks are exposed on the blocks of mean ± SD. Dissimilar colures on bars illustrating significant disparity. (G1: Control , G2: Paraquat , G3: NMN , G4: Protective, G5: Therapeutics)

Impact of NMN on antioxidant Enzymes

Paraquat supplementation prompted a considerable ($p < 0.001$) reducing in SOD and GPx levels while NMN administration considerably ($p < 0.001$) decrease total their levels. Figure 4 (A &B).

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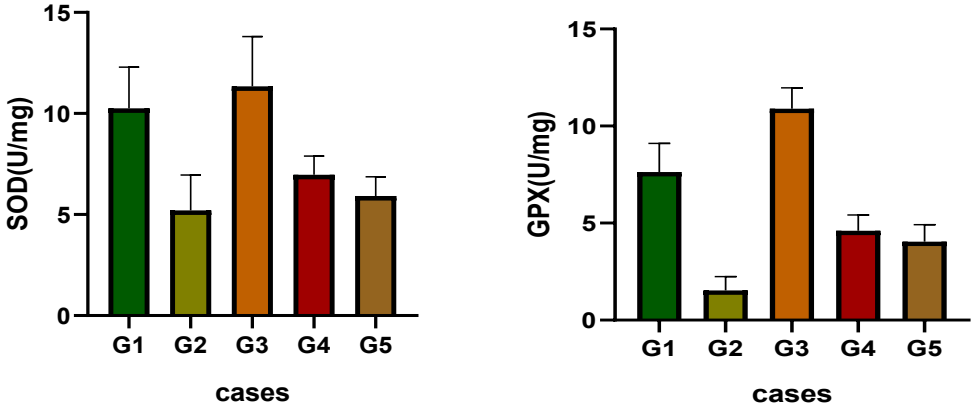

(A) (B)

Fig. 4. Protective and therapeutic impact of NMN upon A) SOD B) GPx Blocks are exposed on the base of mean ± SD. Dissimilar colures on blocks illustrating significant disparity. (G1: Control , G2: Paraquat , G3: NMN , G4: Protective, G5: Therapeutics)

Discussion:

Nicotinamide mononucleotide NMN, a well-well-known NAD+ precursor, has gathered significant attention due to its ability to raise NAD+ levels and prompt encouraging health aids in preclinical models [19]. Nicotinamide mononucleotide NMN is a precursor material for vitamin B3, and can be altered into NAD+ which is a vital pyridine material for cellular bioenergetics, metabolism, DNA damage repair, epigenetic alterations, cellular autophagy, as well as aging [20]. NAD+ is a central coenzyme essential for over 500 oxidoreductases, administration of NAD+ greatly improves liver, kidney, cardiac and skeletal muscle functions [21,22]. Enlargement of NAD+ enable a Convincing ATP creation through many mechanisms including fatty acid oxidation, sirtuins activator, mitochondrial fission inhibitor and increase cell signaling systems which defend oxidative metabolism through serving as PARP1 as well as CD38 inhibitor [23, 24,25, 26].

The results of the current study showed that administering NMN to rats significantly reduced the effect of the paraquat on the kidney in both the protective and therapeutic groups by lowering both urea and creatinine levels in the plasma. As kidney tubular cells are very metabolically active, they are very sense toward NAD+ reduction as well as deficiency of ATP formation, increasing of NAD+ concentrations through supplementation of its precursors, including NMN has been showed a useful role against fibrosis as well as age-linked illnesses [27]. NAD+ contributes in DNA repair by acting as a substrate used for poly-ADP-ribose polymerase as well as sirtuins, in addition NAD+ also provide adenylate to DNA ligase IV, a chief enzyme used for repairing the breaking in the DNA double-strand [28]. NMN might have significant protective roles against DNA injury and improving the long-standing profibrotic reaction resulting from acute kidney injury, NMN obviously weakened tubular oldness and prevented the enlargement of extracellular matrix mechanisms and inflammation [29]. Many researches have submitted the defensive influence of NMN for kidney in different causes of experimental acute kidney injury simulation [30], other researches have showed the roles of salvage path activation via the supplementation of NMN, Nam as well as NR, these studies have attentive on the stimulation of sirtuins brought by enlarged NAD+ concentrations, sirtuins are DNA deacetylating enzymes which control gene expression, metabolism, DNA repair, reactive

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oxygen species as well as inflammation in different organs [31, 32]. The supplementation of NMN improved kidney injury, both functionally as well as histologically, in the murine adriamycin induced focal glomerulosclerosis in mice model by maintaining the NAD+ levels in the mice kidneys and changed the expression levels of Sirt1, Nampt, as well as Nmnat1 [33].

The chief mechanism of paraquat poisoning due to its capacity to undertake intracellular redox cycling, paraquat receives electrons from electron givers like NADPH- as well as FAD-dependent enzymes, liberating a paraquat free radical that consequently transmissions the electron to molecular oxygen, generating superoxide anion [34]. In the current study, treating the rats with the paraquat led to a significant increase in liver enzyme levels including AST, ALT, significant increase in the total bilirubin, and it caused a notable decrease in total protein levels. Paraquat induced liver injury and caused centrilobular cholestasis, apoptosis in liver cells and macrophage infiltration in the portal spaces, in addition to the enlargement of the portal tracts owing to an enlargement in collagen stroma [35]. The liver is the chief organ for the transformation of xenobiotics and pesticides detoxification, it is involved in metabolism and has a greater ability for creating ROS, so it is more sense to toxins effect. Antioxidants could inhibit health dangerous resultant from the contact to pesticides [36]. Nicotinamide mononucleotide NMN improved hepatic insulin sensitivity and enhanced gene expression associated with oxidative stress via SIRT1 initiation [37]. NMN might repair damaged DNA in old mice livers [23]. NMN might conserve the length of the telomere, reduce the DNA injury and reduce fibrosis in the liver of telomerase enzyme knockout mice [38]. Via mouse models for liver fibrosis, a study demonstrated that NMN declined oxidation- mediated 15-PGDH degradation to induce prostaglandin E2 degradation and inhibit hepatic stellate cell HSC activation, HSC is the main source of extracellular matrix ECM that control liver fibrosis activation [39]. NMN supplementation improve liver development by stimulating transcription route in the nucleus, via triggering SIRT1-JAK1-STAT3 path in immune-deficient mice [17]. Paraquat treatment caused a remarkable lessening in both SOD and GPx activity, antioxidant enzymes act as a main protection line against damaging free radicals, SOD alters superoxide ions into hydrogen peroxide, while GPx aids in reducing hydrogen peroxide and lipid peroxide levels by reducing free radical formation, supplementation with NMN restored the levels of these antioxidant.

In the current study paraquat treatment significantly reduced thyroxin and thyronin levels while NMN treatment significantly increase their levels. NMN may recover thyroid function chiefly by raising cellular NAD+ levels, which improves mitochondrial energy creation, lowers oxidative stress, and reduces inflammation inside the gland. Phosphorylation of NAD+ into NADP might increase the protection mechanisms counter to oxidant stress via inducing the lessening of glutathione as well as via the vasodilator nitric oxide [40,41]. Enlarged NAD+ concentrations have been showed to stimulate sirtuin, a set of NAD-taking enzymes, and to decrease inflammation plus reactive oxygen species [24]. NMN can improve age-associated thyroid decline by enhancing cellular energy metabolism and supporting all thyroid hormone metabolism. Oral NMN administration definitely influences energy metabolism and protein synthesis [42]. NMN supplementation prevented the aging-related rise of acetylation on proteins adaptable fatty acid oxidation, the Krebs cycle and valine degradation [43]. Enhancing NAD+ levels may help the thyroid's capacity to control inflammation in autoimmune disorders such as Hashimoto's disease. NMN inhibits inflammatory responses via triggering IDO-kynurenine-AhR path, suggesting that the supplementation of NMN in early-stage immuno-activation may led to an adverse health influence [44]. In addition, NMN aids repair injured mitochondria and helps mitochondrial biogenesis, which is critical for the high-energy demands of the thyroid gland.

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Conclusion:

The conclusions of the current study exposed that paraquat administration resulted in an increasing in the liver enzymes activity, total bilirubin, urea and creatinine, decreased the antioxidant enzymes, total protein Indicates deterioration of liver and kidney function. Also paraquat administration led to hypothyroidism (decreasing T4 and T3 levels and elevating TSH) Nevertheless, NMN treatment improved all these paraquat induced adverse disorders in liver, kidney and thyroid gland on account of its boosting NAD+ levels and anti- antioxidant capacity. As a result, it may be established that NMN might be used to treat liver, kidney plus thyroid gland damage. These conclusions expand our understanding of NMN's as a potential therapeutic agent and open the way for unique strategies in controlling metabolic disorders.

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