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Hepatic Fibrosis-Induced by Sodium Nitrate in Rats Fed on Moringa Oleifera Leaves

Taghreed Fouad[1], El-Sayed Abd El-hady[2], Ayman Hyder[1] and Kadry El-Bakry[*1]

[1]Department of Zoology, Faculty of Science, Damietta University, 34517 New Damietta City, Egypt.
[2]Department of Zoology, Faculty of Science, Mansura University, 35516 Mansoura City, Egypt.

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[*]Corresponding author's E-mail: kadrym@du.edu.eg

Abstract

Liver fibrosis is a pathological process that can progress to liver failure if left untreated. *Moringa oleifera* (MO) is known as a 'miracle tree' or 'tree of life' due to its therapeutic and nutritional benefits. MO exhibits powerful antioxidant properties, which may reduce fibrosis expression. The aim of this study is to determine the effect of MO leaf powder (MOLP) against hepatic fibrosis induced by sodium nitrate ($NaNO_3$). Five groups of rats were put together. G I: rats fed on normal diet for 6 weeks; G II: rats fed on 10% of MOLP mixed with diet; G III: rats received 500 mg/L of $NaNO_3$ daily in drinking water for 6 weeks; G IV: rats received $NaNO_3$ for 3 weeks in drinking water then fed MOLP 10% mixed with diet; and G V: rats fed on 10% MOLP mixed with diet and $NaNO_3$ in drinking water for 6 weeks at the same time. The results showed that TGF-β1 and α-SMA expression, collagen deposition, apoptosis marker (Caspase-3), and DNA fragmentation percentage in the liver were increased significantly in $NaNO_3$ group. On the other hand, these parameters were significantly decreased with MOLP treatment. In conclusion, MOLP may protect and treat hepatic fibrosis induced by $NaNO_3$.

Keywords: Moringa oleifera, Sodium nitrate, Fibrosis, Apoptosis.

Introduction

Liver fibrosis is a common pathological process that can progress to liver failure if left untreated **(Qian et al., 2015)** which results in the synthesis of collagen and various cytokines, including TGF-β, a strong inducer of extracellular matrix (ECM) synthesis and fibrosis expansion **(Heeba and Mahmoud, 2014; Bona et al., 2015).** TGF-β1 has been found to have cytostatic and apoptotic effects in hepatocytes **(Caballero-Díaz et al., 2020).** Effector caspases carry out apoptosis. Caspases are intracellular enzymes that cause controlled cell death by destroying essential proteins. Caspase-3 is particularly important because it promotes typical apoptotic properties, including DNA fragmentation and cell death **(Musumeci et al., 2013; Giunta et al., 2015).**

Nitrate (NO_3) is a common pollutant in

drinking water **(Kalteh et al., 2022).** NO_3 is an oxidation product that can easily produce nitric oxide (NO). NO combined with superoxide, to generate peroxynitrite, a highly reactive radical **(Chow and Hong, 2002).** Peroxynitrite causes lipids, proteins, and nucleic acid bases damage resulting in apoptosis and cell cycle arrest **(Chaâbane et al., 2017).** Also, nitrate can be reduced to nitrite and so induce reactive species, causing hematological, metabolic alterations and injury to the liver **(González Delgado et al., 2018)**. Teratogenesis and mutagenesis are health problems caused by elevated levels of NO_3 in drinking water **(Wu et al., 2018; Kom et al., 2022).** Also, DNA damage can be induced which results in malignant lesions **(Gurjao et al., 2021; Georgeson et al., 2022).**

Moringa oleifera (MO) is extensively grown in sub-tropical and tropical climates and is regarded as the miracle tree or tree of life because of its tremendous therapeutic and nutritional benefits **(Pareek et al., 2023).** MO exhibited powerful antioxidant properties by preventing the induction of reactive oxygen and nitrogen species **(Muhammed et al., 2020).** Bioactive polyphenols found in MO extracts combat reactive oxygen species (ROS) and shield the body from oxidative damage **(Oguntibeju et al., 2020).** Additionally, flavonoids like rutin, myricetin catechin, kaempferol, genistein, luteolin isoquercetin, quercetin, astragalin, and apigenin **(Dhakad et al., 2019)** have anti-ROS properties. MO leaf extract reduced hepatic TGF-β expression and α-SMA expression in rats **(Hamza, 2010; Aly et al., 2020).**

The present study aims to detect hepatic fibrosis induced by $NaNO_3$ and test the therapeutic and protective effects of *Moringa oleifera* leaves.

Material and Methods

Animals

Twenty five adult male albino rats, each weighing between 80 and 100 grams, were purchased from the Egyptian VACSERA Organization in Helwan, Egypt. They were housed in the animal house of Zoology Department, Mansoura University, Mansoura, Egypt in stainless steel cages with a 12-hour light/dark cycle and a temperature of 25±2 °C. Water and a rodent diet were allowed *ad libitum*. Animal experiments procedures have been approved by Mansoura University in compliance with EU Directive 2010/EU and the recommendations set forth by the National Research Council **(NRC, 2011).**

Experiment design

Rats were acclimatized for a week and divided randomly into 5 groups (five / each group) as follow:

- **G I:** fed on normal diet for six weeks.
- **G II:** fed on MOLP (10%) mixed with diet daily for six weeks **(Stephen Adeyemi et al., 2017)**,
- **G III:** drink 500 mg/L of $NaNO_3$ every day for six weeks in drinking water **(Anwar and Mohamed, 2015)**.
- **G IV:** drink $NaNO_3$ (500 mg/L) in drinking water for three weeks, then, fed on MOLP (10%) mixed with diet daily for another three weeks.
- **G V:** fed on diet mixed with MOLP (10%) and drink $NaNO_3$ in water at the same time for six weeks.

Preparing powder from Moringa oleifera leaf

Fresh leaves from MO trees grown on a private farm in Mansoura City, Egypt, were collected. The leaves were examined by a scientist at the Department of Botany at Mansura University. MO leaves are stripped off, washed with tap water, drained, and then spread out in a thin layer with a cotton cloth in a well-ventilated room and allowed to dry for five days in the shade. After being shade-dried, leaves were crushed using a blender, put through a 2-sieve, and kept in the refrigerator at - 4°C, to be used at a later time.

Samples preparation

A known weight of each liver tissue was cut and stored at -80°C for biochemical analysis. The other part of liver tissue was fixed in (10%) formalin solution for histological examination.

Hepatic fibrosis marker

The concentrations of hepatic transforming growth factor beta-1 (TGF-β1), alpha smooth muscle actin (α-SMA) were determined by ELISA kits in accordance with

instructions provided by the manufacturer of Cloud-Clone Corp., (USA) and Novus Biologicals Company (USA) respectively.

Collagen fibers examination

Livers from each rat were removed and sliced into tiny pieces, then fixed in neutral formalin (10%). Subsequently, for 30 minutes, tissues underwent dehydration in 100% ethyl alcohol and an ascending series of ethyl alcohols (70, 80, 90, and 95%), cleared in xylene for 20 minutes. Tissues were embedded in Paraffin wax. The prepared blocks were cut using microtome in a thickness of 4-5 µm. Collagen fibers were identified by staining sections with Masson's trichrome **(Foot, 1993).**

Hepatic apoptosis marker (Caspase-3)

Caspase-3 concentration in liver was determined by ELISA kits in accordance with instructions provided by the manufacturer of BioVesion Company (Milpitas, CA, USA).

Hepatic DNA fragmentation with flow cytometry

The method was done according to the manufacturer's instruction of Apo-Direct™ kit (Cat. NO. 51-6536) purchased from Pharmingen ™ Company (San Diego, CA, USA). Briefly, after two phosphate-buffered saline (PBS) washes, frozen liver tissues were centrifuged at 300 x g and re-suspended in 3.7% (w/v) paraformaldehyde (PFA) prepared in PBS. The supernatant was disposed of after two washes in PBS, and the liver pellet was mixed with 1 ml of PFA. After depletion of PFA, samples were re-suspended in ice-cold ethanol (70% v/v) batched and kept in -20 °C until analysis.

Staining protocol

Samples were twice rinsed with "wash buffer" to eliminate any remaining ethanol. Following the manufacturer's instructions, after removing the buffer, freshly prepared staining solution (50 µl) was added to each tube. This solution contains TdT enzyme, distilled water, reaction buffer, and fluorescein isothiocyanate-tagged deoxyuridine triphosphate nucleotides (FITC-dUTP). Each specimen was incubated in the dark for 60 minutes. Rinse buffer (1ml) was added and 2 centrifugations were used to eliminate excess stain. Finally, samples were re-suspended and incubated (30 min) in PI/RNase solution (0.5 ml) for flow cytometric analysis **(Agarwal et al., 2016).**

Statistical analysis

Data analysis was performed using IBM SPSS Statistics software, version 20, with a one-way ANOVA test and post-comparison Tukey test to determine differences between groups. Statistical significance was considered at $p \leq 0.05$. Results are presented as mean ± SE.

Results

Hepatic fibrosis markers

After receiving $NaNO_3$, TGF-β1 and α-SMA expression levels were elevated significantly ($P \leq 0.05$) as compared to the control group **(Fig. 1)**. On the other hand, treatment with MOLP with or after drinking of sodium nitrate induced significant decrease in TGF-β1 and α-SMA expression in hepatic tissue when compared to those of the $NaNO_3$ treated group ($P \leq 0.05$).

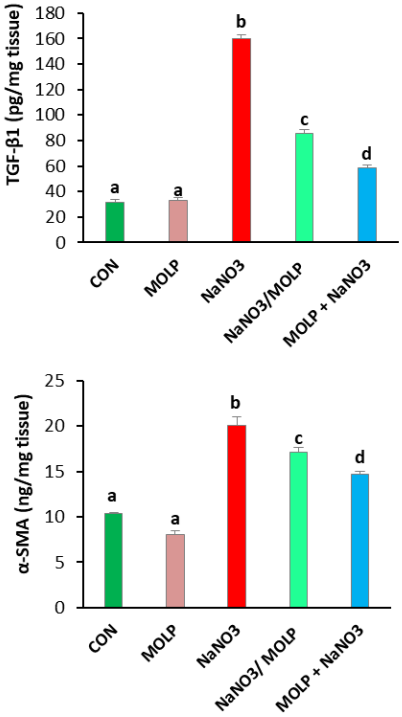

Fig.1. *Moringa oleifera* leaves impact on hepatic fibrosis markers (TGF-β1 and α-SMA) in rats drinking $NaNO_3$. The mean ± SE (n=5) was used to express data, after being analyzed by one-way ANOVA, then Tukey's test. Different letters (a, b, c, d) denote significant differences at $P \leq 0.05$

Collagen fibers examination

Figure 2 showed high intensity of collagen fibers surrounding the central veins and portal tract after drinking $NaNO_3$ indicating severe hepatic fibrosis. However, after treatment of rats drinking $NaNO_3$ with MOLP displayed slight collagen fibers deposited around the central vein and blood sinusoid. As well as moderate collagen fibers were observed around the central vein of treatment of rats drinking $NaNO_3$ with MOLP at the same time.

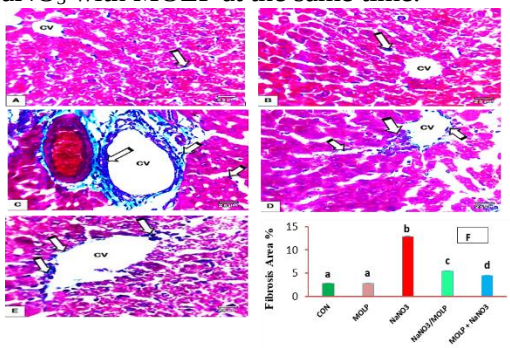

Fig.2. *Moringa oleifera* leaves impact on collagen fibers in liver stained with Masson's trichrome, with magnification x 400, where (A: control group, B: MOLP group, C: $NaNO_3$ group, D: $NaNO_3$/MOLP group, E: MOLP + $NaNO_3$), and F: percentage of fibrosis areas in rats' livers. The mean ± SE (n=5) was used to express data, after analyzed by one-way ANOVA, then Tukey's test. Different letters (a, b, c, d) denote significant differences at $P \leq 0.05$.

Hepatic apoptosis

As shown in **Fig. 3** $NaNO_3$ drinking resulted in significant increase in the expression of caspase-3 ($P \leq 0.05$). After treatment of rats drinking $NaNO_3$ with MOLP causes significant reduction in caspase-3 expression in hepatic tissue.

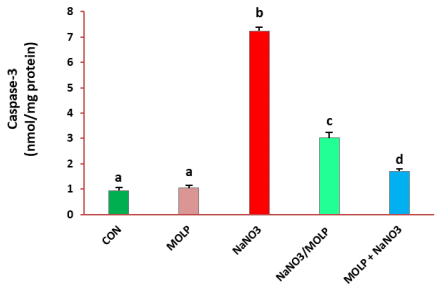

Fig.3. The hepatic apoptotic marker (caspase-3) in rats drinks $NaNO_3$ and treated with MOLP. The data were presented as mean ± SE (n=5), analyzed by one way ANOVA, and followed by Tukey's test. Different letters (a, b, c, d) are significantly different from each other at $P \leq 0.05$.

Hepatic DNA fragmentation

As shown in **Fig. 4** $NaNO_3$ drinking resulted in significant increase the expression of hepatic DNA fragmentation ($P \leq 0.05$). After treatment of rats drinking $NaNO_3$ with MOLP causes significant reduction in hepatic DNA fragmentation in hepatic tissue.

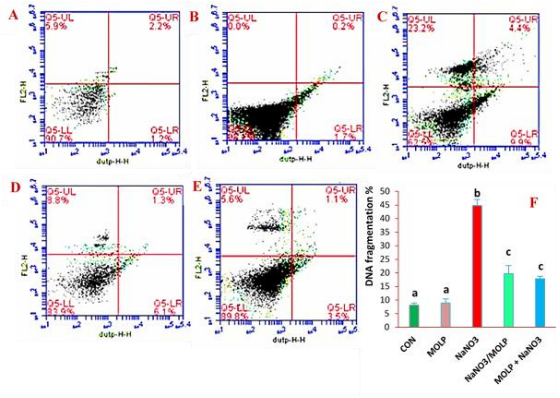

Fig.4. *Moringa oleifera* leaves reduce hepatic DNA fragmentation in male rats treated with $NaNO_3$. Flow cytometric dot plot quadrant analysis of liver cell suspension from male rat stained with dUTP/PI stains. Where A: Control group; B: MOLP, C: $NaNO_3$ group; D: $NaNO_3$ /MOLP group; E: MOLP + $NaNO_3$ group. The data were presented as mean ± SE (n=4) and statistically analyzed by the Tukey test after one-way ANOVA test. Values with different letters are significant at $P \leq 0.05$

Discussion

Nitrates are precursors of highly reactive molecules like peroxynitrite, which resulting in oxidative stress and damage to numerous biological molecules like lipids, nucleic acids and proteins, which result in disruption of cell cycle and apoptosis **(Bouaziz-Ketata et al., 2014).**

The present study demonstrated that $NaNO_3$ significantly elevate hepatic fibrosis markers such as TGF-β1 and α-SMA expression as confirmed by Masson' trichrome staining which revealed intense fibrosis characterized by deposition of thick collagen fibers in the liver. $NaNO_3$-induced liver fibrosis may be a result of the oxidative stress in hepatic tissue which results in tissue inflammation due to production of inflammatory cytokines such as TGF-β1 and α-SMA expression a mechanism reported by **Kattaia et al. (2017)** and **Elzoheiry et al. (2022).**

Damage to liver parenchyma cells from oxidative and nitrosative stresses results in alterations in the extracellular matrix (ECM). These changes stimulate non-parenchyma cells like hepatic stellate cells (HSCs) and Kupffer cells and draw immunological and inflammatory cells to the site of damage **(Dutta et al., 2018)**, then undergo morphologic changes and develop into myofibroblasts, which express the primary α-SMA and ECM components and promote liver fibrosis. This agrees with our findings. **Hong et al. (2013)** found that α-SMA is crucial to the pathogenesis of fibrotic scars. Additionally, lipid peroxidation has a significant impact on collagen synthesis and expression **(Li et al., 2015)** and is a potent mediator of liver fibrosis.

From the results of the present study, treatment of rats drinking sodium nitrate with MOLP (10 %) reduces liver fibrosis induced by $NaNO_3$, as determined by the reduction in TGF-β1and α-SMA expressions and collagen fiber deposition in liver tissue. This effect may be due to the reduction of oxidative stress by flavonoids, which are well-known as effective anti-fibrotic compounds, are likely what gave MOLP its anti-fibrotic effect and reduced collagen fiber deposition **(Wu et al., 2018)** and so the levels of TGF-β1 and α-SMA expression, and prevents HSCs activation as found in the present study.

Besides the fibrotic effect of $NaNO_3$ drinking causes liver tissue to undergo cell death or apoptosis, as shown by increasing both caspase-3 expression and the percentage of hepatic DNA fragmentation in the liver. Oxidative stress, which raises mitochondrial permeability and causes the release of pro-apoptotic proteins and activation of caspase-3, may be the cause of increased hepatic caspase-3 activity **(Kowaltowski et al., 2021).** DNA is indirectly affected by caspases-3 activation during irreversible apoptosis **(Gargioni et al. 2006).** Additionally, lipid peroxidation generates a hydroxyl radical, which attaches the double-bond structure of DNA and/or removes its hydrogen atoms. This results in single and double-strand breaks and changes in the bases purine and pyrimidine and degrades deoxyribose sugars **(Cooke et al., 2003).**

Treatment of rats drinking sodium nitrate with MOLP results in a reduction in hepatic caspase-3 and DNA fragmentation. This suggests that MOLP may have an anti-apoptotic function as previously found by **Albasher et al. (2020)** and **Abou El-Naga et al. (2022).** Quercetin, a flavonoid found in MO leaves, is a potent antioxidant that supports cells involved in reproduction, growth, and cell death that alter signal transmission **(Singh et al., 2006).** Reduced DNA fragmentation could be due to phenolics and flavonoids **(Abdel Fattah et al., 2022)**; polyphenols are potent antioxidants that chelate the redox-active transition of metal ions to shield DNA; or it could be because MO leaves can suppress free radicals **(Hamza, 2010).**

Conclusion

It can be concluded that MOLP treatment can protect the liver of rats from fibrosis and cell death induced by $NaNO_3$ due to its content of antioxidants such as flavonoids and polyphenol compounds that act as ROS scavengers.

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الملخص العربي

عنوان البحث: دراسات بيوكيميائية على التليف الكبدي المستحث بنترات الصوديوم في الجرذان التي تتغذى على أوراق المورينجا أوليفيرا

تغريد فؤاد[١]، السيد عبد الهادي[٢]، أيمن حيدر[١]، قدري البكري*[١]

[١]قسم علم الحيوان– كلية العلوم – جامعة دمياط – مصر.
[١]قسم علم الحيوان – كلية العلوم – جامعة المنصورة– مصر.

تليف الكبد هو حالة مرضية يمكن أن تتطور إلى الفشل الكبدي إذا تُركت دون علاج. يُعرف نبات المورينجا أوليفيرا (MO) بإسم "الشجرة المعجزة" أو "شجرة الحياة" وذلك لفوائدها العلاجية والغذائية. لدى أوراق المورينجا خصائص مضادة للأكسدة، مما قد يقلل من التليف الكبدي .
الهدف من الدراسة الحالية هو بيان تأثير مسحوق أوراق المورينجا أوليفيرا (MOLP) على التليف الكبدي الناتج عن نترات الصوديوم (NaNO3) في مياه الشرب. تم تجميع خمس مجموعات من ذكور الجرذان معا. المجموعة الأولى: تم تغذية الجرذان بالطعام القياسي لمدة ستة أسابيع؛ المجموعة الثانية: تم تغذية الجرذان بمسحوق أوراق المورينجا (MOLP) بنسبة ١٠ % ممزوجة بالطعام القياسي لمدة ستة أسابيع؛ المجموعة الثالثة: تلقت الجرذان ٥٠٠ مجم/لتر من نترات الصوديوم (NaNO3) يوميا لمدة ستة أسابيع في مياة الشرب؛ المجموعة الرابعة: تلقت الجرذان نترات الصوديوم (NaNO3) في مياه الشرب لمدة ثلاثة أسابيع ثم تم تغذيتها بـ ١٠% بمسحوق أوراق المورينجا لمدة ثلاثة أسابيع أخرى؛ المجموعة الخامسة: تم تغذيت الجرذان ١٠% من مسحوق أوراق المورينجا (MOLP) ممزوجة بطعام الجرذان القياسي بالإضافة إلى نترات الصوديوم (NaNO3) في مياه الشرب لمدة ستة أسابيع. أظهرت النتائج أن التعبيرعن TGF-β1 و SMA -αو ترسب الياف الكولاجين، و دلالة موت الخلايا المبرمج و نسبة تكسير الحمض النووي في الكبد قد ارتفعت بشكل معنوي في مجموعة نترات الصوديوم (NaNO3). من ناحية أخرى انخفضت هذه الدلالات بشكل معنوي نتيجة العلاج بمسحوق أوراق المورينجا أوليفيرا (MOLP). تشير هذه النتائج أن مسحوق أوراق المورينجا (MOLP) قد يقي و يعالج التليف الكبدي الناجم عن نترات الصوديوم (NaNO3).