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Research Paper

Green Synthesis of Manganese Oxide Nanoparticles Using Basil Extract for Biocompatibility and Therapeutic Targeting of Metribuzin-poisoned Heart and Lung Tissues in Wistar Rats

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ABSTRACT

Introduction: Manganese oxide nanoparticles (MnO NPs) have garnered interest for use in a variety of fields, such as biomedical applications, including cancer theranostics and drug delivery. This work aimed to investigate the potential therapeutic and preventive benefits of green-synthesized MnO NPs made from basil extract against metribuzin-induced oxidative stress, metabolic toxicity, inflammation, and histological changes in the lungs and heart.

Materials & Methods: The green synthesis of MnO NPs using basil extract was performed. The shape and size distribution of the MnO NPs were analyzed using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Eighteen male albino Wistar rats were divided into three groups (n=6), which consisted of a control group, a metribuzin-treated group, and a MnO NPs-treated group. The evaluation of the oxidative stress status by measuring the levels of superoxide dismutase (SOD), glutathione peroxidase (GPx), Glutathione S-transferase (GSTs), catalase (CAT), glutathione (GSH), and malondialdehyde (MDA) in the lungs and heart tissues. Additionally, the tissue histology of the organs was examined, and various biochemical parameters (aminotransferase [GOT], lactate dehydrogenase [LDH], and creatine phosphokinase [CPK]) and inflammation markers (white blood cells [WBC], lymphocytes [lymph], Mid-sized cells [MID], and granulocytes [Gran]). were estimated. The green synthesis of MnO NPs was indicated by the gradual shift in color from golden yellow to dark brown. The morphological characteristics and particle size distribution of the MnO NPs were identified using TEM and SEM.

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Results: The analyses revealed that the MnO NPs were uniformly spherical in shape, with an average particle size of 6.52±0.88 nm. Results of the in vivo rats study showed that treatment with metribuzin induced an increase in organs weight, oxidative stress, biochemical toxicity, inflammation, and histological changes in the lungs and heart, as well as a significant ameliorative effect of MnO NPs against the toxic effects induced by metribuzin by reversing all of the aforementioned parameters.

Conclusion: In conclusion, the results of the in vivo investigation showed that rats given the metribuzin herbicide suffered from organ weight gain, oxidative stress, biochemical toxicity, inflammation, and histological alterations in their lungs and heart. Additionally, MnO NPs showed effective therapeutic and preventive actions against lung and heart damage caused by metribuzin. Basil extract's phytochemical components enhance MnO NP biocompatibility, reduce toxicity, and provide antioxidant and anti-inflammatory properties, making them safe and therapeutic for biomedical applications.

1. Introduction

Metribuzin, identified as a 4-amino-6-(1,1-dimethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one compound categorized as an asymmetric triazine, was officially approved for use in the United States in 1973 specifically for herbicidal utilization [1]. Metribuzin is frequently utilized in the cultivation of potatoes, soybeans, peas, tomatoes, and lentils [2]. Adverse impacts on humans, fish, and domestic animals have been recorded in relation to its usage [3]. Metribuzin, a xenobiotic, exemplifies the mechanisms of toxicity common to the majority of xenobiotics, which are chemical compounds that are foreign to the body and include herbicides and environmental pollutants. These mechanisms include disturbance of the body's overall antioxidant capacity and stimulation of free radical production-induced lipid peroxidation [4].

Over the last several years, manganese oxide nanoparticles (MnO NPs) have garnered interest for use in a variety of fields, such as water treatment, catalysis, and solar cells, as well as in biomedical applications, including biosensors and bioimaging, cancer theranostics, and drug delivery [5]. MnO are a mixed oxide substances that finds extensive application in fields such as electrochemistry, medicine, and catalysis. This is because they are affordable, environmentally benign, occur in diverse oxidation states of manganese, and are abundant in nature [6]. NPs can be created using a variety of methods, such as chemical, physical, and biological ones [7]. The green synthesis of NPs has been developed to lower costs, minimize pollution, improve the environment, and protect human health by using plant extracts instead of industrial chemical components to reduce metal ions [8]. Phytochemicals found in medicinal plants can be used to create biocompatible, affordable, and renewable green NPs [9]. The purpose of the current study was to examine the therapeutic and preventive effects of MnO NPs green synthesized using basil extract against organ weight gain, oxidative stress, biochemical toxicity, inflammation, and histological alterations caused by metribuzin exposure in the lungs and heart.

2. Materials and Methods

2.1. Plant materials collection

Professor Youssef Hallis identified the plant used in this experiment. The basil was harvested in August 2022 from the El-Oued (Guemar) region of Algeria. The basil leaves were cleaned, dried, and stored at room temperature away from direct sunlight. A mechanical grinder was then used to grind the dry leaves into a fine powder. *Ocimum basilicum* L. powder was stored at room temperature in airtight containers until the experiment started.

2.2. Aqueous extract preparation

Ten g of dried leaves were heated for two hours at 50 °C in 100 mL of distilled water to make basil aqueous extract. The extract was macerated for 24 hours at room temperature, then filtered through Whatman filter paper. Following that, it was evaporated using a rotary evaporator, and then dried in an oven.

2.3. Compounds analysis

The aqueous plant extract was subjected to a thorough examination using a standardized methodology to identify the presence of different phytochemicals.

2.4. Green synthesis of MnO NPs

MnO NPs were created using a green synthesis approach mediated by *O. basilicum* L. leaf extract, with minor modifications to the methodology of Saod et al. (2022) [10]. This procedure entailed the amalgamation of the aqueous extract

of basil with a manganese (II) chloride ($MnCl_2.4H_2O$) solution. To attain a pH of 8, sodium hydroxide (NaOH) solution was incrementally added to the mixture while maintaining continuous stirring, which facilitated the generation of small particles. The resultant solution was subsequently subjected to magnetic stirring at a temperature of 65 ˚C for a duration of 6 hours, during which a colorimetric transition from golden yellow to dark brown occurred, indicative of the successful biosynthesis of MnO NPs. Following this, the mixture was centrifuged at 5000 rpm for 20 minutes, after which the supernatant was discarded. The resulting precipitate was subjected to three washing cycles utilizing distilled water and ethanol prior to being desiccated to yield the final product.

2.5. Characterization of MnO NPs

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) analyses were conducted to evaluate the morphological characteristics and particle size distribution of the MnO NPs green-synthesized using basil extract.

2.6. Animal care and experimental design

In our investigation, 18 male Wistar rats, weighing 206±9.02 g, were used. The rats were eight weeks old when they were obtained from the Pasteur Institute in Algiers. The Faculty of Natural and Life Sciences at Echahid Hamma Lakhdar University-El Oued animal husbandry laboratory is where these animals were housed. The rats had the same living conditions, including a 12-hour light/dark photoperiod and room temperature, and were kept in plastic cages with metal mesh coverings. They were also given a standard diet and free access to food and water. Over the course of eight weeks, the experiment was conducted.

Following a two-week adaptation period, the animals were divided up into three experimental groups, each with six animals:

Group 1 (control): Healthy rats received water and were administered intraperitoneally with physiological saline solution.

Group 2 (MTZ): Rats were exposed to metribuzin and were administered intraperitoneally with physiological saline solution.

Group 3 (MnO NPs): Rats were exposed to metribuzin and were administered intraperitoneally with MnO NPs (one dose/day, 5 mg/kg).

An oral dose of metribuzin in drinking water (220 mg/kg) was used to induce intoxication for eight weeks. The rats received four weeks of treatment with MnO NPs. We injected groups 1 and 2 with physiological saline solution to subject rats to the same experimental conditions.

2.7. Sacrifice, blood sampling, and tissue collection

Following an eight-week treatment period and a 16-hour fast, the rats were sacrificed by inhaling a small amount of chloroform (94%). During the animal sacrifice process, blood samples were placed into dry tubes to obtain serum by centrifugation for 10 minutes at 3000 rpm, which was used to assess aminotransferase (GOT), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) activity, and into Ethylenediaminetetraacetic acid (EDTA) tubes for leukocyte line studies. The lungs and heart were carefully sampled, cleaned, weighed, and kept at -20 ˚C in order to prepare homogenates for the measurement of oxidative stress. In addition, the organs were preserved in 10% formaldehyde for histological examination.

2.8. Biochemical parameters and inflammation markers

The following reference codes, which correspond to commercial kits from Spinreact, were used to measure enzymatic activity of GOT, LDH, and CPK: GOT-1001161, LDH-1001260, and CPK-1001217. The hematology autoanalyzer (Sysmex) was used to measure the counts of inflammation markers (white blood cells [WBC], lymphocytes [lymph], Mid-sized cells [MID], and granulocytes [Gran]).

2.9. Tissue samples preparation and lungs and heart oxidative stress parameters

The procedure used by Derouiche et al. [2] was followed to prepare homogenates from lung and heart tissues. Following the methods of Beauchamp and Fridovich [11], Flohe and Gunzler [12], Habig et al. [13], Regoli and Principato [14], Weckbecker and Cory [15, 14] and Draper and Hadley [16], the levels of superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S-transferase (GSTs), catalase (CAT), glutathione (GSH), and malondialdehyde (MDA) were measured, respectively.

2.10. Histopathological study

Following the sacrifice of the rats, the tissues from the lungs and heart were removed and kept in a fixative solution containing 10% formaldehyde until slide preparation. The tissues were then washed with toluene, immersed in paraffin, and stained with hematoxylin and eosin (H&E)

Table 1. Bioactive compounds of *O. basilicum* L. aqueous extract

Bioactive Compounds	Basil Extract	Test
Phenols	+	Ferric chloride test
Flavonoids	+	Magnesium test
Catechic tannins	+	Ferric chloride test
Terpenes	+	Salkowki's test
Saponins	+	Froth test
Reducing sugars	+	Fehling test
Alkaloids	+	Dragendorff's test

after being dehydrated using an increasing series of ethanol. The final slides were examined under a microscope equipped with a camera, and the images captured by the camera were displayed on a computer screen.

2.11. Statistical analysis

In order to express the results as Mean±SD, the study used the student's t-test for independent samples. Minitab software, version 13.0 was used to analyze all the data, and a $P<0.05$ was used to assess statistical significance.

3. Results

3.1. Bioactive compounds analysis

Phytochemical examination revealed the presence of phenols, flavonoids, catechic tannins, terpenes, saponins, reducing sugars, and alkaloids in *O. basilicum* L. aqueous extract (Table 1).

3.2. Synthesis and characterization of MnO NPs

The change in color from golden yellow to dark brown over time indicates the green synthesis of MnO NPs using basil extract (Figure 1).

The images from the scanning and transmission electron microscopes (Figures 2A and 2B) show that the MnO NPs are uniformly spherical in shape and have homogeneous dispersion. The average particle size of MnO NPs was determined to be 6.52±0.88 nm (Figure 2C).

3.3. Relative lung and heart weight

The MTZ group showed a significant increase in relative lung and heart weights when compared to the control group, but the MnO NPs group showed a significant decrease when compared to the MTZ group (Table 2).

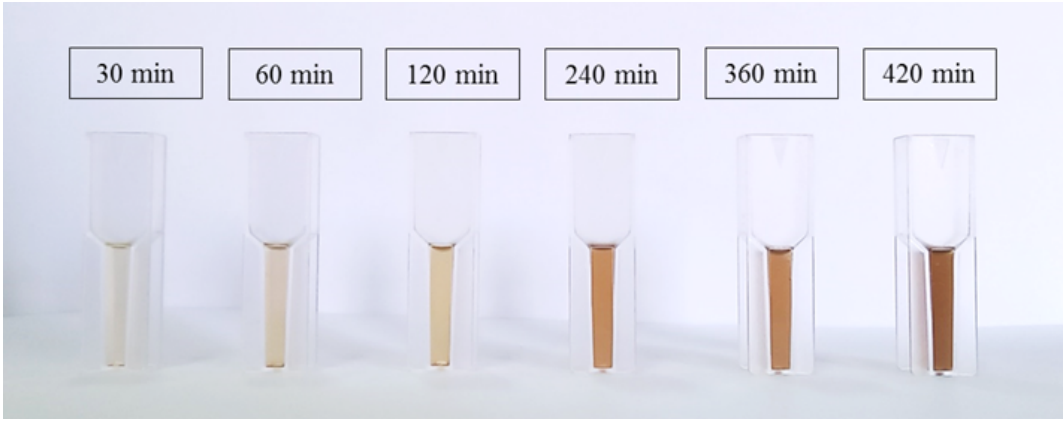

Figure 1. Green synthesis of MnO NPs using *O. basilicum* L. extract at different times

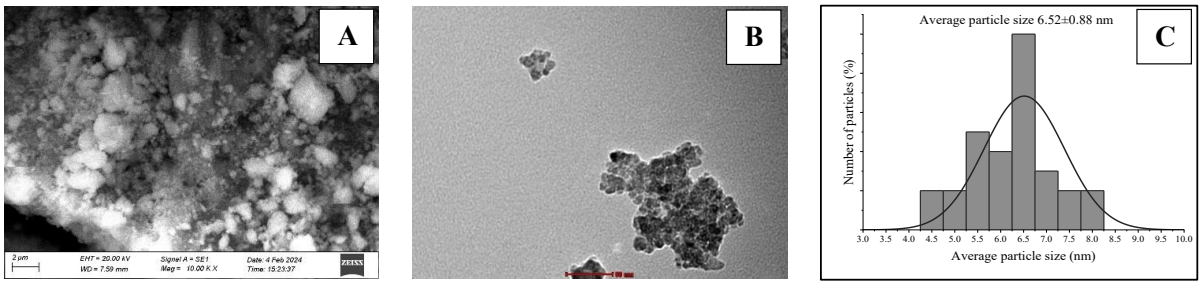

Figure 2. Morphological characteristics MnO NPs based on SEM images (A), TEM images (B), and particle diameter (nm) (C)

3.4. Biochemical parameters

The activity levels of GOT, LDH, and CPK showed a significant increase (P<0.05) in the MTZ group in comparison to the control group, and there was also a partial improvement observed in the MnO NPs group when compared with the MTZ group (Figure 3).

3.5. Inflammation markers

The levels of inflammation markers (WBC, Lymph, Mid, and Gran) in the MTZ group were found to be significantly higher than those in the control group (P<0.05). On the other hand, there was a highly significant decrease (P<0.001) in the levels of WBC, Mid, and Gran with no significant change (P>0.05) in the levels of Lymph in the MnO NPs group compared to the MTZ group (Figure 4).

3.6. Oxidative stress parameters

The results of the enzymatic activity tests indicated that there were no noticeable changes in the activity of SOD and CAT in the lungs, a significant increase in the activity of GSTs in both the lungs and heart, and a significant decrease in the activity of GPx in the lungs as well as in the activity of SOD, GPx, and CAT in the MTZ group compared to the control group. In contrast, there was only a partial improvement in the activity of these enzymes in the group treated with MnO NPs compared to the MTZ group (Figure 5).

Our research findings showed a significant decrease in the level of GSH in both the lungs (P<0.01) and heart (P<0.001) tissues of the MTZ group compared to the control group. Additionally, there was a very highly significant increase in MDA levels in both tissues (P<0.001). However, there was a remarkable improvement in GSH and MDA levels in the MnO NPs group compared to the MTZ group (Table 3).

3.7. Histopathological study

The control rats' lung sections showed typical histological features, including thin alveolar septa. In contrast, the MTZ-treated group's lung tissue exhibited several histological changes, such as thickened interalveolar septa and completely blocked air spaces. These areas displayed evidence of hemorrhage and inflammatory cell infiltration within the markedly thickened septa. The MnO NPs group demonstrated partial lung tissue recovery, with some alveoli remaining collapsed while others were expanded and ruptured. Control rat heart tissue revealed normal myofibrillar structure and cells under microscopic examination. Conversely, MTZ-treated rat heart tissues showed muscle fiber abnormalities, including hemorrhage, inflammation, necrosis, and vacuolization of cardiomyocytes. The MnO NPs group, however, exhibited considerable improvement, with heart tissue morphology more closely resembling that of the control group (Figure 6, Table 4).

Table 2. Relative lung and heart weights in control, MTZ, and MnO NPs groups (n=6)

Organ	Mean±SD		
	Control	MTZ	MnO NPs
Lungs	0.665±0.005	2.138±0.503**	0.990±0.110*/###
Heart	0.254±0.003	0.324±0.023*	0.298±0.004***/##

*P<0.05, **P<0.01, ***P<0.001: Significantly different from the control group, ##P<0.01, ###P<0.001: Significantly different from the metribuzin-exposed group.

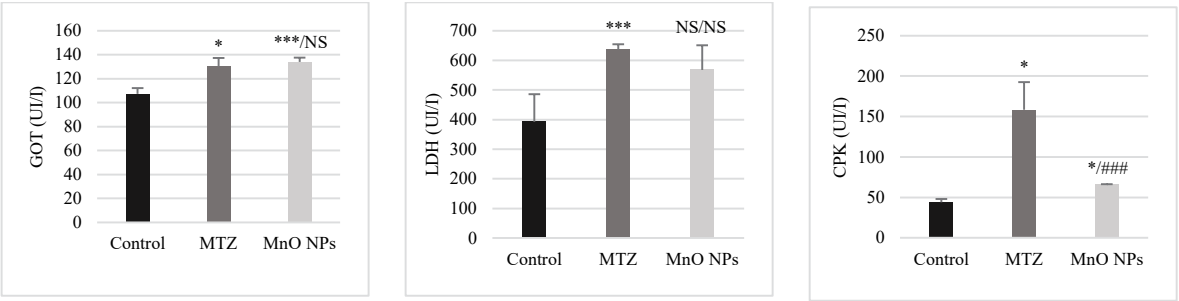

Figure 3. GOT, LDH, and CPK activity in the heart in control, MTZ, and MnO NPs groups

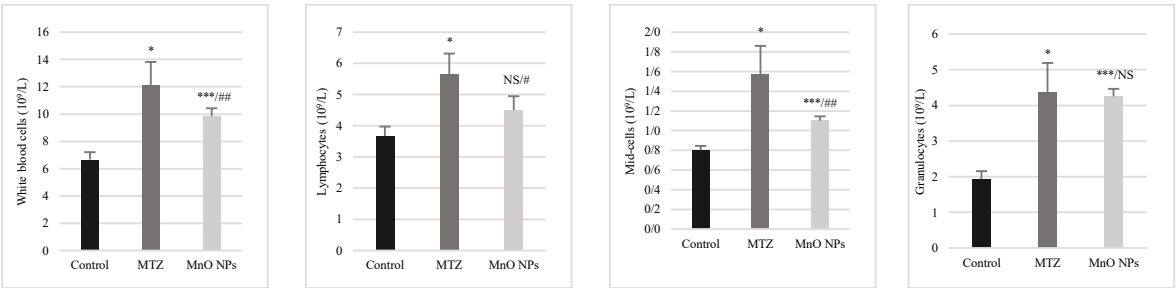

Figure 4. Inflammation marker levels in control, MTZ, and MnO NPs groups

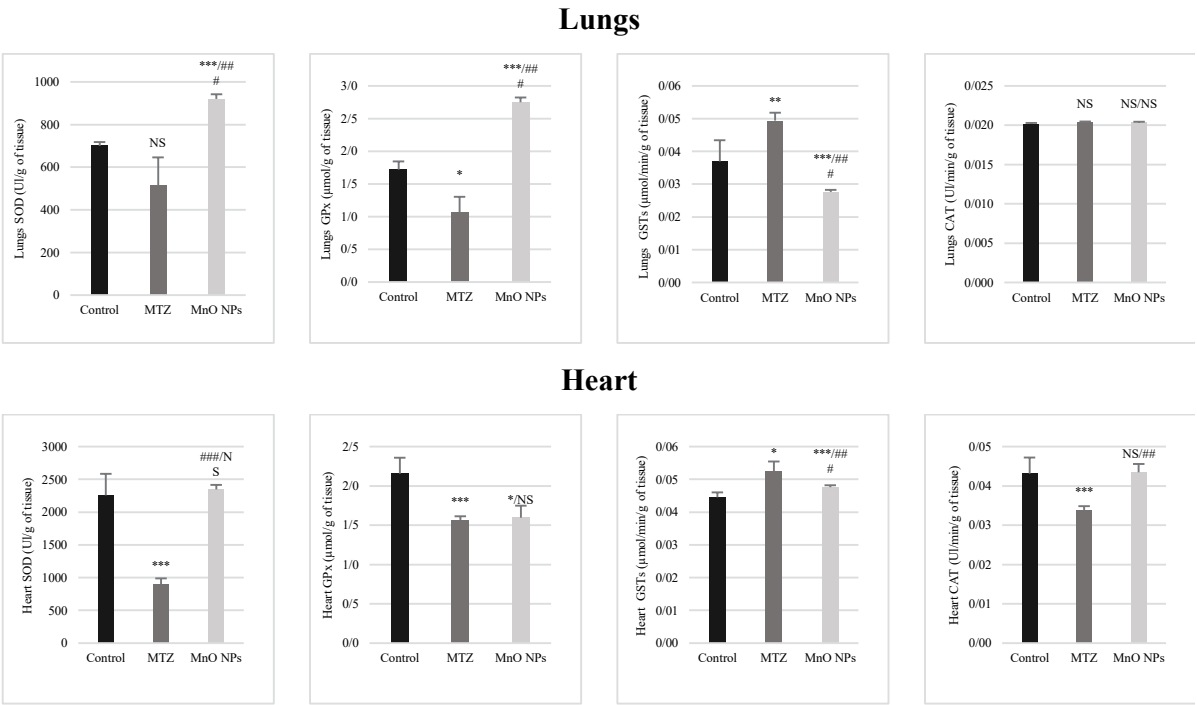

Figure 5. Enzymatic antioxidant activity in the lungs and heart in control, MTZ, and MnO NPs groups

Table 3. GSH and MDA levels in the lungs and heart in control, MTZ, and MnO NPs groups (n=6)

Organ	Parameter	Mean±SD		
		Control	MTZ	MnO NPs
Lungs	GSH levels (nmol/g of tissue)	9.377±0.606	4.402±0.897**	7.946±0.36*/###
	MDA levels (nmol/g of tissue)	8.627±0.305	10.088±0.205***	9.647±0.105***/##
Heart	GSH levels (nmol/g of tissue)	3.8713±0.0778	2.6428±0.0553***	3.058±0.311*/NS
	MDA levels (nmol/g of tissue)	17.46±1.64	25.15±0.913***	21.92±1.15*/#

NS: Not significantly different.

*P<0.05, **P<0.01, ***P<0.001: Significantly different from the control group, #P<0.05, ##P<0.01, ###P<0.001: Significantly different from the metribuzin-exposed group.

4. Discussion

This study investigated the therapeutic and preventive benefits of MnO NPs against metribuzin-induced organ weight gain, oxidative stress, biochemical toxicity, inflammation, and histological alterations in the heart and lungs.

Our study revealed the presence of phenols, flavonoids, catechic tannins, saponins, reducing sugars, alkaloids, and terpenes in the basil aqueous extract. Based on the information from Nadeem et al. [17], the current findings are consistent with their results, which indicated the presence of alkaloids, phenols, tannins, flavonoids, terpenoids, steroids, and glycosides in basil leaf aqueous extract. According to published research, the active substances in medicinal plants, called phytochemicals, are thought to have pharmacological potential.

The solution's hue changed from golden yellow to dark brown during the green synthesis of MnO NPs, indicating the biosynthesis of MnO NPs using basil extract. Initially, visual observation of color change was used to confirm the plant extract's ability to create NPs [18].

The color shift of the metal ion solution, which serves as a visual cue, is necessary for the synthesis of MnO NPs, as Kumar et al. [19]. The average particle size and shape were investigated using TEM and SEM images. The findings showed that the average size of MnO NPs was 6.52±0.88 nm and that they were spherical in shape.

Comparing the MTZ group to the control group, there was a significant increase in relative lung and heart weight; whereas, there was a significant decrease in the MnO NPs group when compared to the MTZ group. Changes in the weight of the organs, either in absolute terms or in relation to body weight, are extremely sensitive markers of early toxicity, especially under strictly regulated circumstances, like in an experiment [20]. Experimental rats that received subacute metribuzin may have experienced negative ef-

Table 4. Grading of histological alterations in the lungs and heart sections of all experimental groups

Parameters		Control	MTZ	MnO NPs
Hemorrhage	Lungs	-	++	-
	Heart	-	+++	-
Inflammation	Lungs	-	+++	-
	Heart	-	++	-
Vacuolization	Lungs	-	-	-
	Heart	-	+++	-
Necrosis	Lungs	-	-	-
	Heart	-	+++	-

Note: None (-); Moderate (+); Severe (++); Very severe (+++).

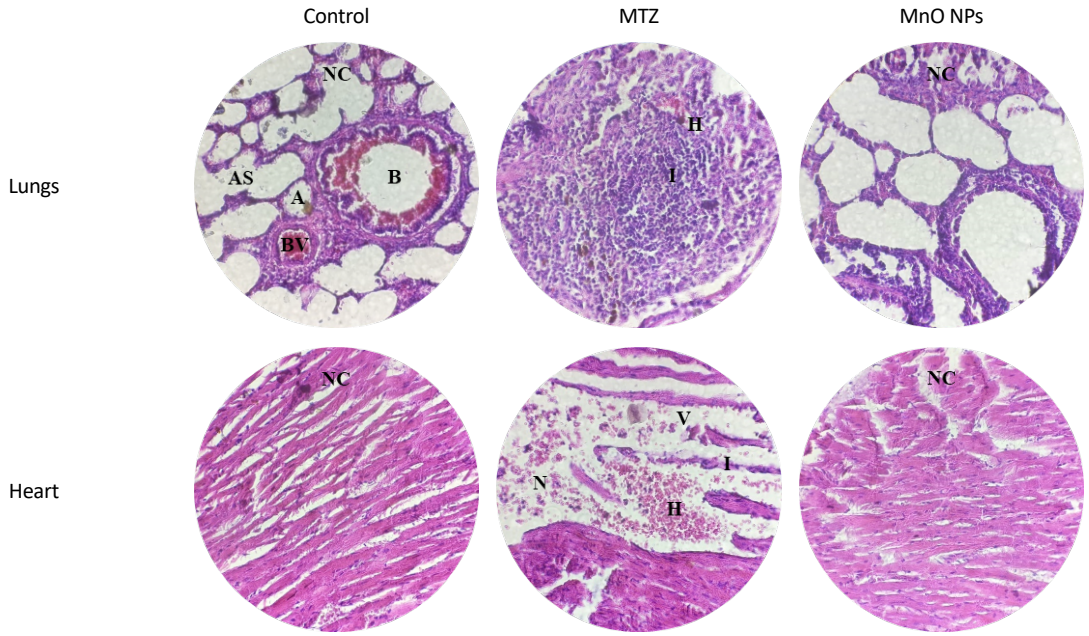

Figure 6. Photomicrographs of lung and heart sections of all experimental groups (×40 magnification, H&E)

Abbreviations: NC: Normal cells; H: Hemorrhage: I: Inflammation; V: Vacuolization: N; Necrosis; B: Bronchiole; A: Alveolus; BV: Blood vessel; AS: Alveolar sacs.

fects, as evidenced by the significant increase in the absolute and relative weight of several vital organs [3]. It has been demonstrated that plant extract-mediated synthesis can decrease toxicity while improving the biological properties (bioavailability, biocompatibility, cell internalization, and antioxidant activity) of metal and metal oxide NPs [5]. Because MnO NPs are less harmful, they have become more important in the synthesis and production processes, which mitigates the metribuzin effect responsible for lung and heart hypertrophy.

When comparing the MTZ group to the control group, the activity levels of GOT, LDH, and CPK were significantly increased, and the MnO NPs group showed partial improvement in comparison to the MTZ group. The three primary cardiac enzymes that are measured are GOT, LDH, and CPK. The enzymes present in cardiomyocytes can be found in the blood, and when cardiac cells suffer inflammation (myocarditis) or necrosis (myocardial infarction) due to a variety of reasons, the activity (levels) of these enzymes increases [21]. The outcomes observed indicate that MnO NPs could potentially have cardioprotective effects by regulating metribuzin-induced oxidative stress and inflammation, which are the principal causes of cell damage and the release of their contents into the blood.

In comparison to the control group, the MTZ group exhibited noticeably higher levels of inflammatory markers. On the other hand, the treated group showed a significant decrease in inflammatory marker levels as compared to the MTZ group. One important organ system to focus on when exposed to pesticides is the immune system [22]. The capacity of pesticides to either promote or inhibit lymphocyte proliferation and cytokine synthesis, in addition to inducing genetic injury and chromosomal irregularities in cultured lymphocytes, has been proposed as plausible mechanisms underlying their adverse effects on the immune system [22]. The large surface area-to-volume ratio of these entities allows them to possess high surface reactivity, which in turn facilitates their interaction with biological membranes and promotes their physical transport within the membrane [10]. NPs exhibit improved penetration into epithelial and inflammatory cells, which contributes to their superior effectiveness and longer persistence in treatment. Additionally, they exhibit better targeting of specific sites, such as inflammatory cells or tissues [23]. Inhibiting pro-inflammatory cytokines is a crucial process, as these cytokines enhance immune responses and are targeted by the vast majority of NPs [23].

The evaluation of oxidative stress biomarkers (SOD, GPx, GSTs, CAT, GSH, and MDA) in the pulmonary and cardiac tissues of male rats revealed that MTZ induces oxidative stress. Concurrently, a significant amelioration was observed in the MnO NPs group compared to the MTZ group. The antioxidant defense mechanisms, including

GSH, CAT, GPx, and SOD, can be inhibited by xenobiotics, which cause the overproduction of excessive and untimely free radicals. This leads to the damage to macromolecules, including DNA [4]. Certain pesticides have the potential to induce a rise in reactive oxygen species (ROS) generation, thus resulting in oxidative stress in unintended organisms [3]. Metal oxide NPs, specifically manganese dioxide, can effectively replicate the functions of antioxidant enzymes by catalyzing the breakdown of superoxide anions and hydrogen peroxide [7].

The observed increase in organ mass, oxidative stress levels, biochemical toxicity, and inflammatory responses documented in the present investigation were substantiated through histopathological analyses of pulmonary and cardiac tissues. Control rats displayed normal histological features in their pulmonary and cardiac tissues upon examination. In contrast, the MTZ-treated group's lungs and heart samples showed various structural changes. Interestingly, the MnO NPs group exhibited considerable improvement, with their lung tissue structure closely resembling that of the control group. There exists indirect corroborative evidence that associates pesticide exposure with specific chronic health conditions, including respiratory ailments, notably chronic obstructive pulmonary disease, as well as cardiovascular disorders [2]. Research involving animal models has indicated that metribuzin may induce deleterious health consequences, such as alterations in tissue histology [4]. Moreover, individual pesticides have been documented to elicit cellular toxicity via oxidant-mediated mechanisms, which encompass both programmed and unprogrammed cell death, lipid membrane damage, metabolic disruption, modification of diverse signaling pathways, or alteration of tight junction integrity [24]. This elucidates the varied histological alterations detected in the tissue specimens from the MTZ-exposed group. The amelioration observed in all aforementioned parameters is substantiated by the findings derived from the histological evaluations of the tissue sections. Conversely, MnO_2 NPs can consume excess H_2O_2 in situ and convert it to O_2, thereby counteracting aberrant ROS generation. Additionally, MnO_2 particles can control the degree of inflammation by affecting the expression of genes that produce cytokines. MnO_2 gradually breaks down during this process to produce Mn^{2+}, which is expelled with bodily fluids and aids in the return of the body's internal environment to its homeostatic state [25].

5. Conclusion

We suggest that the phytochemical components of the basil extract used in the green synthesis of MnO NPs play a crucial role in enhancing their biocompatibility by acting as natural reducing, capping, and stabilizing agents, which help produce uniformly sized and shaped NPs. These plant-derived compounds reduce toxicity by eliminating the need for harsh chemicals and create a biofriendly surface that improves cellular interactions and uptake. Additionally, functional groups from phytochemicals enhance biological compatibility, while their antioxidant and anti-inflammatory properties further contribute to the safety and therapeutic value of MnO NPs, making them well-suited for biomedical applications.

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Compliance with ethical guidelines

The authors declare that all ethical standards have been respected in the preparation of the submitted article.

Data availability

The data that support the findings of this study are available upon request from the corresponding author.

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The paper was extracted from the PhD dissertation of Islam Boulaares, approved by the Department of cellular and Molecular Biology, Faculty of Natural and Life Sciences, University of El-Oued, El-Oued, Algeria.

Authors' contributions

Conceptualization, study design, and writing the original draft: Islam Boulaares; Data acquisition, project administration, technical, and material support: Islam Boulaares and Sara Chetehouna; Analysis, data interpretation, and statistical analysis: Islam Boulaares and Samir Derouiche; Supervision, review and editing: Samir Derouiche and Janetta Niemann; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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