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Synthesis of Mn_2O_3 Nanoparticles and Determination of Its Inhibition Effect On Sera of Iraqi Patients with Diabetes Mellitus Type-2 and Diabetes Nephropathy

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Abstract

Manganese is essential for the synthesis of antioxidant enzymes and metabolic issues in Diabetes type 2 (DMT2), which is a worldwide disease, Chronic metabolic disorders cause insulin resistance, hyperglycemia, and complications like diabetic nephropathy. Arginase converts arginine to ornithine and urea. Increased arginase activity in DMT2 and diabetes nephropathy (DN) which has been linked to kidney damage, and arginase inhibitors can increase NO which is essential to vascular function. However, the molecular mechanisms of arginase disregulation are in DMT2 and DN are still unclear. This study examined the effect of manganese oxide nanoparticles (Mn_2O_3 NPs) on arginase activity inhibition in serum samples from DMT2 and DN patients. We hypothesized that Mn_2O_3 NPs alter cell redox status and signaling pathways, affecting DMT2 and DN arginase activity. We used a colorimetric assay to measure arginase activity in 80 serum samples from DMT2 and DN patients treated with different MnO2 NP concentrations to test our hypothesis. The current study characterized nanoparticles using various techniques such as IR, SEM, AFM, XRD, and EDX, which found it within nanoscale nature. Our findings are that Mn_2O_3 NPs modulate arginase activity specificity in DM2 samples. Suggestions Mn_2O_3 NPs could be used to develop new treatments for these conditions.

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1. Introduction

Manganese is an essential trace element and it is needed for human health. It is vital for antioxidant enzyme production, cellular protection, and protection from radical damage its daily intake is 2–5 mg/day in humans [1]. Manganese deficiency elicits a decrease in hair and nail growth and leads to metabolic problems [2]. Research showed that manganese oxide has great potential to help in antioxidant functioning, metabolic activities, and growth [3]. Due to their low toxicity, high surface area, varied morphology, and exceptional redox properties, manganese oxide nanoparticles have garnered a lot of attention in a variety of fields [4]. Consequently physicochemical characteristics and potential use in various applications, it is attracting a lot of attention, in various biomedical applications, such as catalysis, adsorption, sensors, and imaging [5]. Also, their therapeutic activity, anti-angiogenesis for cancer, antiviral activity, antibacterial and anti fungal agent and antioxidant reagent, make them an ideal candidate for the management of diabetes type two [6]. Studies have shown that manganese oxide nanoparticles play a significant effect on glucose homeostasis in diabetic animal models [7-8].

Manganese oxide nanoparticles reduce the levels of blood glucose, improve insulin sensitivity, and improve glucose uptake [9]. Manganese oxide nanoparticles also decrease oxidative stress in the body, which is another significant cause of insulin resistance [10]. Inhibiting the enzyme arginase which turns l-arginine into l-ornithine and urea, is one of their potential uses [11]. Numerous illnesses, including erectile dysfunction, diabetes mellitus, cancer, hypertension, and asthma, are impacted by arginine kinase. By inhibiting arginase, manganese oxide nanoparticles may increase the availability of l-arginine for the production of nitric mono oxide (NO), which is a vasodilator and a modulator of immune responses [12]. The shape, size, and phase of the nanoparticles may affect their arginase inhibition activity. For example, α-MnO_2nano-rods are more effective than ß-MnO_2nano spheres in inhibiting arginase in vitro [13]. The mechanism of arginase inhibition by manganese oxide Nanoparticles may involve the interaction of metal ions with the active site of the enzyme or the generation of reactive oxygen species (ROS) and reactive nitrogen species that can damage the enzyme [14]. Manganese oxide nanoparticles have some advantages over other types of arginase inhibitors, such as boron-based amino acid derivatives or plant-derived compounds. They are more stable, and more biocompatible than some chemical inhibitors [15]. They also have multifunctional properties that can be used for the diagnosis and treatment of diseases associated with arginase deregulation [16]. However, there are also some challenges and limitations in using manganese oxide nanoparticles as arginase inhibitors.

For instance, they may have low bioavailability, poor solubility, or undesired side effects in vivo. Therefore, further research is needed to optimize the synthesis, characterization, and delivery of manganese oxide nanoparticles for arginase inhibition.

The effects of manganese oxide NPs on arginase inhibition are not well understood, but some studies have suggested that they may have some benefits or drawbacks depending on the conditions. For example, manganese oxide NPs can enhance the MRI signal of arginine by increasing the longitudinal relaxation rate (R1) of water protons [12]. This can improve the detection of arginine-rich tissues or cells, such as tumors or bacteria [17]. Additionally, manganese oxide NPs can also trigger the release of nitric oxide from arginine by catalyzing its oxidation. This can have anti-inflammatory, anti-bacterial, and anti-tumor effects [12,13].

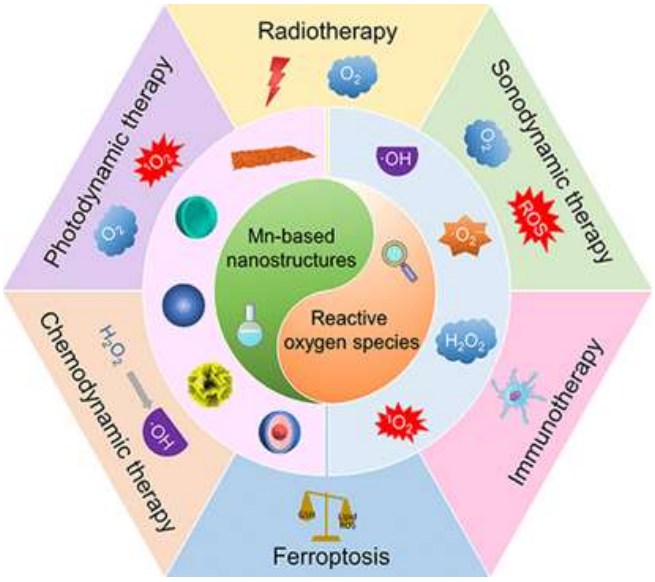


Figure1. Manganese Nanostructures and Their therapeutic Application[14]

However, Manganese oxide NPs may also cause oxidative stress, cytotoxicity, and gene-toxicity to Arginine-containing cells or tissues by generating (ROS)reactive oxygen species or disrupting the cellular redox balance. This can lead to cell death, DNA damage, or inflammation [14]. Disadvantages of Manganese nanoparticles such as decrease in the blood circulation time and accumulation in the brain, resulting in changes in the central nervous system followed by cognitive and movement abnormalities [20]. Therefore, the effects of manganese oxide NPs effects on arginine connection may depend on several factors, such as the size, shape, surface, and concentration of the

nanoparticles, the pH and temperature of the environment, the presence of other molecules or ions and the type and state of target cells or tissues. Below are some of the previous studies' guidelines examples reviews:

One study suggests testing different NP-to-serum ratios and measuring Matrix metalloproteinase 2 (MMP2)enzyme activities to find the best ratio. The work describes a standard operating procedure (SOP) for an enzymatic activity inhibition assay, including the catalytic reaction, optimal conditions, active enzyme fraction and concentration, substrate and inhibitor concentrations [21]. In vitro testing of corpuscular NPs requires technical considerations, according to another study. The study suggests counting NPs rather than weighing them because their biological activity depends on their number. This study also describes how the relationship between NP size, weight, and number complicates activity comparisons [22]. Further study examines NP therapeutic efficacy and pulmonary delivery routes. The work showed that an in healable drug must overcome pulmonary clearance and enzyme detoxification to work. This study also states that rapid particle clearance reduces drug delivery and particle translocation may bring NPs to unwanted body locations [23]. A previous study found that protein (albumin) molecules initially surround only 20% of NPs, but increasing the protein-to-metal ratio reverses this tendency and converts all rod-shaped NPs to conjugated form after 2 h [24].

In 2015, MicrochimicaActa tested gold NPs' acetylcholinesterase inhibition at a 1:5 volume ratio of NPs to serum[25] .Due to that, a Protocol Operating System (POS) in the current study combined the serum with 1:5 ratios of five diluted NP concentrations (10^{-1} to 10^{-5} M). Mustered serum (250 µL) = 200µL serum + 50µL of opting NPs suspension in distal water.This study aims to synthesize manganese oxide Nanoparticles using the sol-gel method, the most efficient chemical method, and the ratio of NPs to serum for enzyme inhibition testing depends on NP type and size, concentration, and experimental conditions.

2. Materials and Methods

The Mn_2O_3 Nanoparticles were produced using the microwave-assisted technique and the produced samples underwent additional annealing at 500 °C. Mn_2O_3 Nano powder was formed from an aqueous solution of $MnCl_2$ (1M) that had been reduced by 1M of NaOH.In this procedure, 100 ml of distilled water and 1 molar (1M) $MnCl_2$ powder were combined in a round-bottomed flask. Then, 1 M NaOH was gradually added to the above solution, drop by drop, and the mixture was continuously stirred for an hour to produce a brown-colored solution. The produced solution was heated in a home microwave oven (540 W, 92 °C) for 20 minutes to increase the formation of nanoparticles. The mixture was then cooled to lab temperature, and the brown precipitate that resulted was separated by centrifugation before being repeatedly washed with distilled water and absolute ethanol to remove impurities and residual materials. The Nanoparticles were washed and then heated in an oven to 65 °C for drying. The final step involved annealing the prepared materials for three hours at 500 °C [27]. With different characterization techniques, the nanoparticles were identified as manganese oxide nanoparticles on the nanoscale with a particle size of 32.86 nm and crystals with a size of 50-60 nanometers. After applying different concentrations, Biostatistical study groups were used to determine the highest concentrations of its inhibitory effect on the arginase enzyme in the blood serum of DM2 and DN patients. The current study included 120 Iraqi sera subjects (average age 53 years), the percentage of men was 62% and women were 38%. The samples were divided into three groups, 40 for a control group, 40 of them with diabetes type 2, and 40 of them had diabetes nephropathy. Patients were confronted during the collection of samples for them in Baghdad Hospital / Medical City, 21 October – 11 November 2022, and they were asked about their medical history and the type of treatment used.

3. Results and Discussion

3.1. Nanoparticles Characterizations

3.1.1. X-ray diffraction (XRD) of Mn_2O_3

The structure of prepared NPS powders was examined using (PW1730 Philips, Holland) diffraction of X-rays (XRD) measurements at the BPC centre in Baghdad. By scanning 2θ in the (20-80 degree) range, XRD spectra of the powder were captured. The Joint Committee on Powder Diffraction Standards (JCPDS) cards have been compared to X-ray diffraction measurements. A Debye-Scherrer's equation was used to calculate the NPs' mean particle diameter:

$$D = \frac{0.9\,\lambda}{B\,cos(\theta)} \quad \dots(1)$$

where λ is the X-ray wavelength, ß is the diffraction peak at full width at half maximum, θ is the position of the diffraction peak determined from the XRD pattern by the line width of the plane refraction peaks and D is the grain size [28]. The peak positions of the prepared sample observed correspond to Mn2O3 When compared to the JCPDS standards (JCPDS card no: 01-089-0436), found to agree with the specified values with spherical lattice type.The characteristics, volume, and density are practically identical to their conventional values as can be shown. The calculated crystallite size is 32.86 nm, and XRD characteristics of the nano structures indicate that they are crystallographically oriented[27], as it was shown in figure 3.

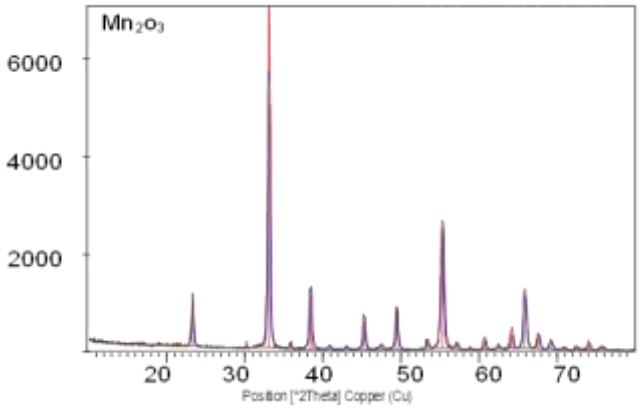
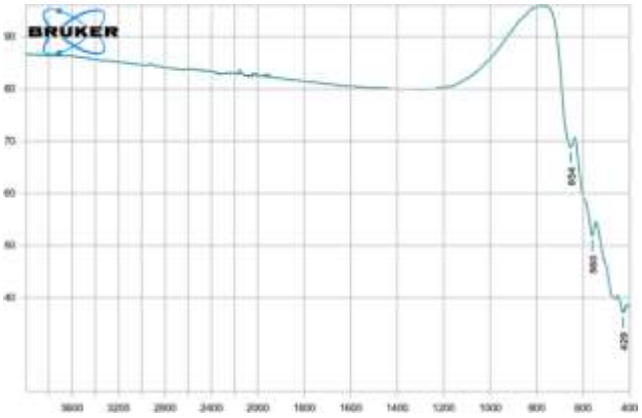


Figure 3. Mn_2O_3 NPs XRD patterns.

3.1.2. Infrared spectroscopy using Fourier transforms (FT-IR):

By using an FT-IR BRUKER in the range of 4000-400 cm-1 at 25°C to record the infrared spectra of the preparations for produced nanoparticles with KBrdisc. The FTIR spectra captured by the Bruker spectrometer were used to validate the creation of the metal-oxide phase, and the occurrence of Mn-O stretching vibrations. The observed band at 560 $cm^{-1}$is due to the stretching vibration of Mn-O bonds, which agrees with a study conducted in 2020[29].Also, it is observed that there are several distinct peaks at 654 and 429cm^{-1} which attributed to Mn-O vibrations[30].Moreover, the absence of any peak in the region (4000-3000) cm^{-1} indicates that the nanoparticles are free of any trace of water molecules, which may be due to solvent residues or air moisture[31].



bands values cm^{-1}	corresponding chemical bond
654	TetrahedralMn-O stretching
560	vibration of octahedral Mn-O
429	vibration of Mn species(Mn^{3+})

Figure 4. FTIR spectrum of Mn_2O_3 NPs

3. Atomic Force Microscopy (AFM):

Using (CSPM-5000) atomic force microscopy to analyze Nanoparticles, the Mn_2O_3 morphology surface is shown in Fig. 5, which shows low particle size molecule distribution. This arrangement in the crystal size is in agreement

with the arrangement that was calculated from the Debye-Scherrer equation. From these results, one can conclude that the Mn_2O_3 exhibited uniform morphological surfaces and small particle sizes.

With an accelerating voltage of 30 kV and a magnification of 10,000 xs, the morphology of the produced Nanoparticles was studied using a scanning electron microscope (SEM) of the type (TESCAN, MIRA III) at the BPC analysis center in Baghdad. As it is widely known, the qualities of a wide range of materials and the performance of a wide range of devices are heavily influenced by their surface characteristics. SEM was used to analyze the morphology of Mn_2O_3Nps. Figure 6 depicts typical SEM pictures of the sample. A 1µm scale bar was used to take the SEM image. Synthesized Mn_2O_3 Nps had an average diameter of about 50 -60 nm and an extremely narrow particle distribution.

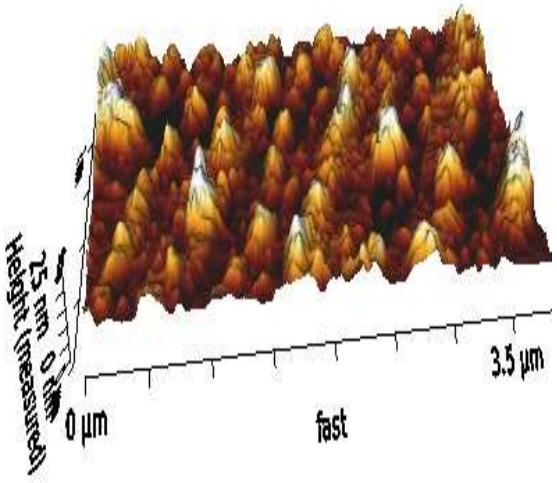


Figure 5. The three-dimensional AFM image of Mn_2O_3NPS with little of Crystal accumulation.

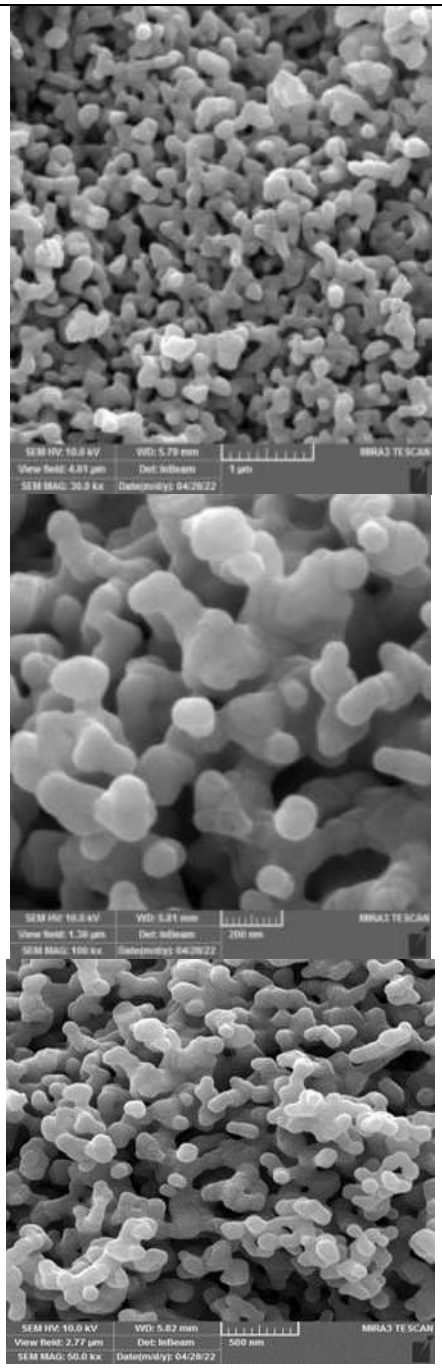


Figure 6. SEM images, of Mn_2O_3 NPs at different magnifications.

5. Energy dispersive analysis (EDAX)

The purity of the chemical makeup of the Nanoparticles was validated by energy dispersive analysis (EDS) spectroscopy of Mn_2O_3 Nanoparticles. Using an SEM equipped with EDS, the existence of magnesium in Mn_2O_3

Nanoparticles was verified. The percentage elemental composition of Mn_2O_3 Nanoparticles was 64.32% Mn and 35.68% O (Figure 7). The elemental proportion of Mn_2O_3 is comparable to the report, Talebi, 2017 [32]. For Mn Nanoparticles of high purity, the highest intensity was at 6.0keV.

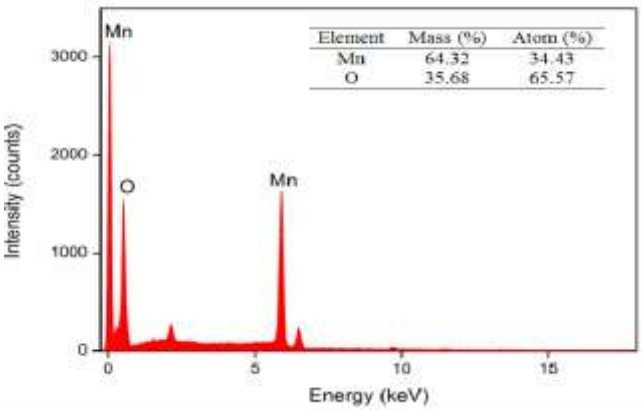


Figure7. EDS measurement of the synthesized Mn_2O_3 NPs

3.2. Arginase Enzyme Activity Inhibition

The arginase enzyme activity was measured for three groups and examined the impact of manganese oxide Nanoparticles on arginase activity and concentration in serum samples from type-2 diabetes mellitus (DMT2), and diabetic nephropathy (DN) patients and healthy individuals and different concentrations of manganese oxide prepared were applied for each group. A result is shown in Figure 8.

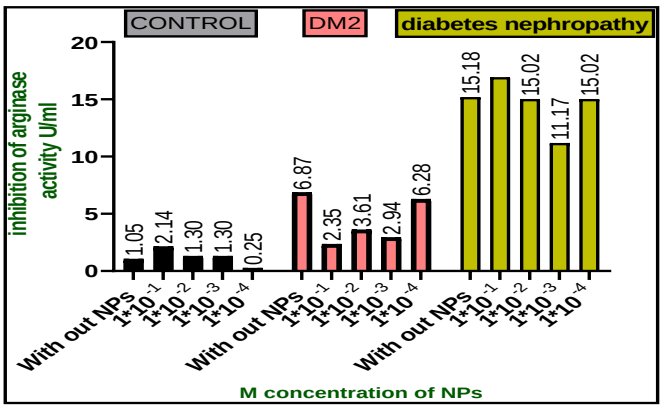


Figure 8. Arginase enzyme activity after Applied Mn_2O_3 NPs on studied sera.

A statistical study was compared with the control health samples, and the statistics results are shown in Table 1 below.

Table1. Mn_2O_3 NPS Test details inhibition percentage. (Vale with *sign meaning activation is accord.)

Concentration of NPs (M)	Control (n=40)	Type-2 Diabetic (n=40)	Diabetic nephropathy (n=40)
1×10^{-1}	29*	65.7	11.4*
1×10^{-2}	20*	47.4	1.1
1×10^{-3}	19*	57.1	26.4
1×10^{-4}	76	8.5	1.11

In table 1, the results indicated that Manganese oxide NPs had varying effects on arginase regulation, depending on the disease status of the patients and the concentration of NPs. Mn_2O_3 NPs effect in the arginase enzyme is seen as a clear and strong inhibition, especially DM2 group. At high concentrations (0.1 M), Manganese oxide NPs activated arginase in DN, control serum samples by 11%, and 29% while it inhibited arginase in DMT2 by 65.7%, while at lower concentrations(diluted) 1×10^{-4} M, they inhibited arginase in DMT2 and DN serum as well as control samples by 47.4%, 1.1% and 76%,respectively. One possible mechanism of inhibition of arginase by manganese oxide nanoparticles is through the formation of a complex between the nanoparticles and the manganese ions in the deactivate site of Arginase between OH and NH_3 as shown below in figure 9 [33].

This could block the access of the substrate (L-arginine) or the cofactor (manganese) to the enzyme, thus reducing its activity [34]. Although our hypothesis is built on the impact of the reduction of NO species, we mention that another possible mechanism is through the generation of reactive oxygen species (ROS) by manganese oxide nanoparticles. ROS could damage the structure or function of arginase by oxidizing its amino acid residues or manganese ions [35].

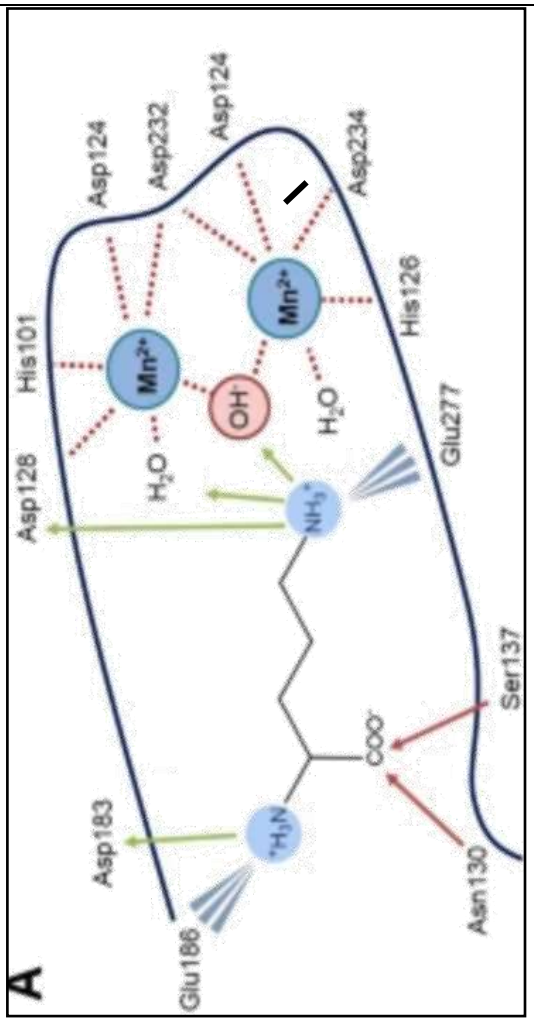


Figure 9. ArginaseStructure and Inhibition sites [33].

A third possible mechanism is through the modulation of the expression or localization of arginase by manganese oxide Nanoparticles. Manganese oxide nanoparticles could alter the transcription, translation, degradation, or trafficking of arginase in the cells, thus affecting its availability or activity[36].

Finally, we suggest conducting further studies on the applications of nano-manganese oxides as an enzyme inhibitor, which achieved the desired result in inhibiting the arginase enzyme at the lowest concentrations for a group of type 2 diabetes samples, in addition to studying its toxicity and other applications on living organisms.

4. Conclusions

The inhibition of arginase activity in samples of diabetes type 2 is more than inhibition in samples of diabetic nephropathy and control groups, and this explains that the mechanism of inhibition could be directly between the manganese nanoparticles and the glucose molecules in the serum. These and other findings in Table 1 above suggest that Manganese oxide NPs can modulate arginase activity and expression by altering the redox status. A high inhibition of arginase in DM2 samples by Manganese oxide NPs could be through the formation of a complex between the nanoparticles and the manganese ions in the deactivated site of arginase, or the modulation of the expression or localization of arginase by manganese oxide Nanoparticles. Conversely, the little inhibition of arginase in DN serum samples by Manganese oxide NPs could be due to the generation of reactive oxygen species (ROS) that stimulate arginase expression. The inhibition of arginase in DMT2 and DN serum samples by Manganese oxide NPs could potentially improve nitric oxide (NO) bioavailability and prevent renal damage. Thus, the study suggests that Manganese oxide NPs may have therapeutic potential for DMT2 by modulating arginase regulation with the help of Nanomaterials. However, further research is necessary to establish the molecular mechanisms and safety of Manganese oxide NPs in vivo.

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Conflict of Interest: All authors declare that there are no conflicts of interest

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