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Biosynthesis of Magnesium Oxide Nanoparticles Using *Opunita ficus-indica* and Their Antifungal Effect Against *Aspergillus Niger*

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ABSTRACT: Magnesium oxide nanoparticles (MgO-NPs) were synthesis via green method using *Opunita ficus indica* extract as reducing and covering agent. The optimal formula for the preparation of MgO-NPs was determined by UV-Vis and DLS (*Opunita ficus -indica* extracted by distilled water and ethanol solvent, magnesium nitrate salt (1mM), stirred at 70 °C for 24 h with pH= 9). UV-Vis analysis showed a peak at 300 nm, while DLS measured the hydrodynamic diameter of the nanoparticles. FTIR results suggested that the polysaccharides, phenols and amines present in the extract might have been involved in the formation of MgO-NPs from Mg (NO3)2 as the reducing agent. Image J was utilized to analyze the SEM results and determine the size, which was on average 99 nm, the shape of the nanoparticles was spherical, and EDX spectrum confirmed the presence of magnesium (Mg). It was found that MgO-NPs are highly toxic against *Aspergillus niger*. Which showed a gradual inhibitory effect when using the concentration of 0.5% and 1.25%, and the inhibitory ability was 66.6%, 100% respectively, when using the poisoned food technique.

KEYWORDS: MgO nanoparticles; Biosynthesis; Succulent; Cactus; Antifungal; Aspergillus niger.

1. INTRODUCTION

Infectious diseases witnessed a massive spread, which led to an increase in the incidence of opportunistic diseases due to the resistance to antifungal drugs [1] [2], and death rates due to invasive fungal infections are often 50% or higher [1]. The risk of failure of surgical operations and medical treatment will increase in the absence of effective drugs [2]. Aspergillus species consists of a group of opportunistic fungi that is virulent when the immunity of the host is compromised. The three main classes of antifungal agents are polyenes, echinocandins and azoles which are utilized for the treatment of aspergillosis. Nevertheless, the resistance towards these three classes has been rising over the years among several *Aspergillus* spp [3]. Aspergillus species are among the most important causes that threaten the lives of patients, especially patients with immunodeficiency [4]. Therefore, there is an urgent need to develop effective antimicrobial agents [1]. Nanotechnology is a science which utilizes various techniques to synthesize nanoparticles with larger surface area possessing unique behaviour and special characteristics [5]. This is useful because many important electrical and chemical reactions occur only at surfaces and are sensitive to the texture and shape of a surface in addition to its chemical composition [6]. In this regard, nanoparticles are studied as antifungal agents due to their size, surface, shape, and structural properties [7]. Among metallic nanoparticles, extensive research has been carried out using MgO-NPs and their applications in biomedical field as drug delivery system [8], anti-microbial [9], and anti-cancer agents [10]. MgO is not only applied in pharmaceutical products, but also in water purification [5] MgO has gained keen interests due to its ecofriendly nature, the availability of greater specific area, the biocompatibility, it is low cost and the convenience of its sources [5]. In addition, Food and Drug Administration (FDA) recommended MgO-NPs as safe materials [11]. Antimicrobial activity does not require photoactivation [12] because the specific surface area of MgO nanoparticles increases as the total

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particle size decreases. This increase shows effective groups on the surface of the particles that are expected to exhibit high antibacterial activity [12]. Recently, green synthesis of metal nanoparticles using plant extract has gained much attention since it is eco-friendly and cost-effective [6]. NPs prepared using plant extracts are more stable, take less reduction time, and are monodispersed. The main reasons why this method is environment-friendly are the safe solvents, the reference agent and the nontoxic materials used, and it can be easily scaled up to make larger quantities and there is no need to use high pressure, energy, or hazardous chemicals. It is a one-step technique. The birth of the term green nanoparticle synthesis closely integrates with the principles of green chemistry [53]. MgO-NPs synthesis via green route is limited in literature and few studies on MgO-NPs green synthesis using *Rhizophora lamarckii* [13], *Trigonella foenum-graecum* [14], *Sargassum wightii* [15], *Chromolaena odorata* [16] were previously reported. In this study, succulent and cactus plants mediated green synthesis of MgO-NPs and continued future experiments with *Opunita ficus indica (O.F.I)* extract which was investigated for first time. *O.F.I* is a well-known elaborate plant belonging to *Cactaceae* [17]. An increasing interest in its cultivation has been observed in recent years due to the importance and success of its cultivation in arid and semi-arid regions, as well as for its use in food and medicine as a source of multiple products [18] It has been used in traditional folk medicine for its antifungal and antibacterial effects [19]. Here in, we report the synthesis of MgO-NPs via a novel green method using *Opunita ficus indica* extract, as antifungal agents against *Aspergillus niger* that exhibits significant resistance to current antifungal drugs that cause life-threatening diseases in humans.

2. RESULTS AND DISCUSSION

The green nanoparticle synthesis method is an incomparable method, where oxidation and reduction are the main reactions. The synthesis of nanoparticles consists of three stages, activation phase, at this stage, the plant metabolites release the mineral ions from the salt under the influence of their reference action. Metal ions are transformed from their oxidized state of mono or divalent form to moderate metallic nanoparticles, after which the process of nucleation of metal atoms occurs**.** Growth Phase: In this phase, the separate metal atoms combine to form metal NPs in conjunction with the process of bioreduction of another metal ion, and during growth, the NPs combine to take a variety of shapes**.** Finally, phase of completion: In this phase, the NPs have reached the stable and most effective form when they are coated with plant metabolites [6]**.**

2.1 OPTIMIZATION STUDIES FOR THE SYHNTHESIS OF MgO-NPs:

UV-visible spectroscopic analysis over a range of wavelengths showed an absorbance peak of ~300 nm for all the samples, and this correlates with the formation of metal oxide nanoparticle [20].

2.1.1 Effect of types of utilized plants:

The best type of ten tested plants for synthesis MgO-NPs was *Opunita ficus indica,* as shown in figure 1 with the highest peak in UV-VIs and follow-up tests were carried out utilizing it. This is due to the active ingredients that are capable of fabricating MgO-NPs which change due to different types of plant [21]. These are some of the compounds that this type of cacti contains: flavonoids, quercetin - 3-O-glucoside, phenolics, kaempferol 3-O-glucoside, pentahydroxy-flavanone, alkaloid and terpenoid [22]. Most of which are known for their ability to synthesize nanoparticles [23][24].

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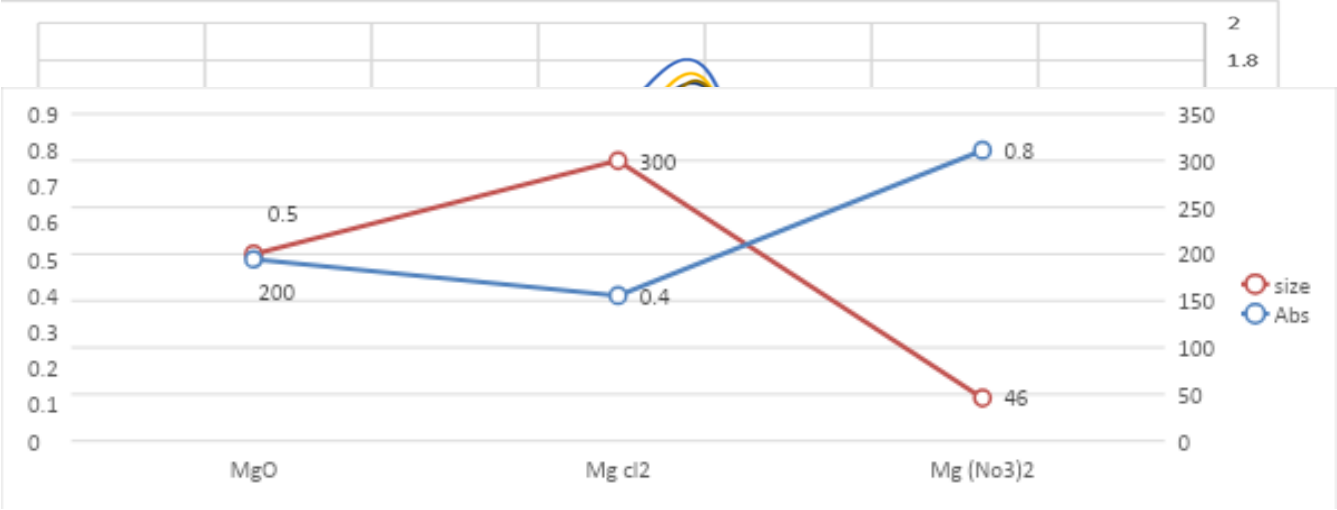

Figure 1. Effect the type of plant on synthesis MgO-NPs

1.2 Effect of solvent extract on the fabricated MgO-NPs:

-Most of the studies depend on aqueous or alcoholic extracts, and it was found that the mixture of DDW – ethanol at a ratio of 2: 1 is the best for higher absorbate (0.9) and less size (100 nm) (Figure 2). This may be due to active plant components that were extracted with the solvent mixture which have different polarities, thus a greater ability to fabricate nanoparticles.

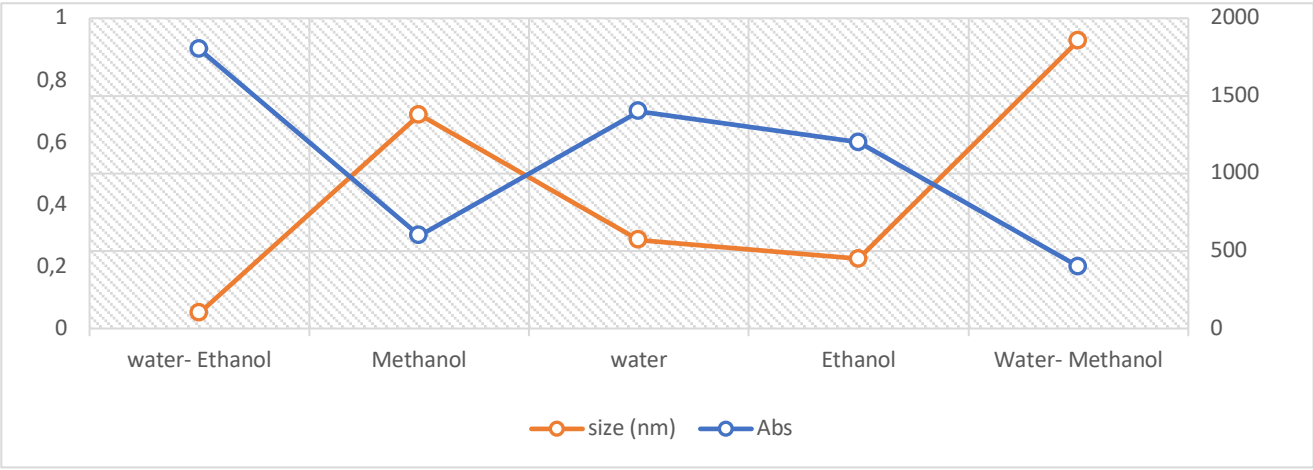

Figure 2. Effect of the solvent extract on MgO-NPs synthesis

2.1.3 Effect of MgO Precursors:

The best result of studied precursors was magnesium nitrate with high absorbance 0.8, and the smallest size 46 nm as shown in (figure 3). This explains the usage of nitrate salts in most studies [25] [26] [27]. It could be explaied by the large solubility of nitrate salt and its low molecular weight [28]. This is consistent with the study [21] which compares between nitrate salt and acetate salts.

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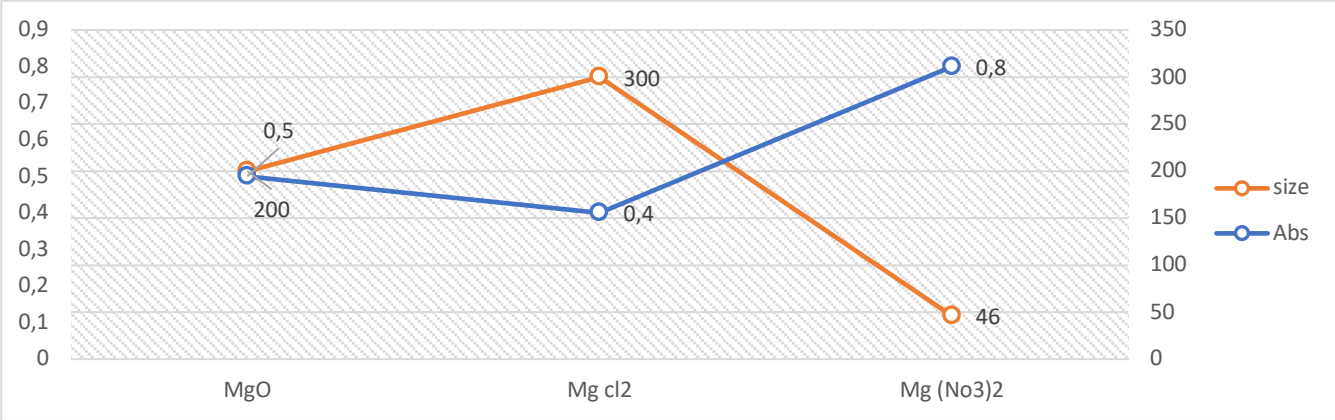

Figure 3. Effect of Precursors of MgO

2.1.4 Effect of Stirring time:

The best result of studied time was 24 hr, with high absorbance 0.8, and the smallest size 157 nm as shown in figure 4. Where, over time with stirring, there is an opportunity for the salt to be reduced by the active plant components, so the size of these particles decreases, but for a specific period of time after that the active ingredients are consumed, and the long time leads to aggregation [25]**.** The Stirring time of the reaction medium significantly affects the size and morphology of the particles. Changes over time also affect the properties of the fabricated nanoparticles such as exposure to light and storage conditions [30]. This differs from studies [30] [31] [32] due to using different plant to fabricate MgO-NPs.

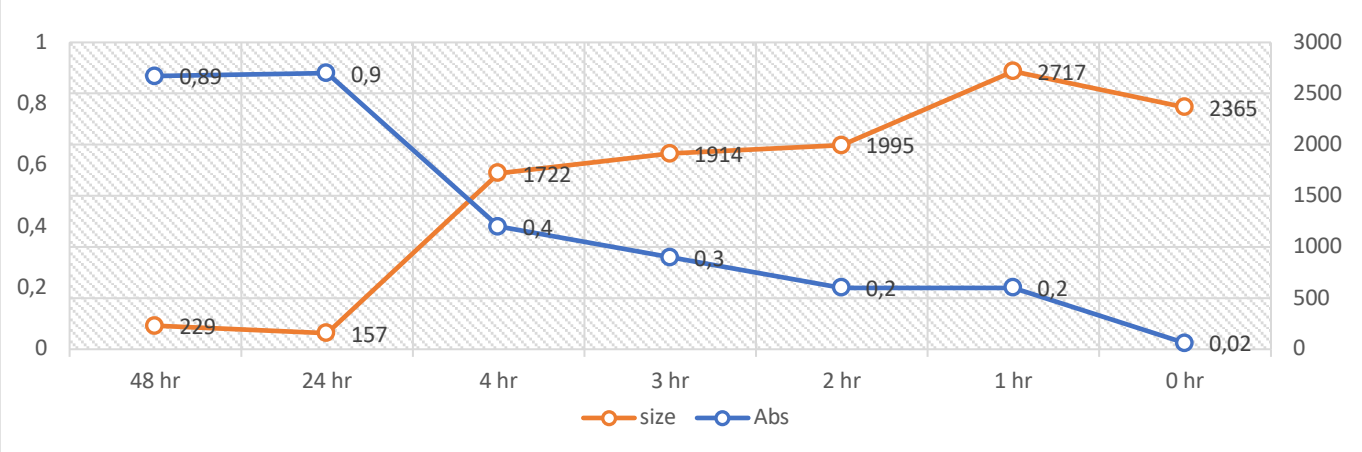

Figure 4. Effect of Stirring time on MgO-NPs

2.1.5 Effect of pH reaction:

The pH of the reaction medium affects the size of the NPs fabricated by the green synthesis method, so these particles are controlled by changing the pH of the reaction medium [30]. The best formation was at pH=9 as shown in (Figure 5) with high absorbance 0.5, and the smallest size 103 nm. This is consistent with a study

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[33], and differs with another study in which the best value was pH=3 [34], This is explained by the use *Dalbergia sissoo* extract in MgO-NPs fabrication. A change in the pH of the medium leads to change in the charge of the phytochemicals responsible for the bioreduction of the metal ions, which in turn affects the synthesis of NPs [26]. There is a need to improve the synthesis protocol for an efficient synthesis of NPs [29]. Where we have the active form of the plant components that are able to fabricate more nanoparticles.

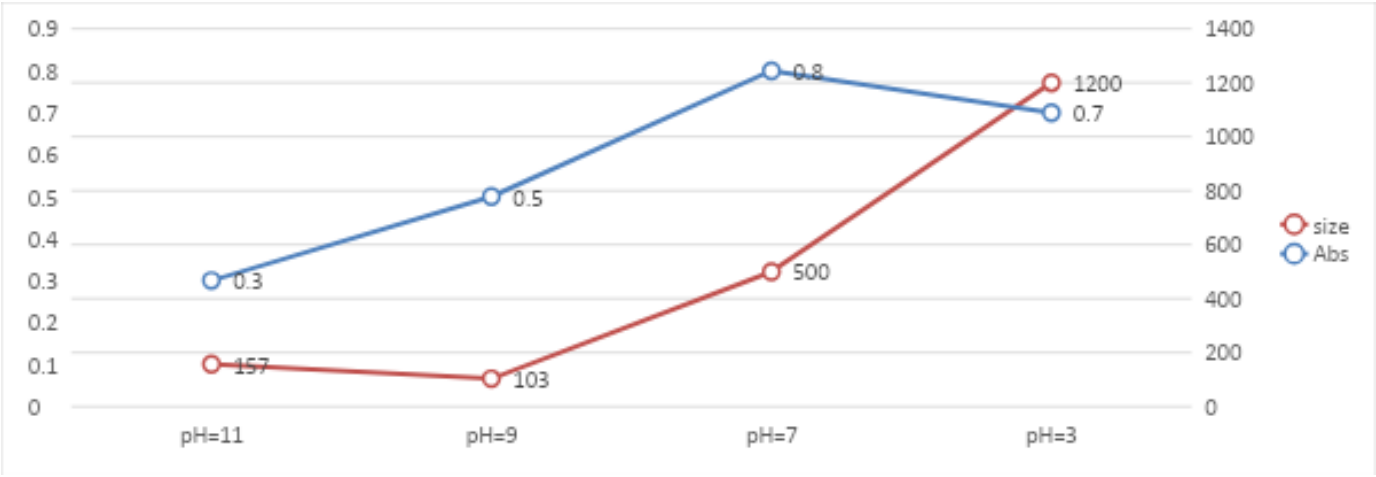

Figure 5. Effect of pH reaction on fabricated MgO-NPs

2.1.6 Effect of temperature (°C):

The best result of studied stirring temperature was 70 °C, with a high absorbance of 1.2, and the smallest size 46 nm as shown in figure 6. This result matches many studies [27] [32] There is often a direct proportion between the size of the particles and the temperature of the reaction, but within a certain range, low degrees are not sufficient to reach the activation energy required to form nanoparticles, while the rise of the temperature to 100°C may lead to the decomposition of phytochemicals in plants [20].

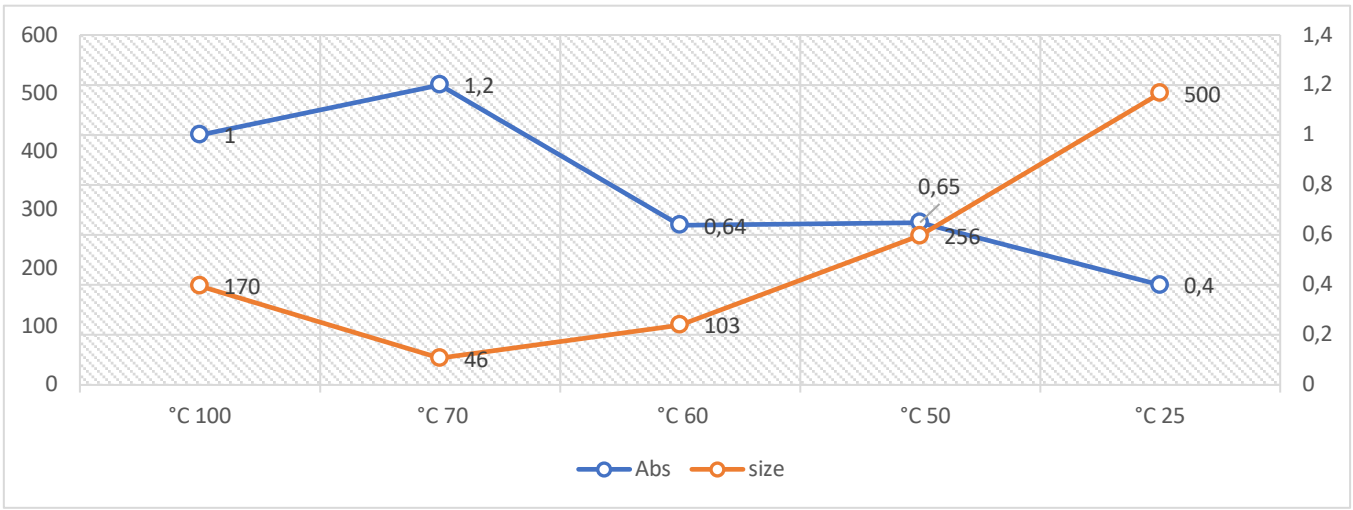

Figure 6. Effect of stirrer temperature on fabricated MgO-NPs

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2.2 Characterization of MgO Nanoparticles:

The best fabricated simples MgO-NPs were characterized by several technologies, to analyze the size and morphology of the particles.

2.2.1 UV–Vis spectroscopy:

The optical property of synthesized MgO-NPs was examined using a UV-visible spectrophotometer (figure 7). It shows a broad absorption peak at ~300 nm which is in good agreement with some studies [36] [13] while differing from other studies. For instance, two studies showed the peak of absorption appeared at 270, 322 nm, respectively [15] [16] The difference of absorption peak is due to using other plants to *synthesyze Rhizophora lamarckii, Chromolaena odorata,* respectively**.**

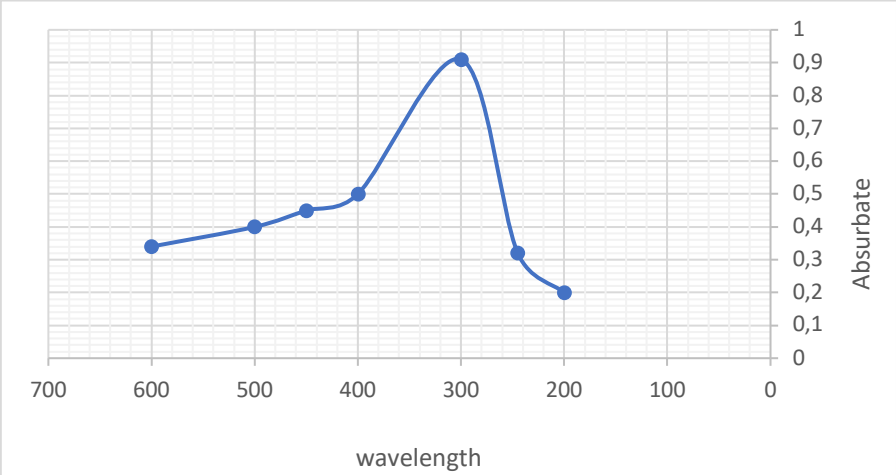

Figure 7. UV-Vis spectra showing a strong broad peak at 300 nm of MgO-NPs synthesized by *Opunita ficus indica* extract

2.2.2 Fourier-transform infrared spectroscopy (FT-IR) Spectrum:

The FT-IR analysis of MgO-NPs showed intensive peaks at 3410, 1603, 1419, 1061 and 660 cm^{-1}. The bands seen at 660 cm^{-1} indicated Mg-O bond stretching. This result is close to a number of studies such as the study in 2014, in which *Nephelium lappaceum L* was utilized in it , gave a peak at 694 - 588 cm^{-1}[27] [14], study [37] which utilized the *Alo vera* extract, gave a peak at 668- 438 cm^{-1}, and study [16] which utilized the *Sargassum wightii* extract in it, gave a peak at 540-660 cm^{-1}. The absorption peaks at 660 and 1061 cm^{-1}corresponded to N-o bending vibrations [38]. A broad absorption peak observed between 1419 and 1061 cm^{-1} was resultant of the C–H group bending vibrations or C–O or C–C group present in the extract group present in protein, flavonoids, carbohydrate or terpenoids [39]. Presence of a strong and broad absorption peak 3410 $cm^{-1}$was corresponding to the overlapping stretching vibrations of –NH2 and –OH groups due to the O–H in phenol/alcoholic (polyphenolic and terpene), and N–H groups of the amino acids, protein present in the *Opunita ficus indica* extract [40]. FTIR results suggested that the polysaccharides, phenols and amins present in the extract might have been involved in the formation of MgO-NPs from Mg (NO3)2 as the reductant agent. (Figure 8)

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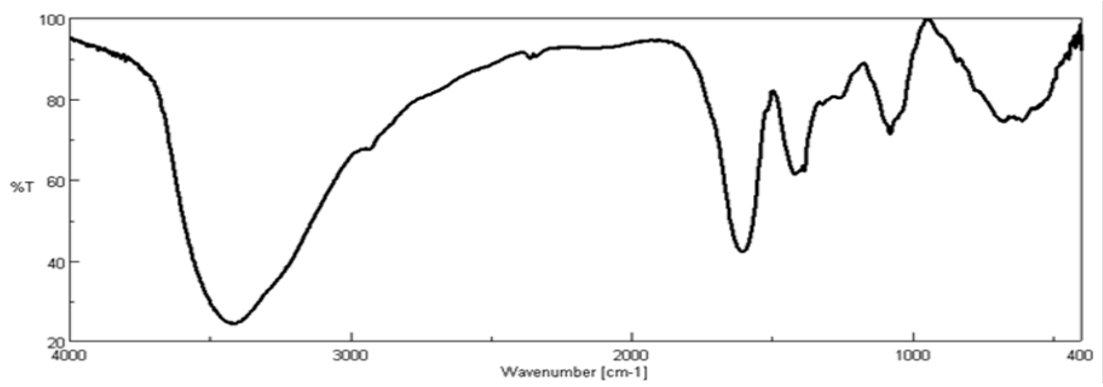

Figure 8. FTIR spectrum of MgO-NPs fabricated using *Opunita ficus indica* extract

2.2.3 Scanning Electron Microscope (SEM):

The Scanning electron microscopy (SEM) has been involved to characterize the shape and size of the fabricated MgO-NPs. The SEM image of the MgO-NPs is displayed in (Figure 9), it can be concluded that the MgO-NPs have spherical shape with a diameter ranging between 44 and 172 nm (the average size was 99 nm) Calculated from the simple statistical equation in the Origin 2017 program from the histogram shown in (figure 10). Our result was close to the two studies [41] [42], in terms of dimensions, while differing from other studies [37] [43], due to the difference in the capacity of the bio-source utilized in fabrication according to its active ingredients.

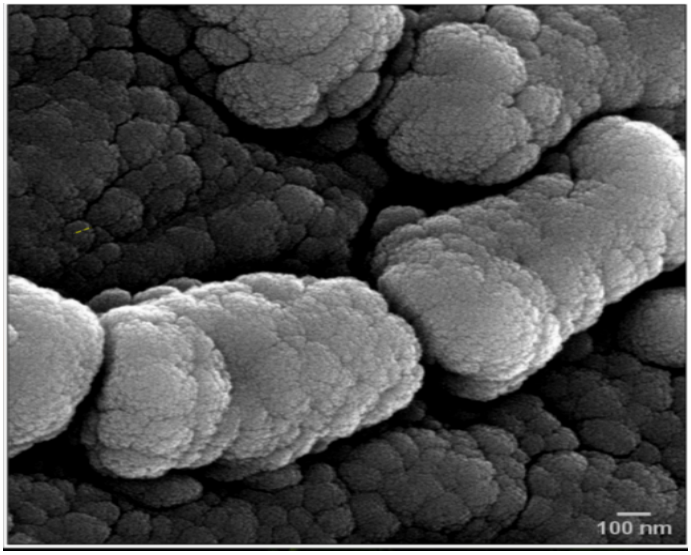

Figure 9. SEM images of MgO-NPs

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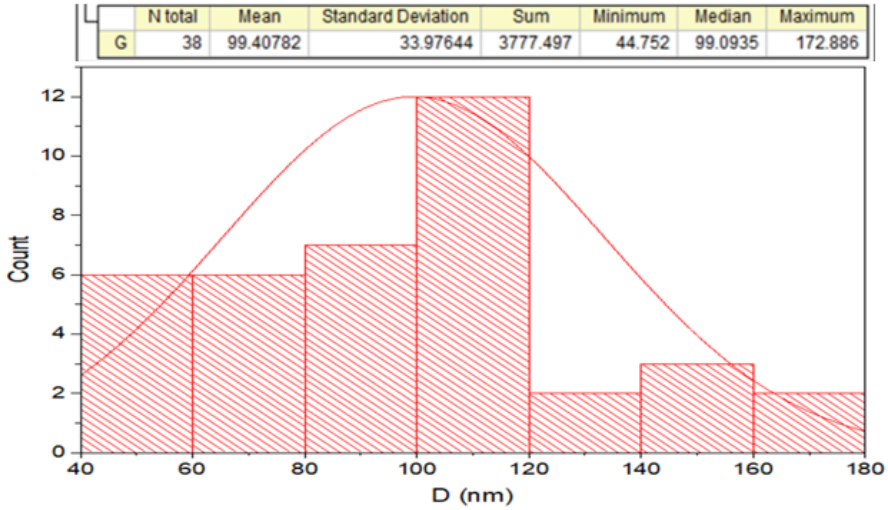

Figure 10. diameter histogram of MgO-NPs

2.2.4 The Energy dispersive x ray spectroscopy (EDX):

The analysis showed good signals to Mg, O together with remarkably stronger peaks confirming that the pellets were MgO-NPs. The other elements are thought to be originated from the *Opunita ficus indica* extract which is depicted in (figure 11) thus confirming the formation of MgO-NPs.

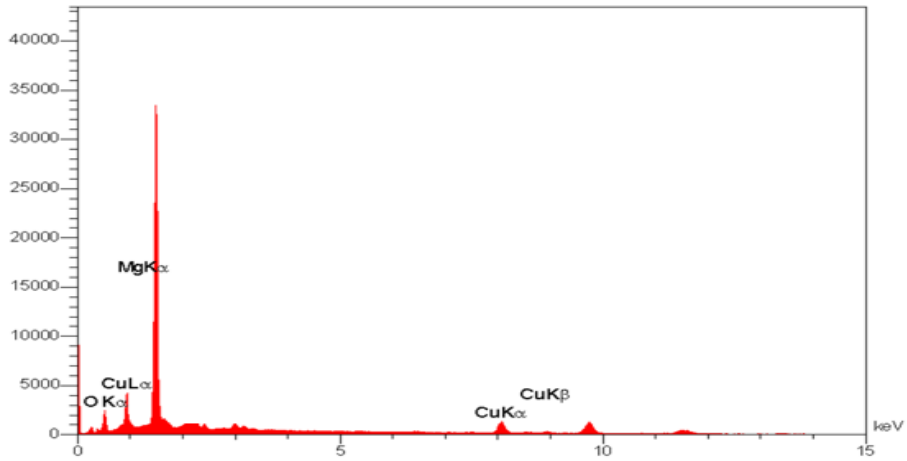

Figure 11. EDX analysis of MgO-NPs

2.3 Antifungal activity:

Within 7 days of *In vitro* incubation, as illustrated in Figure 12, it was found that MgO-NPs restrained the mycelial growth of fungi under test conditions, displaying dramatic concentration-dependent toxicity effects, showed a progressive inhibitory effect when we were utilized a progressive concentration 0.5%, 1.25% and 2.5%, the inhibitory ability was 100%, 100%, 66.6% when substituting in the equation. This study is in agreement with the previous study [45], In which they also found higher concentrations to be more effective

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than lower concentrations. In the current work, the inhibitory ability was higher than in the study [46] which was 19% and 89% in the concentration (0.5% and 1%) of MgO-NPs. This is due to the difference in the plant utilized in fabrication, and therefore the size, shape and characteristics of the manufactured nanoparticles. Antifungal activity of MgO-NPs may be explained by the generation of reactive oxygen species (ROS) [47], and may also affect the expression of some microbial proteins and enzymes. Disruption of DNA replication has also been documented [48], which was in accordance with other metal nanoparticles ZnO NPs [49], Ag-NPs [50] and Au-NPs [51].

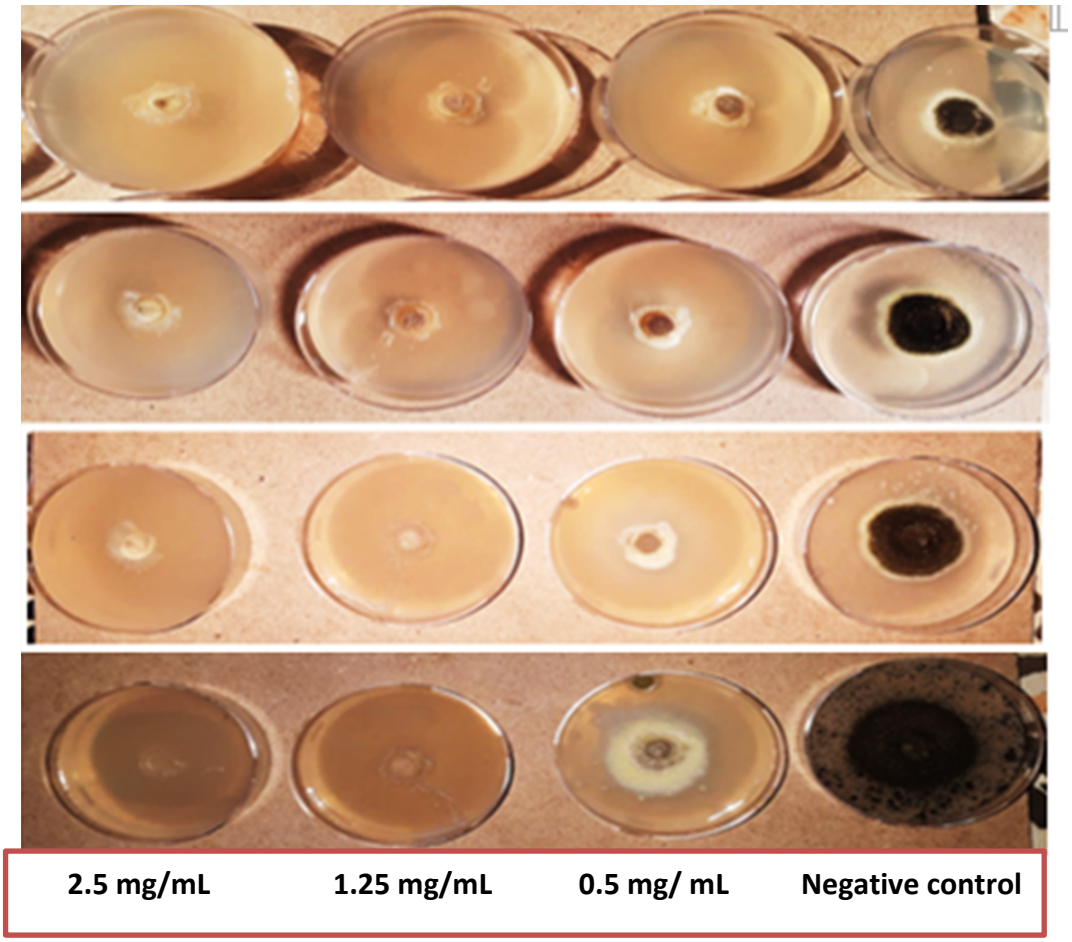

Figure 12. Antifungal activity of MgO-NPs against *Aspergillus niger*

3. CONCLUSION

Nanomaterials an emerging area that allows the use of antimicrobial compounds in a more efficient manner. In this study, antifungal activity of the MgO-NPs fabricated using *opuntia ficus indica* extract was evaluated. Characterization of nanoparticles shown SPR peak at 300 nm confirms the formation of MgO-NPs. Functional groups responsible for the bioreduction and stabilization of the synthesized MgO-NPs using the extract were identified in FTIR analysis. SEM analysis revealed that the size was less than 100 nm with spherical shape, and EDX spectrum confirmed the presence of magnesium (Mg), and oxygen. In addition, MgO NPs have shown the considerable antifungal activity against *Aspergillus niger* by Poisoned Food Technology. MgO nanoparticles, alone or in combination with other antifungal compounds, could be a better choice in various future applications like coating on medical devices or in food preservations and paints. In addition to its low cost, which is a priority for patients.

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4. MATERIALS AND METHODS

4.1 MATERIALS:

Ten types of cacti and succulent plants (figure 13) were collected from wild plants growing in Homs, Syria (34°21′N 38°19′E). Double-distilled water (DDW) was used in the experiments. Sodium hydroxide 98% (Medex, UK), Ethanol GR (Eurolab, UK), and the chemical materials were obtained from Aldrich.

Aspergillus niger isolate culture: *Aspergillus niger* isolate was obtained from the Microbiology lab at Pharmacy College, Al-Baath University, Syria.

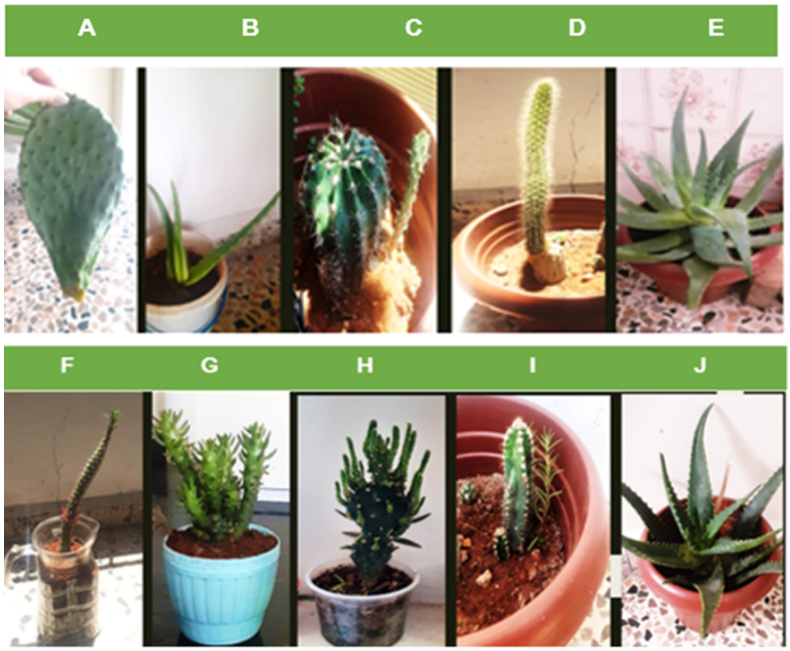

Figure 13. Cacti and succulent plants utilized to fabricated MgO- NPs

4.2 METHODS: Experiments were performed in triplicate.

4.2.1 Preparation of the extract: The healthy succulent and cactus plants were collected, washed under running tap water, dried for 5 minutes at room temperature and finely chopped. Briefly, 50 g of plant were suspended in 500ml beaker consisting of (100 :50 mL) (DDW: Ethanol) and treated with ultrasonic waves for 30 min at 50°C. The extract obtained was filtered through Whatman number 1 filter paper, and it was concentrated by rotary evaporator until remove of all the ethanol. Freshly prepared extract was used for the synthesis of MgO-NPs.

4.2.2 Green synthesis of MgO-NPs: in the experiment MgO-NPs were prepared after reaching optimization of parameters shown in (table1, figure 14), by slowly mixing 10 ml of plant extract with 90 ml of 10^{-3} M aqueous solution of magnesium nitrate dropwise under stirring by mixer *(Germany DI 18 basic)*, and adding NaOH (0.1 N) until pH is 11. Then, the mixture was left overnight with magnetic stirring and at 35°C. The Magnesium nitrate ions were reduced to Magnesium Oxide nanoparticles by using plant extract. The formation of MgO-NPs was observed by color change. Thereafter, the solvent of nanoparticles was evaporated with rotary evaporator *(Switzerland, Heidolph Instruments)*. Finally, the obtained precipitate was dried at 60°C and calcinated at 500°C for 3 h to produce MgO-NPs.

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Table 1. Design of experiment for the optimization of parameters

Fixed parameters	Parameter to be optimized
A: Opuntia ficus indica, B: Aloe albida, C: Echinopsis cristata, D: Peniocereus serpentinus, E: Aloe camperi, F: Austrucylindropunita subulata, G: Eve's needle, H: Opuntia monacantha, I: Cereus peruvianus, J: Aloe vera	Type of plant
Water, ethanol, Methanol, Water: Ethanol (2:1), Water: Methanol (2:1)	Solvent of extract
Magnesium nitrate, Magnesium chloride, Magnesium oxide	Precursors of Mg
0, 1, 2, 3, 4, 6, 24, 48 hr	Stirrer time
25, 35, 50, 70, 100 °C	Stirrer temperature (°C)
3, 7, 9, 11	pH of reaction

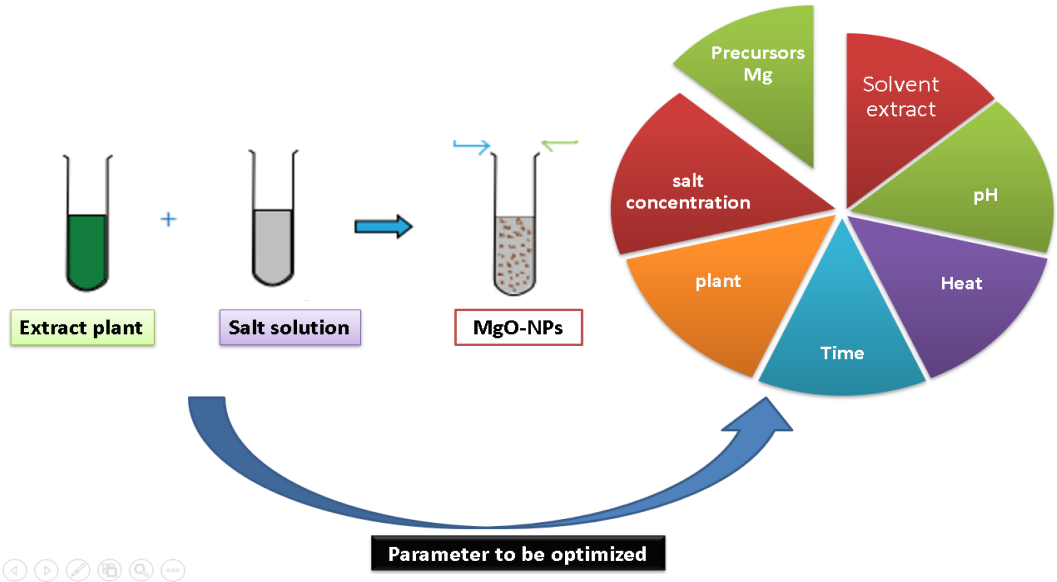

Figure 14. Process of green synthesis of MgO- NPs from *Opunita ficus indica*

4.2.3 Characterization of MgO-NPs: the parameters were optimized based on the average particle size of the samples by analyzed by dynamic light scattering (DLs) (Zeta-size and Nano-ZS; Malvern Instruments, UK) at 25°C, and the concentration of MgO nanoparticles was determined by UV-Vis spectrophotometer (SHIMADZU, Japan). To obtain the UV–Vis absorption spectrum, a stock solution of the MgO-NPs diluted with distilled water (1:1 ratio) and the spectrum was recorded in the range of 200-600 nm to ensure the presence of specific Surface Plasmon Resonance (SPR) peak of MgO-NPs. It is important to synthesize nanoparticles with a smaller size and higher absorbance [52]. The MgO-NPs were palletized with KBr and analyzed using FTIR(SHIMADZU) spectrometer. To confirm particle size and shape utilized FESEM, SEM were used and Image J and Origin 2017 were used to prepared the histograms for dimensions. Finally, the EDX analysis confirmed the presence of MgO -NPs.

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4.2.4 Preparation of media: Two different media were used in this study, Potato Dextrose Agar (PDA) for isolation of fungi and Czapek Dox Agar (CDA) for testing antifungal potential of MgO-NPs. The media was then sterilized at 121°C for 15 min.

4.2.5 Antifungal activity of MgO-NPS: assessment of the antifungal activity of the MgO-NPs was carried out using the poisoned food technique: CDA medium with different concentrations of MgO-NPs (o.5, 1,25, 2.5 %) were prepared by adding appropriate quantity of MgO-NPs, to the melted medium, followed by manual rotation of erlenmeyer to disperse the nanoparticles. About 15 ml of the medium were poured into Petri-dishes (6 cm). Each Petri dish was inoculated at the center with a mycelial disc (6 mm diameter) taken at the periphery of *A. niger* colonies grown on PDA for 48 h. Control plates (without MgO-NPs) were inoculated following the same procedure. Plates were incubated at 25°C for 7 days and the colony diameter was recorded each two days. Diameter of fungal colonies of treated and control sets was measured, and inhibition percentage (I) of fungal growth was calculated according to following formula:

$$I = C\text{-}T/C \times 100$$

C: the diameter of growth zone in the test plate

T: the diameter of growth zone in the control plate

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Conflict of interest statement: Authors have declared there are no competing interests.

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