Original Article

Novel green synthesis of Fe2O3 nanoparticles using persimmon extract and study their anti-cancer and anti-bacterial activity

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Abstract

Iron oxide nanoparticles (Fe2O3NPs) were produced using the persimmons aqueous extract. The ability to produce pure Fe2O3NPs was demonstrated using the transmission electron microscope (TEM), field emission scanning electron microscope (FE-SEM), X-ray diffraction (X-ray), and fourier transform infrared spectroscopy (FTIR). In addition to being evaluated for antibacterial activity against both Gram positive and Gram negative bacteria, including Escherichia coli and Staphylococcus aureus, iron oxide NPs were also examined for anticancer activity against the hepatocellular carcinoma cancer (Hep-G2) cell line. Investigations into Fe2O3NPs considerable inhibitory efficacy against pathogenic bacterial strains revealed a wide range of biological uses for the particles.

Furthermore, the Hep-G2 hepatocellular carcinoma cancer cell line is significantly cytotoxic to Fe2O3NPs. Consequently, the research demonstrates a minimal toxicity, making them suitable for use in a wide range of biological applications.

Keywords: Green synthesis, Fe2O3NPs, Nanoparticles, Persimmon extract, Staphylococcus aureus, Escherichia coli.

1. Introduction

Nanoscience is the study of items with the smallest dimensions, which can be as little as a few nanometers or as large as 100 nm while nanotechnology is primarily concerned with the processing of materials by one atom or one molecule for separation, consolidation, and deformation [1]. The word nano refers to a Greek prefix that means dwarf or very little, and represents a thousand millionth of a meter (10-9) m [2].

The utilization of metallic and metal oxide nanoparticles, carbon nanotubes, liposomes, for particular biological purposes. These materials surface chemical and physical features allow them to be used in diagnostics, biosensing and bioimaging devices, medication delivery systems, and bone replacement implants [3]. Nanoparticle-based medicine is presently being researched as a way to treat complicated illnesses with more efficacy and fewer side effects, resulting in unequaled medical diagnostic advantages [4].

Nanoparticles (NPs) are minuscule particles with a size of 1-100 nm. These particles have unique physical features including conductivity, stability, and optical qualities, making them useful for biology and materials research [5]. Nanotechnology is a burgeoning field today, exploiting the physicochemical characteristics that result from the manipulation of matter at the nanoscale. Catalysis, optical, thermal, mechanical, electrical conductivity, and chemical processes are where nanomaterials get their enormous efficiency and productivity. Nanomaterials are increasingly being offered for sale as commodities due to their numerous uses in a variety of industries [6].

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Access this article online

Quick Response Code:

Website: www.pnrjournal.com

DOI: 10.47750/pnr.2022.13.03.150

How to cite this article: Sarah Abd Al-hameed, Ahmed Mishaal Mohammed, Novel green synthesis of Fe2O3 nanoparticles using persimmon extract and study their anti-cancer and anti-bacterial activity, J PHARM NEGATIVE RESULTS 2022;13: 958-967.

Nanomaterials have a wide range of uses in society, including the energy, health, and industrial sectors. Products using nanomaterials have become increasingly prevalent as a result of the enormous expansion of the industry. The realm of medicine is one of the most interesting uses of nanotechnology [7]. Because of their enormous surface area and strong conductivity, nanomaterials have found a wider range of applications in catalysis in the optical and sensing industries. Recent advancements in its synthesis and use have sparked an interest [8].

Metal oxides and metal nanoparticles are the most promising materials and more effective, safer, and risk-free ways to combat microbial diseases. Silver, gold, iron oxide, and zinc oxide nanoparticles, for example, have a strong antibacterial effect on microorganisms, especially pathogens [9]. These nanoparticles have been shown to be successful as additional antimicrobials, antimicrobial agents, food packaging, textiles, deodorants, skin-care products, oral hygiene, and strengthening the surfaces of medical equipment that are susceptible to microbial infections [10]. Metal and metal oxide nanozyme are used in chemical detection and biosensing, cancer treatment, water purification, and antibacterial efficiency [11]. The present progress of nanotechnology has ushered in a new trend in the production of unique biomaterials with improved properties and functionalities for particular biomedical applications, such as pharmaceutical applications in biomedicine. Nanoparticles are increasingly being used in biomedical applications such as targeted medication delivery, hyperthermia, photoablation therapy, biosensors, bioimaging, and gene transfer [12].

Green or biological synthesis has a number of advantages. The following are some of the advantages of green synthesis energy conserving, production at a low cost. There will be fewer accidents, product that is risk free and economical because it produces less trash, it is sometimes referred to be environmentally friendly. Human health and communities are protected through competitive advantages. Applications in the pharmaceutical sector and other biomedical fields [13].

Phenolic chemicals which are found in abundance in plants, are an important element of the human diet and are of great interest owing to their antioxidant characteristics and possible health benefits. These compounds range structurally from a simple phenolic molecule to complex high molecular weight polymers [14]. There is a ton of evidence that supports the idea phenolic acids are so prevalent, individuals regularly consume them in meals including cereals, fruits, and vegetables. Because phenolic acids primarily function as antioxidants and protect against oxidative diseases including cancer and coronary heart disease, these foods enhance health [15].

The inorganic compound iron oxide, often known as ferric oxide, has the formula Fe2O3. Iron (II) oxide (FeO), which is uncommon, and iron (II,III) oxide (FeO) are the other two primary oxides of iron (Fe3O4) for the steel industry, Fe2O3 is the primary source of iron. Rust is a term used to describe iron (III) oxide [16].

Iron oxide NPs have a wide range of uses that urge scientists to employ them in a variety of sectors including biomedicine, cosmetics, bioremediation, diagnostics, and material engineering. Their function has been demonstrated before in MRI and medication in a regulated manner for tumor treatment and tissue [17]. Fe2O3NPs have a huge surface area, a small band gap, and are quite stable in nature, making them useful in a variety of applications. Furthermore, the biological production of Fe2O3NPs is low cost. As a result, diverse medicinal plants are being used to create phytofabricated new nanomaterials with a wide range of uses. Biological production of Fe2O3NPs revealed great antibacterial activity and significant biocompatibility in preliminary investigations [18]. Iron oxide nanoparticles are chemical substances that are frequently referred to as "ferric oxide " have unusual features that many researchers are studying in depth because of their potential utility in a wide range of applications, including sensors, catalysis, gas, hydrogen, and lithium ion storage, and controlled medication delivery. The size, shape, and porosity of iron oxide nanoparticles have a big impact on their performance. As a result, the form of nanoparticles has a big impact on their characteristics in the biomedical industry [19].

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer and the fourth leading cause of cancer-related deaths in the world. Globally, lower to middle income nations have the highest frequency of HCC [20]. Chronic alcohol intake, hepatitis B and C virus infections, nonalcoholic fatty liver disease, an aflatoxin B1contaminated diet, and other factors can all lead to hepatocellular carcinoma [21]. Surgical resection, liver transplantation, transcatheter arterial chemoembolization (TACE), radiation, and cryoablation are all used to treat liver cancer, however they are ineffective and have major side effects include hair loss, depression, renal failure, and liver failure [22].

Due to its extraordinary adaptability, the Hep-G2 cell line is one of the most commonly utilized cancer cell lines in various areas of biological research. It is a hepatoblastoma cell line that represents the human endodermal lineage [23]. In the vast majority of situations, those who acquire HCC are already cirrhotic. Histological abnormalities such as increased cell density and nuclear to cytoplasmic ratio, unpaired arteries, and pseudo-glands development are all associated to the early phases of malignant transformation [24]. Because nanotechnology is a rapidly increasing field of research that helps to the development of new pharmaceuticals and pharmaceutical treatments, feasible nanotechnology based medical remedies are required to cure this sickness [25]. Plant based medications have lately gained a lot of attention due to their exceptional chemotherapeutic and chemopreventive characteristics. They're well tolerated, non-toxic, low cost, and easy to use. Natural antioxidants and anticancer medications delivered in nanocarriers may have a

synergistic impact for many years where was drugs have been delivered to tumor sites using nanocarriers [26].

Bacteria is a kind of prokaryotic cell bacteria in general. Bacteria is just one of the many microorganisms that have been discovered in the human body, including the skin, mucous membranes of the mouth and nose, and the reproductive and digestive systems [27]. The thickness of the peptidoglycan layer encircling the cytoplasmic membrane distinguishes Gram-negative Escherichia coli (E.coli) and Grampositive bacteria Staphylococcus aureus (S. aureus). Gram-positive bacteria have a coating of peptidoglycan strands that can be as thick as (30-100) nm or even thicker, whereas Gram-negative bacteria have only a few nanometers of peptidoglycan strands [28]. Another technique for improving bacteria eradication and bioavailability is to encapsulate antibiotic medicines in nanocarriers. In comparison to traditional treatment, medication delivery using nanosystems enhances effectiveness while lowering potential toxicity.

Nanoparticles contribute to effective antibacterial action with their strong affinity for bacteria due to their high surface to volume ratio, the ability to surface functionalize, and the capacity to load medication molecules [29].

Fruits and vegetables are examples of bioactive or functional foods that support health advantages. Due to their active ingredients, bioactive foods have been shown to help with diabetes, cancer, and cardiovascular disorders. Carotenoids, flavonoids, vitamins, and minerals are some of the compounds active components [30].

Persimmons have one of the greatest antioxidant capabilities of any fruit due to their high gallic acid content, making them potentially valuable as a meal to reduce oxidative stress [31]. The antioxidant capacity of persimmon functional components is also responsible for their anti-malignant and anti-melanogenic properties [32].

The objective of the current work was to create Fe2O3NPs using a biological process using persimmon extracts, and to test their effectiveness against the Hep-G2 cancer cell line, Escherichia coli, Staphylococcus aureus, and other bacteria.

2. Materials and Methods

2.1 Materials

Cancer cell lines Hep-G2 was collected from the Baghdad Cancer Research Centre. RPMI-1640, trypsin-EDTA, and fetal bovine serum were obtained. Santacruz Biotech (USA) was used to procure dimethyl sulfoxide, and MTT was obtained from Bio World (USA). Muller-Hinton (M-H) agar and NiCl2.6H2O were obtained from Hi-Media (India) and Annular Normapur (Germany), respectively. Chem-Lab provided deionized water (H2O, Belgium). Fresh Persimmon was obtained from the local market in Iraq in November.

2.2 Methods

2.2.1 Preparation of persimmons extract

Fresh persimmons were purchased in the month of November from the local market in Iraq. The persimmons were separated and purified from the branches and seeds and washed several times in deionized water. The persimmons 250 g were smashed well with 250 mL deionized water form a homogeneous mixture in the mixer. The mixture was filtered through Whatman paper No. 1. A light brown persimmon extract was obtained as shown in Fig. (1).

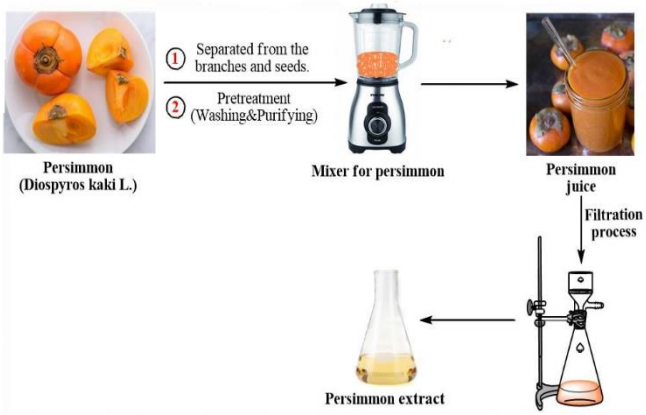


Figure (1): Preismmon extract preparation

2.2.2 Synthesis of Fe2O3NPs

20 mL FeCl3 concentration 0.04 M was taken with 50 mL of persimmon extract. This was achieved by pouring 10 mL of persimmon extract in five batches with an interval of 10 minutes between each batch. The mixture was heated for 2:30 h using a magnetic stirrer at 85 °C. The colour changed from light orange to dark brown, after 1M NaOH solution was added dropwise to adjust the pH of the mixture (monitored using a pH meter) to pH 9 the resulting solution was then centrifuged at 10000 rpm indicating that Fe2O3 nanoparticles formed as shown in Fig. (2).

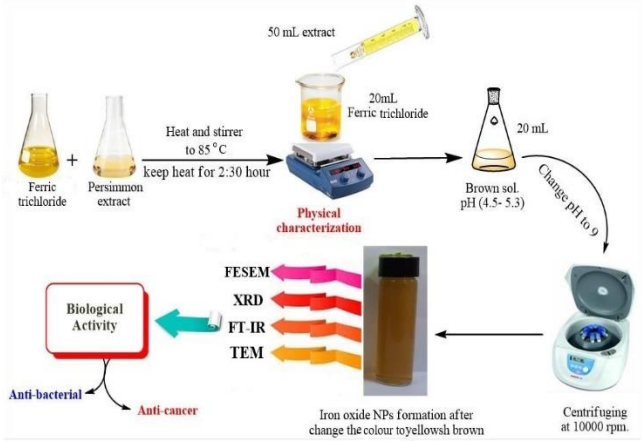


Figure 2: Synthesis of Fe2O3NPs

2.2.3 Mechanism of formation of Fe2O3NPs

Initially, the addition FeCl3, to a persimmon extract containing phytochemicals may result in a decrease in iron

ions, as well as nanoparticle stability. A change in colour and a reduction in pH have been noticed in the synthesise process when precipitates occur and it denotes the involvement of the –OH groups in the reduction of iron ions. Because of the presence of carbohydrates amino acids, and alcohols, the -OH group is typically detected in extract. The –OH groups in this case come from polyphenols present in the extract, which absorb iron cation and reduce it to Fe0.

Polyphenols –OH groups have also been shown to reduce iron ions and other metal ions, making them reducing agents [33,34]. The reduction of metal ions produces ferric hydroxide and ultimately solid Fe2O3 nanoparticles. Following the creation of these solid particles, phytochemicals begin to act as capping agents. The phytochemicals in persimmon extract with the functional groups, such as C–N, N–O, –OH, C=C, C=O, C–O, etc., participate in the particle's surface. These functional groups are found in a variety of phytochemical families, including flavonoids, alkaloids, and others [35,36].

These are groups that attach to the surface of iron oxide and alter its form, growth, and aggregation selectively [37] . Nanocrystals may spin in a controlled manner, resulting in well-organized structural assemblies. Finally, high crystallinity multi-structured Fe2O3 is produced as shown in Fig.(3). [38].

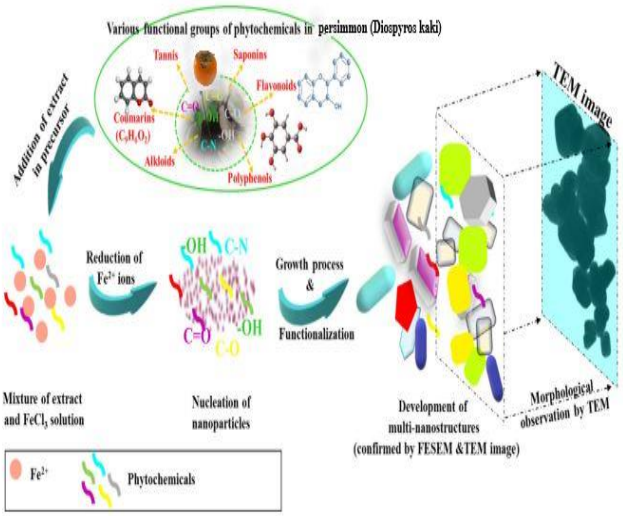


Figure 3: Mechanism of formation of iron oxide nanoparticles [38]

2.2.4 Characterization of Fe2O3NPs

The morphological properties of the Fe2O3NPs, such as size and shape, were studied using FE-SEM, TEM and X-ray diffraction (XRD) was used to determine the crystalline size and structure of the NPs using an automated diffraction meter (Shimadzu 6000 XRD). FTIR was used to identify the functional groups in the Fe2O3NPs solution (Shimadzu 8400).

2.3 Anti-cancer activity

2.3.1 Maintenance of cell cultures

RPMI-1640 supplemented with 10% fetal bovine serum, 100 units/mL penicillin, and 100 µg/mL streptomycin was used to sustain Hep-G2 cells. Trypsin-EDTA was used to passage the cells, which were then reseeded at 80% confluence every other day and cultured at 37 °C [39,40].

2.3.2 Cytotoxicity determination using MTT Assay

96-well plates were used for the MTT experiment to assess if Fe2O3NPs were cytotoxic [41,42]. At 1×104 cells per well, cell lines were planted. Cells were treated with Fe2O3NPs at various concentrations after 24 hours or when a confluent monolayer was obtained. By removing the media, adding 28 L of a 2 mg/mL solution of MTT, and incubating the cells for 2.5 hours at 37 °C, cell viability was assessed after 72 hours of treatment. After the MTT solution was removed, the crystals in the wells were solubilized by adding 130 µL of DMSO (Dimethyl Sulphoxide), which was then incubated at 37 °C for 15 min while being shaken [43]. The experiment was carried out in triplicate, and the absorbency was measured using a microplate reader at 492 nm. The following calculation was used to quantify the rate at which cell growth was inhibited (the percentage of cytotoxicity) [44,45].

Inhibition rate = A- B/A*100 …… (1)

Where A is the optical density of control, and B is the optical density of the samples [46].

The cells were planted into 24-well micro titration plates at a density of 1×105 cells mL−1 and cultured for 24 hrs. at 37°C. In order to observe the morphology of the cells under an inverted microscope. Following that, cells were exposed for 24 hrs. to Fe2O3NPs. The plates were stained with crystal violet dye following the exposure time, and they were then incubated at 37°C for 10-15 minutes [47]. It took several gentle washes with tap water to thoroughly remove the colour off the spot. A digital camera attached to the microscope was used to take pictures of the cells as they were being examined under an inverted microscope at a 100x magnification [48-50].

2.3.3 Statistical analysis

With GraphPad Prism 6 an unpaired t-test was used to statistically assess the acquired data [51]. The results were shown as the mean ±SD of three independent measurements [52].

2.3.4 Anti-bacterial activity

With the use of an agar well diffusion assay, the produced Fe2O3NPs were tested for their antibacterial ability against Gram-negative E. Coli and Gram-positive S. aureus bacterial strains [53]. Muller-Hinton (MH) agar was aseptically poured 20 mL at a time onto sterile Petri dishes. A sterile wire loop was used to capture the bacteria from their stock cultures [54].

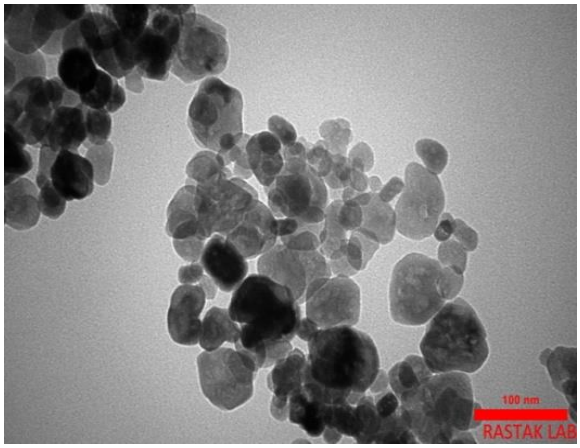
After the organisms had been cultured, sterile tips were used to bore 6 mm-diameter wells on the agar plates. Fe2O3NPs

were injected at various concentrations into the bored wells. Before measuring and recording the average of the zones of inhibition diameter, the cultivated plates containing the Fe2O3NPs and the test organisms were incubated overnight at 37°C [55,56].

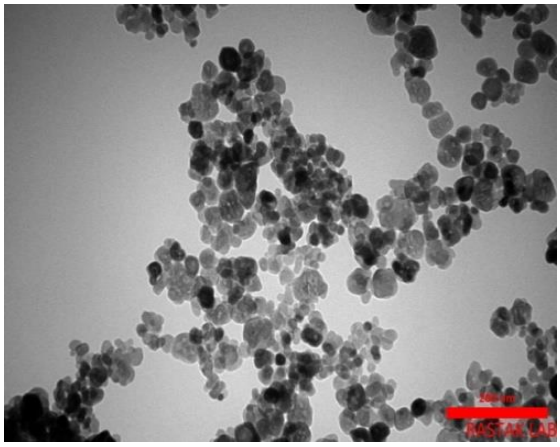
3. Results and discussion

3.1 TEM

TEM analysis was recorded to study the morphological characterization and determine the size and structure of Fe2O3. The images show the synthesised Fe2O3NPs by persimmon and that most of Fe2O3 nanoparticles or spherical in their shapes as seen in Fig. (4).



(a)

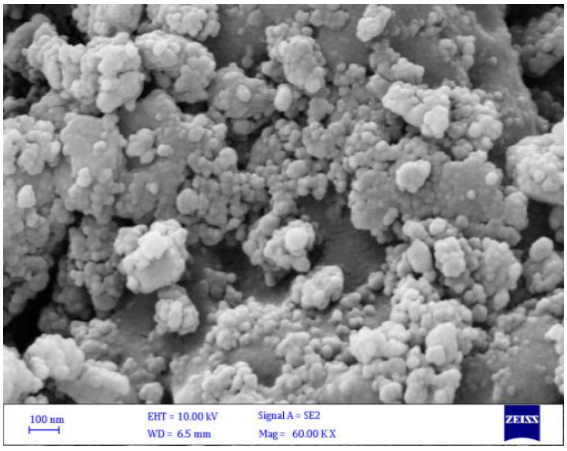


(b)

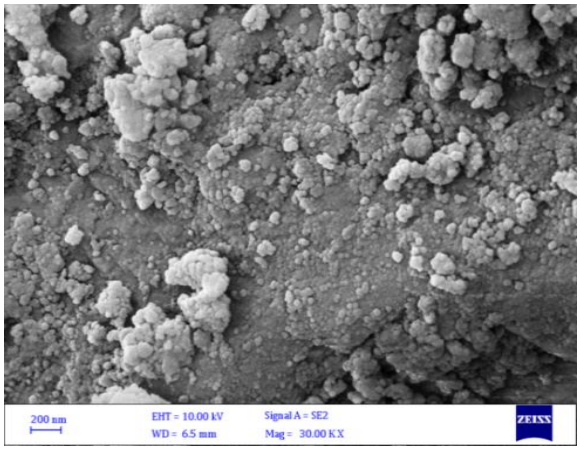
Figure 4: TEM for Fe2O3NPs (a) 100 nm and (b) 200 nm.

3.2 FE-SEM

FE-SEM technique is used to observe the surface physical morphology of the Fe2O3NPs. Fig.(5) shows atypical surface of Fe2O3NPs prepared from persimmon by biosynthesis. The images of FE-SEM showed a relatively nanoparticles of Fe2O3 that formed with diameter ranges from (30-60) nm.



(a)



(b)

Figure 5: FE-SEM for Fe2O3NPs (a) 100 nm and (b) 200 nm.

3.3 XRD

The XRD patterns of the synthesized Fe2O3NPs by persimmon extract as shown in Fig.(6). The strong characteristic peaks of Fe2O3NPs are obtained at 2θ = 33.36, 35.92, 41.02, 49.86, 54.27, 57.98, 62.65, and 64.11, which were respectively assigned correspond to diffraction peaks of (104), (110), (113), (024), (116), (018), (214), and (300). All the reflection peaks could be indexed to structure of Fe2O3NPs (JCPDS NO. 00-033-0664). These findings are analogous with the crystalline nature of Fe2O3NPs [57].

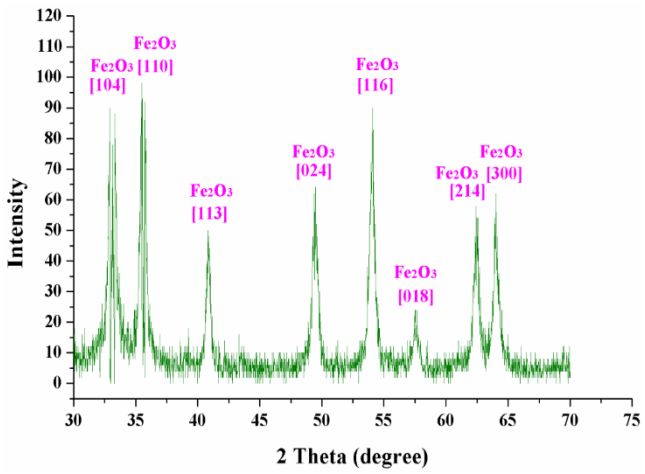


Figure 6: XRD patterns of Fe2O3NPs synthesized by persimmon extract

3.4 FTIR

In the FTIR spectra of Fe2O3NPs, Fig.(7). reveals the emergence of three well defined peaks at 543.93, 574.79, and 601.79 cm-1. These peaks were attributed to the FeO bonds stretching and bending modes, according to the literature [58]. As well as a peak at 1033.85 cm-1 of C–O groups in carboxylic acids or phenols [38].

The phytoconstituents of the extract are indicated by the presence of other and hydroxyl groups of water/polyphenols and keton group of Fe2O3, the O-H and C=O stretching and bending vibrations of surface were connected to the broad bands at 3259.70 cm-1 and 1631.78 cm-1, respectively [59].

Other FTIR absorption peaks associated with the amide C≡N functional group may be detected about 2129.41cm–1 [60].

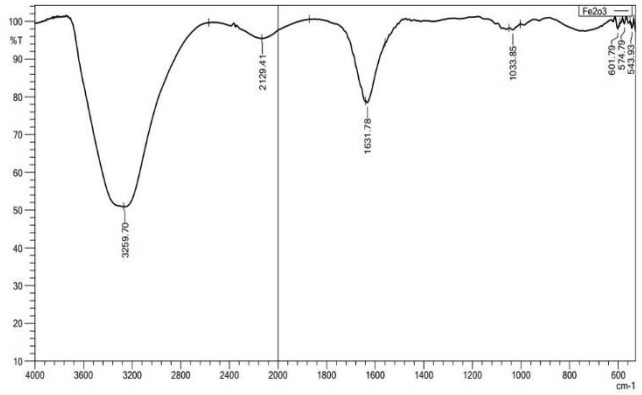


Figure (7): FTIR spectrum for Fe2O3NPs

3.5 Anticancer activity of Fe2O3NPs

Due to the variety in illness presentation, development, and recurrence, cancer is a complicated and clinically challenging disease. The unique attributes of NPs, such as their huge surface to volume ratio, simplicity of synthesis, and wide range of optical properties, enable the creation of new and effective cancer therapy techniques. The iron oxide NPs have shown to be safe and have a wide range of therapeutic uses, including cancer diagnostics and hyperthermia therapy, according to the food and drug administration (F&DA). Apart from being widely accessible and inexpensive, Fe2O3NPs also have a role in a variety of biological processes, making them a fascinating metal for NPs. The MTT assay was used to investigate the anticancer activity of the produced Fe2O3NPs against cancer cell lines, including Hep-G2 after exposure for 72 h. Cytotoxicity in Hep-G2 cells were treated with Fe2O3NPs at different concentration. The dose dependent inhibition of cancer cells was achieved by cancer cells treated with varying concentrations of Fe2O3NPs (125,250,500 and 750) µg/mL. Our results have shown the good anticancer activity using Fe2O3NPs and the outcomes are shown in Figs. (8 and 9).

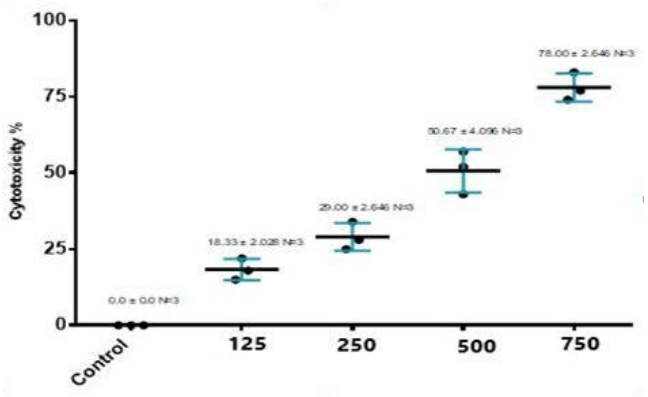
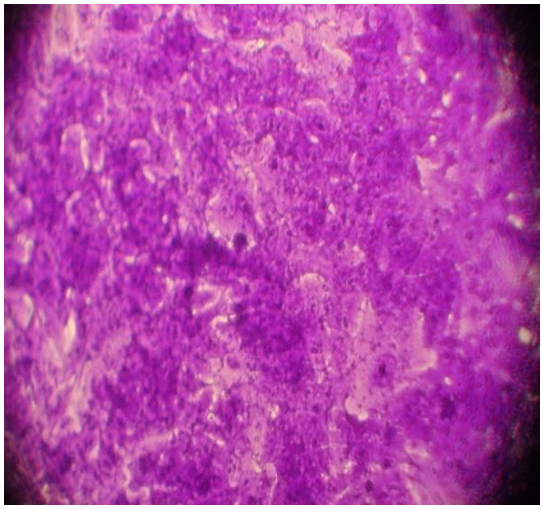


Figure 8 : Cytotoxicity effect of Fe2O3NPs in Hep-G2 cells



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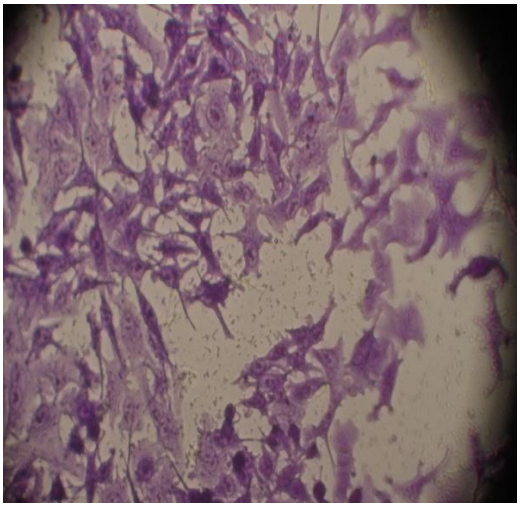


(b)

Figure 9: (a) Control untreated Hep-G2 cells (b) Morphological changes in Hep-G2 cells after treated with Fe2O3NPs

3.6 Antibacterial activity Fe2O3NPs

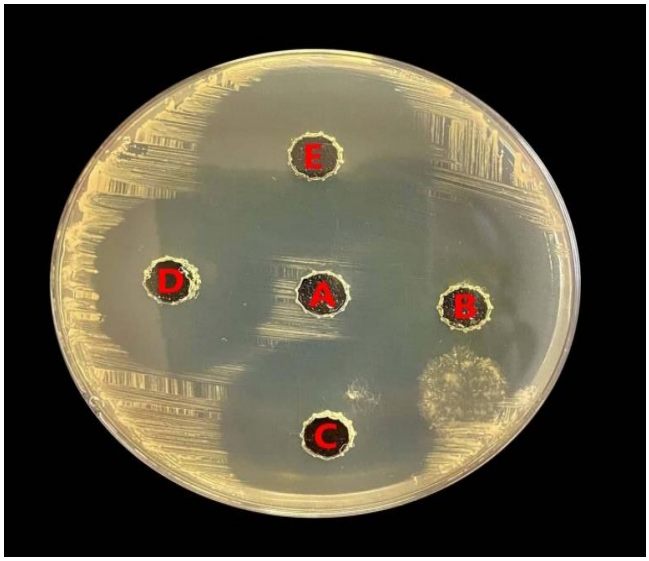
There is growing interest in metallic nanoparticles with antibacterial action as a result of the rise of antibiotic resistance among microbial diseases.

Iron oxide nanoparticles have attracted interest for their use in biomedicine for targeted drug administration, magnetic resonance imaging, and as potential anticancer agents in addition to their potential antibacterial uses. Antibacterial activities of synthesized Fe2O3NPs were performed against Gram-negative and Gram-positive bacteria. It was concluded that Fe2O3NPs showed effective results against these bacterial strains. showed effective Fe2O3NPs antibacterial activities against Gram-negative E.coli and Gram-positive bacteria S.aureus. the growth of against E.coli and S.aureus was completely inhibited by Fe2O3NPs.

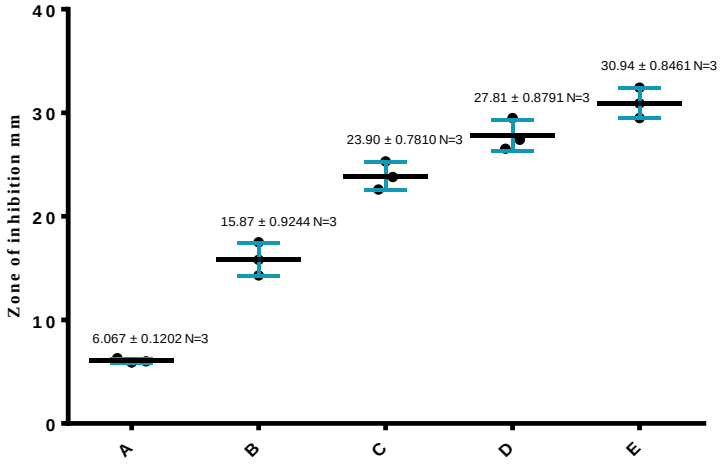
Fe2O3NPs displayed an inhibition zone with a diameter at various concentrations against S.aureus, as shown in the Table (1) and Fig. 10 (a,b) . Fe2O3NPs were shown to have significant inhibition with increased concentration.

Table (1): Growth inhibition of Fe2O3NPs against S.aureus

Concentration(µg/mL)	Inhibition zone (mm)
500	30.94 ± 0.84
250	27.81 ± 0.87
125	23.90 ± 0.78
62.5	15.87 ± 0.92



(a)



(b)

Figure (10): (a) Antibacterial activity of Fe2O3 against S.aureus.

A. Control untreated bacterial strains

B. Bacterial strain treated with 62.5 µg /mL

C. Bacterial strain treated with 125 µg /mL

D. Bacterial strain treated with 250 µg /mL

E. Bacterial strain treated with 500 µg /mL

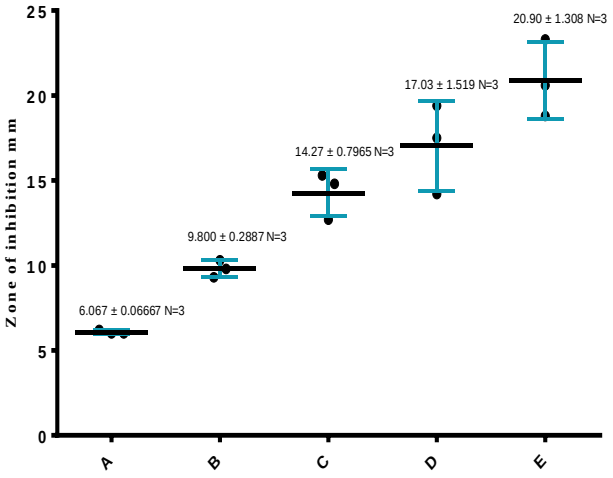
(b) Zone of inhibition for iron oxide NPs in µg /mL

Inhibition areas with the diameter as shown in Table (2) and Fig. 11 (a,b) are the activity of Fe2O3 NPs as antibacterial at various levels in E.Coli. Fe2O3NPs demonstrated considerable inhibition of growth with increased dose concentration.

Table (2): Growth inhibition of Fe2O3NPs against E.Coli

Concentration (µg /mL)	Inhibition zone (mm)
500	20.90 ± 1.30
250	17.03 ± 1.51
125	14.27 ± 0.79
62.5	9.80 ± 0.28

(a)



(b)

Figure 11: (a) Antibacterial activity of Fe2O3 NPs against E.Coli.

A. Control untreated bacterial strains

B. Bacterial strain treated with 62.5 µg /mL

C. Bacterial strain treated with 125 µg /mL

D. Bacterial strain treated with 250 µg /mL

E. Bacterial strain treated with 500 µg /mL

(b) Zone of inhibition for iron oxide NPs in µg /mL

4. Conclusion

An environmentally friendly method was used to create Fe2O3NPs from persimmon extract. This approach is the most cost-effective, easiest, and ecologically benign way to create nanoparticles. The anti-cancer and anti-bacterial properties of biogenic Fe2O3NPs appear promising. Gram-positive and Gram-negative bacteria were used to test the antibacterial activity of the Fe2O3NPs produced, and the antibacterial activity was shown to be potent. Fe2O3 nanoparticles created using persimmon extract also showed excellent results against the Hep-G2 cancer cell line. In addition, a variety of biological applications using green Fe2O3NPs call for greater research.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to acknowledge the contribution of the University Of Anbar (www.uoanbar.edu.iq) via their prestigious academic staff in supporting this research with all required technical and academic support.

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