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Lychee Honey-Mediated Synthesis and Characterization of Maghemite Nanoparticles: A Novel Approach for Potential Cancer Hyperthermia Applications

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Abstract

Iron oxide nanoparticles, specifically magnetite (Fe_3O_4-NPs), have become widely used and a significant area of research due to their superparamagnetism and distinctive properties. As a result, scientists are diligently looking into new uses for these nanoparticles. The choice and use of synthesis techniques are important variables that can affect the size and characteristics of the nanoparticles (NPs). The use of toxic chemicals that are absorbed on the surface of the nanoparticles has been linked to a number of negative effects of chemical synthesis methods. The Green synthesis of nanoparticles has emerged as an eco-friendly method in response to environmental concerns, giving researchers the chance to worldwide investigate the potential of various herbs for nanoparticle synthesis. Green synthesis is considered as a novel, rapid, and eco-friendly method for obtaining metallic nanoparticles (NPs). This study presents a novel and sustainable approach to synthesizing maghemite (γ-Fe_2O_3) nanoparticles using Lychee honey as a natural reducing and stabilizing agent. The green synthesis method eliminates the need for toxic chemicals, aligning with the principles of eco-friendly nanotechnology. The synthesized nanoparticles were characterized using a suite of techniques to confirm their structural, optical, thermal, and magnetic properties. Fourier Transform Infrared Spectroscopy (FTIR) identified functional groups from Lychee honey responsible for particle stabilization. Differential Thermal Analysis–Thermogravimetric Analysis (DTA-TGA) assessed thermal stability, while Ultraviolet-Visible (UV-Vis) Spectroscopy confirmed nanoparticle formation. Field Emission Scanning Electron Microscopy (FESEM) revealed uniform morphology and size, and Vibrating Sample Magnetometry (VSM) demonstrated superparamagnetic behavior, suggesting suitability for biomedical applications. These findings indicate that the synthesized nanoparticles possess the requisite properties for potential use in cancer hyperthermia therapy. Future research will focus on in vivo and in vitro studies to validate their clinical applicability. This work underscores the potential of green synthesis in advancing nanotechnology for sustainable and biomedical applications.

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Introduction

Nanotechnology has revolutionized multiple disciplines by offering materials with unique physical, chemical, and biological properties at the nanoscale. Among these, iron oxide nanoparticles, particularly maghemite (γ-Fe_2O_3), have garnered significant attention for their biomedical applications, including targeted drug delivery, magnetic resonance imaging (MRI), and cancer hyperthermia therapy. The superparamagnetic behavior of maghemite nanoparticles makes them ideal for generating localized heat under alternating magnetic fields, a principle that underpins their application in magnetic hyperthermia for selective cancer cell destruction. (Kobayashi 2011; Fernández-Álvarez *et al.* 2021; Yadav *et al.*, 2018; Múzquiz-Ramos *et al.* 2015; Sangaiya *et al.* 2018).

Despite their potential, conventional synthesis methods for maghemite nanoparticles, such as thermal decomposition and chemical precipitation, often require harsh chemicals, high temperatures, and energy-intensive processes. These methods pose environmental risks and raise concerns about biocompatibility, particularly for medical applications (Philip 2010; Schwaminger *et al.*, 2020; Nikiforov *et al.*, 2017; Rasouli *et al.*, 2018). In response, green synthesis approaches have emerged as sustainable alternatives, utilizing natural materials like plant extracts, microorganisms, and biopolymers as reducing and stabilizing agents. These eco-friendly methods minimize toxic byproducts while producing biocompatible nanoparticles (Bali Ogholbeyg *et al.*, 2018; Nadaroglu *et al.*, 2017; Grazyna *et al.*, 2009; Pisane *et al.*, 2017). Honey, with its rich composition of natural sugars, amino acids, and antioxidants, has shown promise as a dual reducing and stabilizing agent in nanoparticle synthesis (Bahari *et al.*, 2023; Bonsignore *et al.*, 2021). Lychee honey, in particular, is an unexplored resource for producing maghemite nanoparticles with biomedical potential. Leveraging its biochemical properties, this study aims to develop a sustainable method for synthesizing maghemite nanoparticles, avoiding toxic reagents and aligning with green chemistry principles. By presenting a novel, sustainable synthesis method, this work contributes to the growing field of green nanotechnology and highlights the potential of maghemite nanoparticles for safer and more effective cancer treatments.

Cancer continues to pose a global health challenge, with millions of new cases diagnosed annually. Despite significant advances in cancer treatments, traditional therapies such as chemotherapy and radiation are often associated with numerous side effects, including damage to healthy tissues, weakened immune systems, and reduced quality of life for patients. These side effects arise primarily because these treatments are not selective; they affect both cancerous and healthy cells, leading to systemic toxicity and other complications. As a result, there is a critical need for more targeted, less harmful treatment options.

One such promising approach is cancer hyperthermia, a technique that uses heat to destroy cancer cells. By raising the temperature of tumor tissues above 43°C, cancer cells can be effectively destroyed through necrosis, without requiring the invasive procedures of surgery. However, the major challenge with current hyperthermia methods is the difficulty in achieving precise, localized heating. Many existing hyperthermia techniques, such as radiofrequency and microwave hyperthermia, often result in the overheating of surrounding healthy tissues. This lack of precision reduces the efficacy of the treatment and increases the risk of side effects, limiting the widespread adoption of hyperthermia as a primary cancer therapy.

Magnetic nanoparticles, such as maghemite (γ-Fe_2O_3), offer a potential solution to this problem due to their ability to generate localized heat when exposed to an alternating magnetic field. This phenomenon, known as magnetic hyperthermia, allows for more precise targeting of tumor cells, as the heat generation can be controlled by the magnetic field's strength and duration. While magnetic nanoparticles have shown promise in preclinical studies, a major obstacle remains in the synthesis process. Many of the existing methods for synthesizing these nanoparticles rely on harsh chemicals, high temperatures, and energy-intensive procedures. These chemical methods not only pose environmental risks but also create biocompatibility concerns, particularly for medical applications where purity and safety are paramount.

The use of toxic chemicals in nanoparticle synthesis can lead to impurities that reduce the nanoparticles' effectiveness and introduce potential risks when used in biological systems. Furthermore, the complex, expensive, and energy-demanding nature of conventional synthesis methods makes scaling up these processes for industrial or clinical use difficult. There is thus an urgent need for eco-friendly, cost-effective, and scalable synthesis methods that produce biocompatible nanoparticles suitable for medical applications.

In recent years, the concept of green synthesis has gained traction as a sustainable alternative to traditional methods. Green synthesis utilizes natural materials—such as plant extracts, microorganisms, and biopolymers—as reducing and stabilizing agents, thereby eliminating the need for hazardous chemicals and high-energy processes. However, green synthesis of magnetic nanoparticles is still in its infancy, and there are limited studies exploring its use in producing nanoparticles for cancer hyperthermia.

This research addresses this critical gap by employing Lychee honey as a natural reducing and stabilizing agent to synthesize maghemite nanoparticles. Lychee honey offers several advantages over chemical reductants, including its rich content of sugars, antioxidants, and amino acids, which not only facilitate the reduction of metal ions into nanoparticles but also stabilize them against aggregation [33]. This biocompatible and sustainable synthesis method provides a safer alternative, particularly for nanoparticles intended for biomedical use. Despite the promise of this approach, several challenges remain. First, it is essential to optimize the synthesis process to produce nanoparticles of the right size, shape, and magnetic properties for effective use in hyperthermia. The size of the nanoparticles directly influences their heating capacity and magnetic behavior, which are critical for the success of magnetic hyperthermia. Additionally, ensuring that the synthesized nanoparticles are stable, biocompatible, and free of toxic residues is crucial for their eventual use in clinical settings.

This paper seeks to develop a green, sustainable method for synthesizing maghemite nanoparticles using Lychee honey, with the specific goal of producing nanoparticles that are optimized for use in cancer hyperthermia. The successful development of this method would not only provide an environmentally friendly synthesis pathway but also produce safer, more effective nanoparticles for targeted cancer treatment, helping to overcome the limitations of current therapies and providing a significant step forward in the field of nanomedicine.

Materials and methods

Maghemite nanoparticles (γ-Fe_2O_3) are nanoscale magnetic materials that have gained significant attention in various scientific fields due to their unique properties and potential applications. Characterized by superparamagnetism at room temperature, these nanoparticles exhibit a size-dependent magnetic behavior, allowing them to respond dynamically to external magnetic fields while losing magnetization in their absence. Their unique magnetic properties, combined with environmentally friendly synthesis methods such as biological processes make them noteworthy for applications in drug delivery, environmental remediation, and advanced imaging techniques.

The synthesis of maghemite nanoparticles can be achieved through various methods, including co-precipitation, polyol, and hydrothermal techniques, each affecting the nanoparticles' size, shape, and stability differently. These methods have raised discussions regarding their efficiency, cost-effectiveness, and environmental impact, highlighting the ongoing exploration for more sustainable approaches in nanoparticle fabrication. Furthermore, the characterization of these nanoparticles through sophisticated techniques like Transmission Electron Microscopy (TEM) and X-ray Diffraction (XRD) is critical for understanding their structural and functional properties, which directly influence their efficacy in practical applications. Despite their potential, concerns have arisen regarding the safety and toxicity of maghemite nanoparticles. Research indicates that they may induce oxidative stress and disrupt cellular functions in biological systems, prompting calls for standardized testing and long-term toxicity assessments to ensure safe utilization in environmental and biomedical contexts. As researchers strive to enhance their efficacy and mitigate risks, future studies aim to refine synthesis methods and improve our understanding of their interactions with biological and environmental systems, addressing both the opportunities and challenges presented by these nanoparticles (Shabatina *et al.*, 2020; Rodriguez *et al.*, 2018).

Materials used

For the synthesis and characterization of maghemite (γ-Fe2O3) nanoparticles, the following materials and reagents were used:

Lychee honey

Sourced from a local farmer in Rajshahi, Bangladesh, lychee honey served as a natural reducing and stabilizing agent in the green synthesis of maghemite nanoparticles.

Ferric chloride ($FeCl_3$)

Used as an iron source in the synthesis, this reagent provided Fe^{3+} ions, essential for forming maghemite nanoparticles in the presence of honey.

Ferrous Sulfate Heptahydrate ($FeSO_4 \cdot 7H_2O$): This compound contributed Fe^{2+} ions, creating the necessary Fe^{3+}/Fe^{2+} ratio for maghemite formation. Sodium Hydroxide (NaOH): A 4 M solution was prepared and added drop wise to adjust the pH of the reaction mixture, promoting the precipitation of iron oxide.

Distilled water and ethanol

Distilled water was used as a solvent for preparing the honey and iron solutions. Ethanol was used in the washing process to purify the nanoparticle precipitate and reduce impurities.

Laboratory glassware

Conical flasks, beakers, and a centrifuge were used in synthesis and purification processes, with an oven employed for drying. The list of chemical used is given in the Table-1.

Synthesis of maghemite nanoparticles

The synthesis of maghemite nanoparticles was conducted using lychee honey as a natural reducing and stabilizing agent. Multiple honey concentrations were tested to evaluate their impact on nanoparticle properties. Initially, honey solutions of 1.0g, 3.0g, and 5.0g concentrations were prepared by dissolving each in 100 mL of distilled water in separate conical flasks. Ferric chloride (0.2 M) and ferrous sulfate heptahydrate (0.1 M) were mixed in a 2:1 molar ratio with 30 mL of the 1.0g honey solution in a beaker for the first trial. To achieve precipitation, 4 M sodium hydroxide (NaOH) was added drop wise until the pH reached 11-13, producing a blackish-brown precipitate. The precipitate was cooled and washed 3-4 times with distilled water and twice with ethanol to ensure purity, with centrifugation performed at 7000 rpm for 10 minutes per cycle. The precipitate was then dried in an oven at 110°C for 3 hours, followed by 65°C for 12 hours. Finally, the dried sample was finely ground using a mortar to yield uniform maghemite nanoparticles. This method allowed for the evaluation of the optimal honey concentration for producing maghemite nanoparticles with desirable properties.

This synthesis process was repeated for 3.0g and 5.0g honey concentrations to observe their effects on the nanoparticles' properties.

Characterizations

Fourier Transform Infrared Spectroscopy (FTIR) was employed to identify the functional groups associated with honey-derived organic stabilizers on the nanoparticle surfaces, with spectra recorded in the range of 4000–400 cm⁻¹. Ultraviolet-Visible (UV-Vis) spectroscopy was performed between 200 and 800 nm to confirm nanoparticle formation and examine optical properties.

Thermo gravimetric Analysis (TGA) and Differential Thermal Analysis (DTA) assessed thermal stability, organic content, and decomposition behavior, with samples heated from room temperature to 800°C under a nitrogen atmosphere at a rate of 20°C/min. Magnetic properties, including saturation magnetization (M_s), remanence (M_r), and coercivity (H_c), were measured using Vibrating Sample Magnetometry (VSM) at room temperature to confirm superparamagnetic behavior. Finally, Field Emission Scanning Electron Microscopy (FESEM) was used to observe surface morphology, particle size distribution, and aggregation tendencies of the synthesized nanoparticles.

Results and discussions

Formation of blackish-brown precipitate

During the synthesis process, a blackish-brown precipitate began to form as sodium hydroxide (NaOH) was added to the iron solution. This color change indicated the successful reduction of iron ions and the formation of iron oxide, specifically maghemite, nanoparticles. The appearance of this dark precipitate served as a visual confirmation that the reaction was proceeding as expected.

Table 1. List of chemicals used.

Chemical Name	Purity/ Assay	Supplier
Anhydrous Ferric Chloride, $FeCl_3$	98%	Sisco Research Laboratories Pvt. Ltd.
Ferrous Sulphate Heptahydrate, $FeSO_4 \cdot 7H_2O$	98%	Sisco Research Laboratories Pvt. Ltd.
Sodium Hydroxide Pellets, $NaOH$	98.7%	Merck Specialities Pvt. Ltd

Magnetic attraction and superparamagnetic behavior

Once synthesized, the blackish-brown precipitate demonstrated a notable attraction to external magnets. This magnetic responsiveness is characteristic of maghemite nanoparticles and highlights their superparamagnetic properties. When exposed to a magnetic field, the nanoparticles aligned with the field, showing a strong response, but they did not retain magnetization once the field was removed, a key feature of superparamagnetic materials. This behavior is particularly advantageous for applications in targeted drug delivery or magnetic hyperthermia, where controlled magnetic responses are essential.

Physical Appearance of the Synthesized Nanoparticles

The final synthesized maghemite nanoparticles appeared as a reddish-brown powder, characteristic of iron oxide nanoparticles. This color indicates the presence of maghemite, aligning with expectations for iron oxide particles and confirming the synthesis process's initial success.

Effect of honey concentration

Testing varying concentrations of lychee honey (0.5g, 1.0g, 3.0g, and 5.0g) provided insight into the influence of the honey's stabilizing and reducing effects on nanoparticle formation. Lower concentrations of honey led to more particle aggregation, while higher concentrations improved stabilization and uniformity, resulting in better particle dispersion and a more consistent size distribution.

Yield efficiency and stability

Across all tested honey concentrations, the synthesis yield was effective, producing a solid mass of maghemite nanoparticles after drying. Concentrations between 1.0g and 3.0g provided optimal stabilization, with balanced particle size and stability. This concentration range achieved better yields of well-defined nanoparticles suitable for further characterization and potential biomedical applications. Hence, some of the tests are performed on these concentrations only.

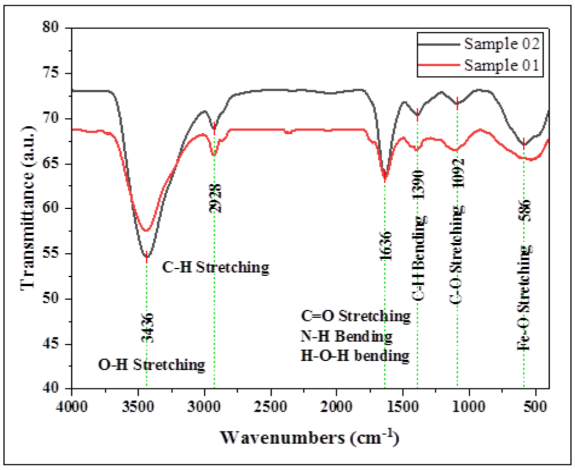

Fig. 1. Comparative FTIR Spectra of Sample 01 and Sample 02.

FTIR Analysis

The FTIR spectra confirmed the incorporation of honey-derived organic molecules into the maghemite nanoparticles, serving as stabilizing agents. A broad peak around 3440 cm^{-1} was attributed to O-H stretching, likely due to adsorbed water and phenolic compounds from honey (Markova *et al.*, 2017). The peak at 2930 cm^{-1} indicated C-H stretching vibrations, associated with sugars and hydroxymethylfurfural (Kumar *et al.*, 2011).

A strong band at 1635 cm^{-1} was assigned to C=O stretching and H-O-H bending, confirming the presence of adsorbed water and polyphenols (Markova *et al.*, 2017; Santos *et al.*, 2011). The peak at 1395 cm^{-1} represented C-H bending vibrations, while the band at 1100 cm^{-1} corresponded to C-O stretching (Biswas *et al.*, 2009). The distinct peak at 532 cm^{-1} confirmed Fe-O stretching, characteristic of maghemite nanoparticles (Stoia *et al.*, 2016). These findings validate the dual role of Lychee honey in reducing and stabilizing maghemite nanoparticles through its organic constituents.

Vibrating Sample Magnetometry (VSM) Analysis

The magnetic properties of the maghemite nanoparticles synthesized using various concentrations of lychee honey (1g, 3g, and 5g) as a reducing and stabilizing agent were evaluated using Vibrating Sample Magnetometry (VSM). Analyzing these properties provides insights into the nanoparticles' suitability for cancer hyperthermia and other biomedical applications, where specific magnetic characteristics are crucial.

For each sample (Sample 01 with 1g honey, Sample 02 with 3g honey, and Sample 03 with 5g honey), key magnetic parameters such as saturation magnetization (M_s), coercivity (H_c), and remanence (M_{rs}) were measured and compared. This analysis focuses on understanding how varying honey concentrations affect the magnetic behavior of the nanoparticles, shedding light on the optimal conditions for superparamagnetic properties.

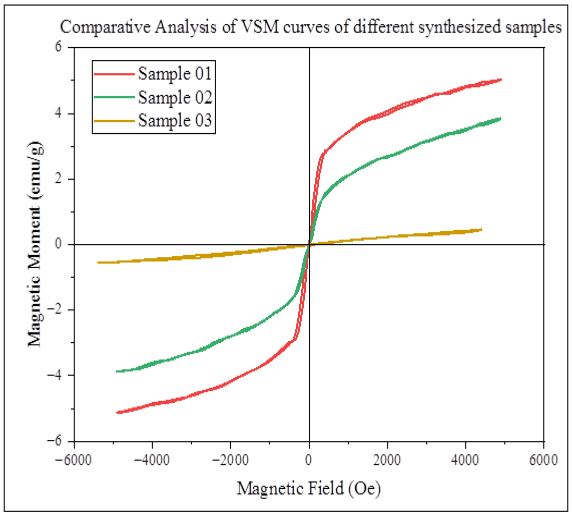

Fig. 2. Comparative VSM Curve.

The VSM analysis of Sample 01, synthesized with 1g of lychee honey, indicates promising magnetic properties. The sample's saturation magnetization of 5.05 emu/g reflects a strong magnetic response under an applied field, while the low remanent magnetization of 0.02 emu/g suggests minimal residual magnetism when the field is removed, which can help prevent unwanted magnetic interactions. Additionally, the coercivity of -6 Oe demonstrates that the sample can be easily demagnetized, a characteristic typical of superparamagnetic materials.

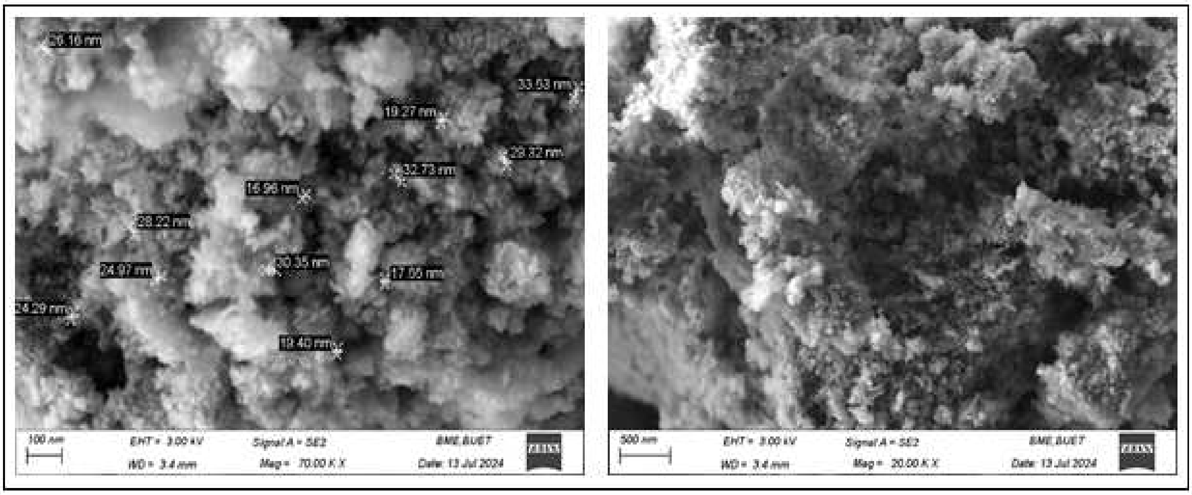

Fig. 3. FESEM images of maghemite nanoparticles synthesized by 1g honey concentration.

The narrow hysteresis loop observed in the VSM curve further highlights the sample's efficient and controlled magnetic behavior. The VSM curve for Sample 02, synthesized with 3g of honey, reveals key magnetic parameters. The saturation magnetization (Ms) is 3.85 emu/g, indicating a moderate magnetic response to the applied field. The remanent magnetization (Mr) is 0 emu/g, meaning that the sample has no residual magnetism when the external field is removed, which is ideal for applications requiring minimal magnetic retention. The coercivity (Hc) is also 0 Oe, signifying that the sample is easily demagnetized, characteristic of superparamagnetic materials.

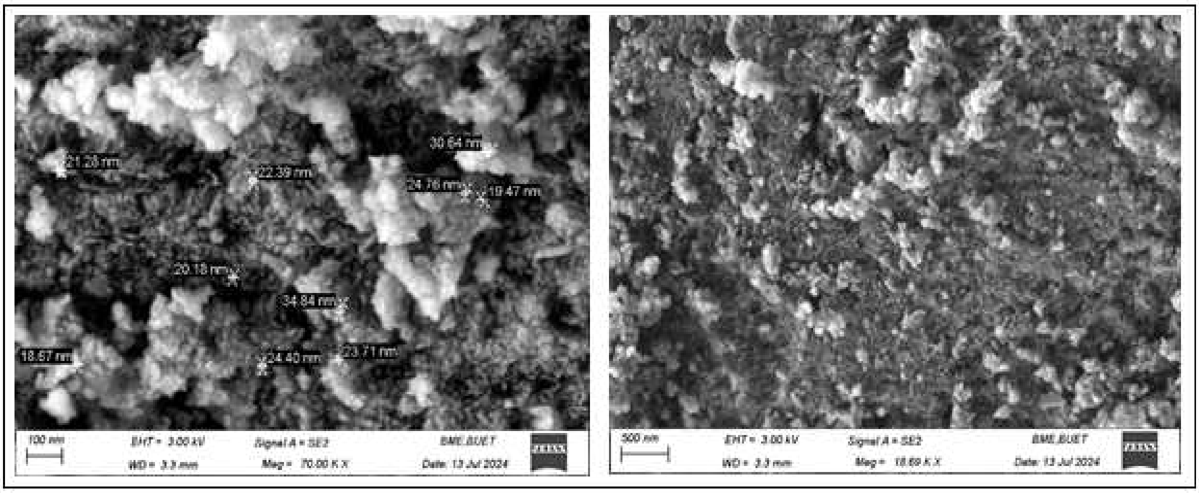

Fig. 4. FESEM images of maghemite nanoparticles synthesized by 3g honey concentration.

The VSM curve shows a narrow hysteresis loop, further confirming the superparamagnetic nature of the sample with efficient magnetic responsiveness and easy demagnetization. The VSM curve for Sample 03, synthesized with 5g of honey, indicates lower magnetic properties compared to previous samples. The saturation magnetization (Ms) values are 0.483 and -0.433 emu/g, reflecting a much weaker magnetic response to the applied field. The remanent magnetization (Mr) is -0.017 emu/g, showing a minimal residual magnetism when the external field is removed, which aligns with a reduced magnetic retention. The coercivity (Hc) is 157 Oe, suggesting the sample requires a slightly stronger external magnetic field to reach zero magnetization after being magnetized, indicating a higher resistance to demagnetization compared to typical superparamagnetic materials.

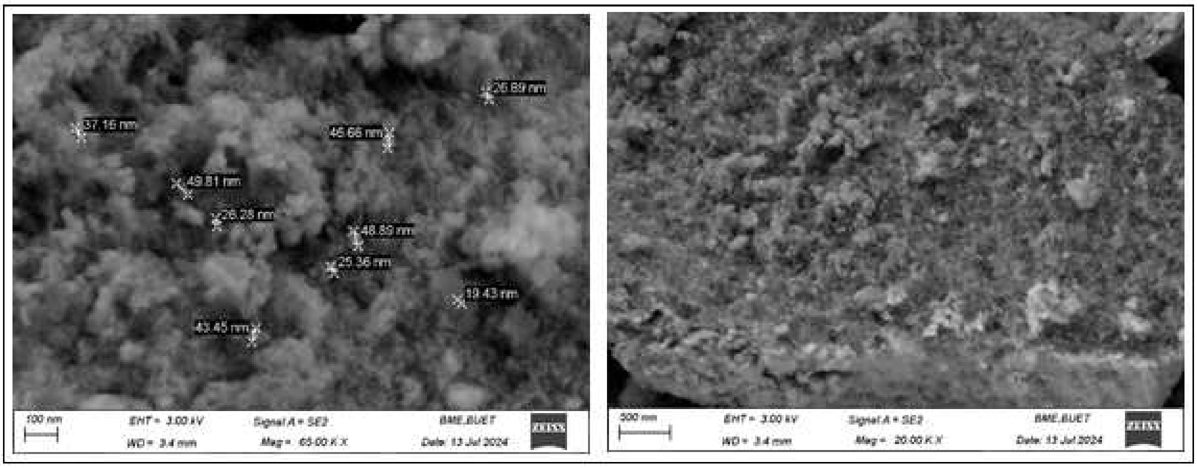

Fig. 5. FESEM images of maghemite nanoparticles synthesized by 5g honey concentration.

The relatively wide hysteresis loop implies a reduced ease of magnetization and demagnetization, which may impact its suitability in applications where rapid magnetic reversibility is critical.

FESEM Analysis

The morphological characteristics were assessed using FESEM, revealing variations in particle size and aggregation across samples. Sample 01 displayed particle sizes ranging from 16.96 to 33.53 nm, with moderate aggregation and relatively uniform morphology. Sample 02 showed slightly larger particles (18.67 to 34.84 nm) and increased aggregation, while Sample 03 exhibited the largest particles (19.43 to 49.81 nm) with pronounced clustering.

The results suggest that lower honey concentrations facilitate the synthesis of smaller, more uniformly distributed nanoparticles, which are desirable for biomedical applications.

UV-Visible spectroscopy analysis

The UV-Vis spectra demonstrated strong absorption peaks around 270 nm, characteristic of maghemite nanoparticles (Bali Ogholbeyg *et al.*, 2018). Sample 01 exhibited higher absorption intensity compared to Sample 02, indicating better dispersion and a higher nanoparticle concentration. The results align with the FESEM analysis, confirming that lower honey concentrations produce nanoparticles with improved optical properties, making them suitable for imaging and hyperthermia applications.

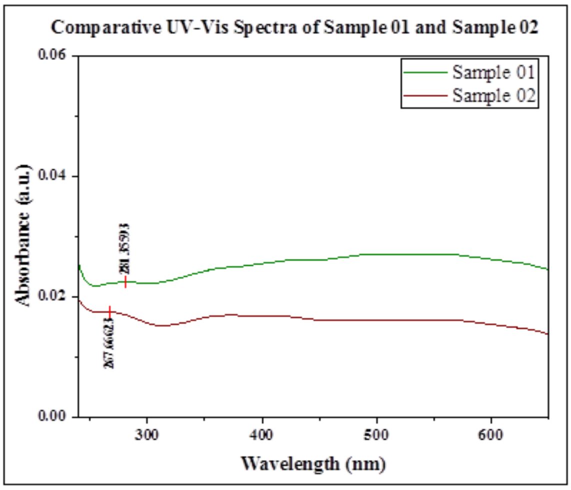

Fig. 6. UV-Vis Spectra of Sample 01 and Sample 02.

Thermal analysis

TGA-DTG and DTA curves revealed the thermal stability of the synthesized nanoparticles. Both samples showed weight loss in several stages, corresponding to water loss, decomposition of organic residues, and further degradation of the honey-derived matrix. Sample 01 exhibited slightly lower total weight loss (20.15%) compared to Sample 02 (21.32%), indicating better thermal stability. This stability is attributed to the reduced organic content in Sample 01, which aligns with its improved magnetic and optical properties.

Discussion

The synthesis of maghemite nanoparticles using Lychee honey demonstrated the efficacy of green chemistry approaches in producing superparamagnetic materials with potential biomedical applications. The FTIR analysis confirmed the role of honey-derived compounds in nanoparticle stabilization, while VSM, FESEM, and UV-Vis analyses highlighted the influence of honey concentration on magnetic, morphological, and optical properties. Thermal analysis further validated the stability of the synthesized nanoparticles.

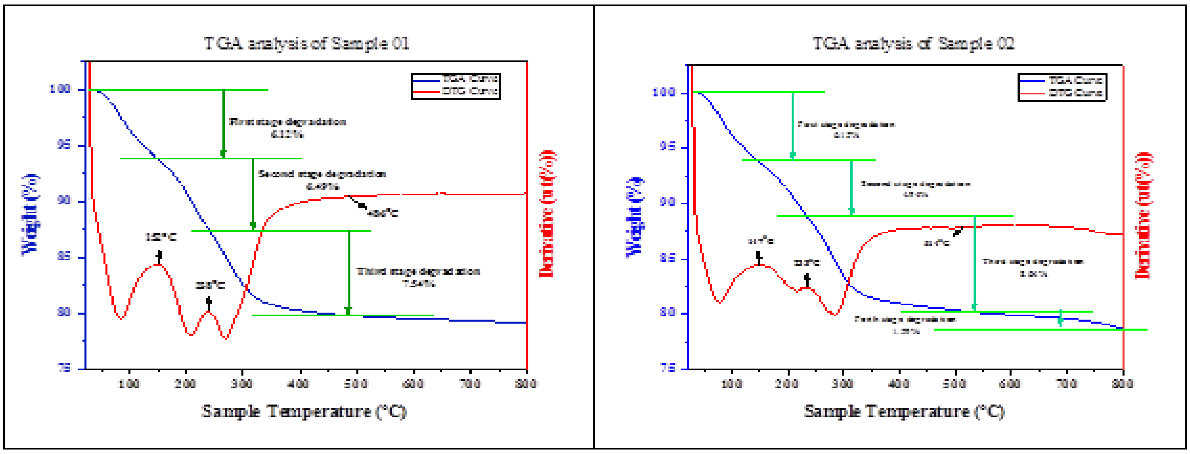

Fig. 7. TGA- DTG Curves of Sample 01 and Sample 02.

Among the samples, Sample 01 emerged as the most suitable candidate for cancer hyperthermia due to its high magnetic responsiveness, uniform particle size, and thermal stability. The findings underscore the potential of Lychee honey-mediated synthesis for sustainable and eco-friendly nanotechnology development. Future work will focus on in vivo and in vitro testing to explore the clinical applicability of these nanoparticles.

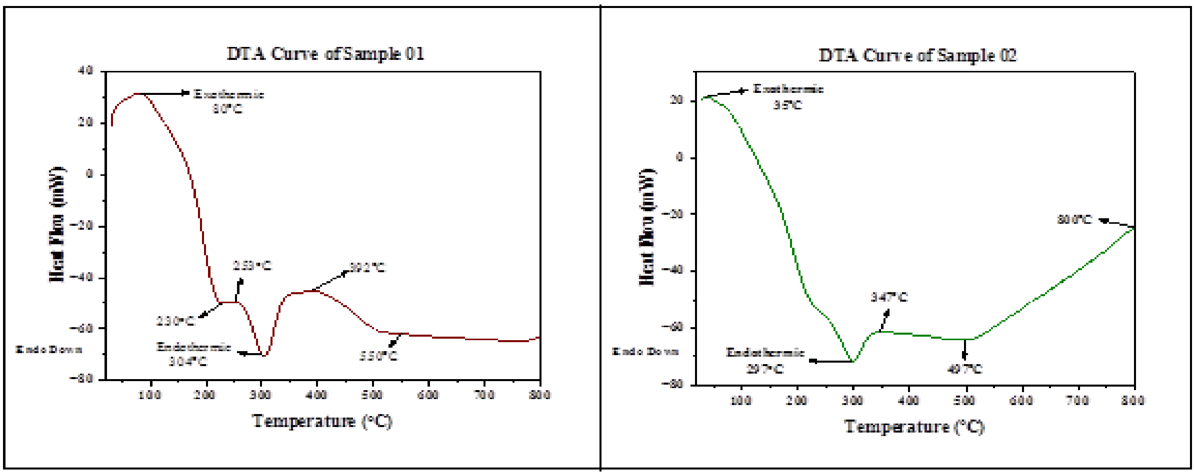

Fig. 8. DTA Curves of Sample 01 and Sample 02.

Conclusion

This study successfully demonstrated the green synthesis of maghemite (γ-Fe_2O_3) nanoparticles using Lychee honey as a natural reducing and stabilizing agent, offering an eco-friendly alternative to conventional methods. The nanoparticles exhibited superparamagnetic behavior, thermal stability, and uniform morphology, making them promising for biomedical applications, particularly cancer hyperthermia.

While characterization confirmed their suitability, future studies should focus on in vitro and in vivo evaluations to validate their therapeutic potential. Additionally, optimizing the synthesis process and exploring surface modifications could further enhance their specificity and performance. This work establishes a sustainable pathway for developing nanomaterials for cancer treatment, bridging laboratory research and clinical application.

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