Discover Chemistry

Review

A novel plant-based approach for synthesis of iron oxide nanoparticles and cancer therapy

Romesa Soomro[1] · Mohamed Abdelmonem[1,2] · Abubakar Dantani Meli[1] · Motia Panhwar[3] · Che Azurahanim Che Abdullah[1]

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Abstract
Cancer remains a major challenge in modern medicine, often hindered by the limitations of conventional treatments such as chemotherapy, including severe side effects and low specificity. Iron oxide nanoparticles (IONPs) have emerged as promising tools for cancer theranostics, owing to their magnetic responsiveness, tunable surface properties, and ability to enhance both therapeutic and diagnostic precision. This review focuses on the advancements in the green synthesis of IONPs using plant extracts rich in polyphenols, which serve as natural reducing agents while providing additional anti-cancer benefits. These green-synthesized IONPs demonstrate potential in targeted drug delivery, controlled release, and enhanced imaging through magnetic resonance imaging (MRI), offering a sustainable and effective approach to cancer treatment. The review highlights the biosafety, biocompatibility, and anticancer efficacy of green-synthesized IONPs through an in-depth analysis of preclinical in vitro studies from the last five years. Key challenges in plant-based synthesis, such as reproducibility and variability in phytochemical composition, are critically discussed alongside strategies to address these limitations. Furthermore, using waste materials in green synthesis is emphasized as a sustainable approach to nanoparticle production, promoting resource efficiency and environmental stewardship. This comprehensive analysis underscores the dual functionality of green-synthesized IONPs as a novel, eco-friendly solution for cancer theranostics, paving the way for sustainable and scalable applications in future biomedical research.

Keywords Green synthesis · Superparamagnetic iron oxide nanoparticles · Cancer therapy · Targeted drug delivery · Theranostics · Nanocarrier

1 Introduction

Cancer remains a formidable global health challenge, characterized by uncontrolled cell growth and the potential to spread throughout the body [1]. Detecting cancer early and providing proper treatment is crucial for enhancing patient results. While traditional approaches such as hormone therapy, chemotherapy, surgery, radiation therapy, and immunotherapy have proven effective in cancer treatment, they come with challenges like detecting tumors in the early stages, a lack of precisely targeted therapy, and harmful side effects on healthy tissues [2]. Targeted therapy is a cornerstone of modern cancer treatment. Unlike traditional chemotherapy, which can harm healthy cells alongside cancer cells, targeted drugs focus on specific vulnerabilities within cancer cells [3]. Iron oxide nanoparticles (IONPs) are becoming a

✉ Che Azurahanim Che Abdullah, azurahanim@upm.edu.my | [1]Department of Physics, Faculty of Science, Universiti Putra Malaysia, 43300 Serdang, Selangor, Malaysia. [2]Department of Pharmaceutics, Faculty of Pharmacy, 6th of October, October University for Modern Sciences and Arts, Giza, Egypt. [3]Department of Pharmacology, Faculty of Pharmacy, University of Sindh Jamshoro, Jamshoro, Pakistan.

game changer in the field of cancer treatment and diagnosis, combining both diagnostic and therapeutic functions in one platform [4, 5]. These tiny particles have unique characteristics that make them very attractive for managing cancer. One major benefit is their ability to be customized for precise delivery, allowing them to gather specifically in cancerous tissues while minimizing exposure to healthy organs [6]. This targeted approach holds the promise of reducing the harsh side effects often linked with traditional cancer treatments. Additionally, the magnetic properties of IONPs make them excellent contrast agents for magnetic resonance imaging (MRI), giving doctors a clear view of tumors [7, 8]. This enhanced visualization not only aids in accurate diagnosis but also facilitates real-time monitoring of treatment response. Beyond their diagnostic prowess, IONPs can be further functionalized for a multifaceted therapeutic assault on cancer cells. One such strategy involves hyperthermia, where light-activated IONPs generate heat within the tumor microenvironment, leading to direct ablation of cancer cells [9]. IONPs have been granted clinical approval as hyperthermia agents for the treatment of multiforme glioblastoma (MagForce©). Current research is investigating the potential effectiveness of these treatments for many types of tumors, such as prostate cancer (Maksoudian et al. 2020). Additionally, IONPs can be designed to produce reactive oxygen species (ROS) under specific light conditions, a phenomenon exploited in photodynamic therapy to induce cancer cell death. Moreover, IONPs hold promise for stimulating the body's immune system to recognize and target cancer cells, offering a potent immunotherapeutic approach [10]. The true value of IONPs lies in their versatility, enabling their combination with other treatment modalities, such as gene therapy, chemotherapy, and radiotherapy. This multi-functional approach offers new possibilities for personalized cancer treatments, with IONPs providing a customizable platform for delivering targeted, effective therapy [11]. Additionally, the method of synthesizing IONPs plays a critical role in their biocompatibility and efficiency, with green synthesis offering several key advantages, as shown in the Fig. 1. The environmentally friendly, non-toxic, and cost-effective nature of biosynthesized IONPs aligns perfectly with their emerging role in cancer treatment. Green synthesis not only reduces energy consumption but also enables rapid production of nanoparticles. These benefits complement the introduction's emphasis on innovative and sustainable approaches, reinforcing the significance of IONPs in modern cancer management strategies.

1.1 Methods for IONPs synthesis in general

The synthesis of IONPs involves various methods, each with distinct advantages and limitations. While traditional chemical synthesis methods like co-precipitation, thermal decomposition, and hydrothermal synthesis offer control over particle characteristics, they often involve hazardous chemicals and energy-intensive processes. These methods face limitations such as poor size control, environmental hazards, and complex purification steps [12]. Nevertheless, these methods are being replaced by easy, cheaper, greener, and repeatable ways to make metallic nanoparticles (NPs) by extracting them from leaves, stems, seeds, and roots [13] (Fig. 2). A comparative study by [14] highlights the efficacy of biosynthesized and chemically synthesized magnetic NPs on different cancer cell lines and the study revealed a dose-dependent inhibition of

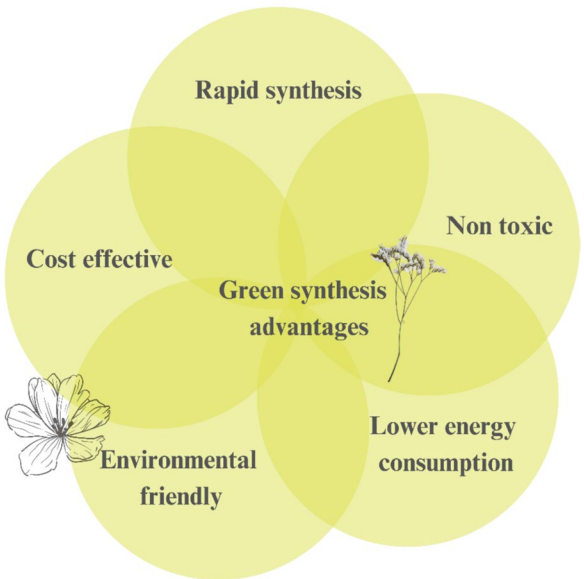

Fig. 1 The advantages of adopting green synthesis for the manufacturing of different nanoparticles

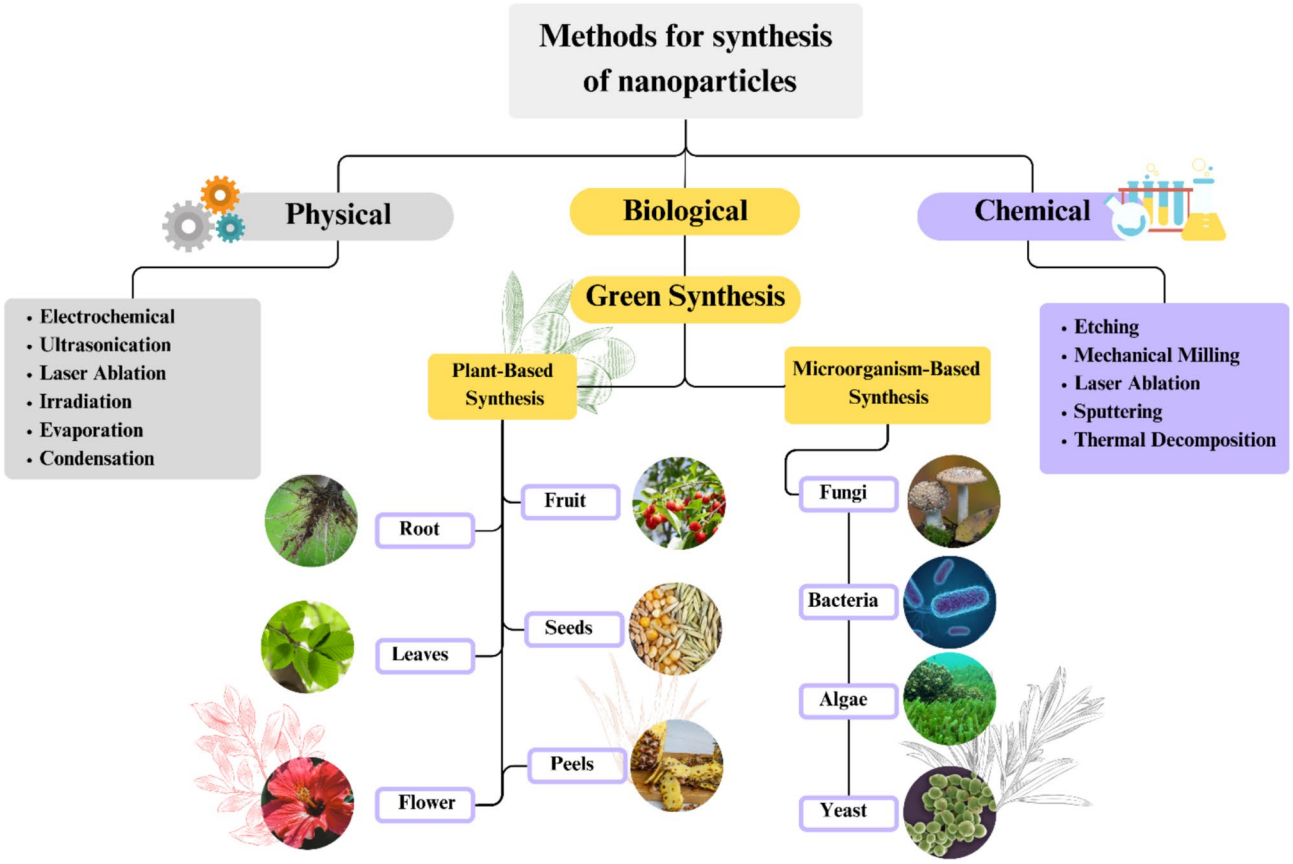

Fig. 2 Various approaches to nanoparticle synthesis

cell proliferation, with biosynthesized NPs showing reduced cytotoxicity while maintaining significant biological activity. This suggests that green synthesis methods produce safer and effective NPs for medical and pharmaceutical applications.

The use of plant-based synthesis methods is increasing in popularity because of their environmentally favorable characteristics and ability to produce innovative materials. Nevertheless, ensuring consistent and dependable outcomes (reproducibility) is essential for practical implementations. [15] discussed the methods and procedures used to optimize the synthesis and ensure the reproducibility of green synthesis NPs. Utilizing precise plant cultivars cultivated in controlled environments can effectively reduce inherent fluctuations in phytochemical composition. Developing precise protocols for the manufacture of plant extracts is crucial for ensuring consistent outcomes. Enhancing reaction parameters such as temperature, pH, and concentration of plant extract can enhance the ability to regulate the synthesis process. Utilizing advanced analytical techniques yields crucial data to ensure consistent material qualities. Several investigations have reported that the biogenic process for synthesizing NPs demonstrates a high degree of reproducibility [16]. Nanomaterials made from plants or derivatives of plants are usually cheap because plants naturally contain reducing organic chemicals that are easy to use in the manufacturing process. Therefore, the ability to make NPs from phytochemicals found in plants is a big step forward for both plant and human studies [17, 18].

1.2 Role of bioactive components in plant-based IONPs synthesis

Plant extracts, abundant in bioactive compounds like polyphenols, flavonoids, and tannins, are essential in the synthesis and stabilization of IONPs. These substances function both as reducing agents and stabilizers, affecting the NPs ' size, shape, and surface characteristics [19]. Also, substances such as vitamins, amino acids, proteins, enzymes, and Polysaccharides can serve as both reducing and capping agents in green synthesis [20, 21]. According to [22], Tannins, particularly rich in polyphenol groups, offer a safe and valuable approach for creating and stabilizing IONPs, tannins achieve this due to their unique structure, which includes phenolic hydroxyl groups and ortho-dihydroxyphenyl units. These structural

features enable tannins to bind (complex) with iron particles during chemical reactions involving electron transfer (redox reactions), thereby facilitating the formation of stable IONPs.

Grape (*Vitis vinifera*) is one of the largest fruit crops globally, yielding over 67 million tons annually. Primarily cultivated for wine production, this process generates significant solid organic by-products known as grape pomace, constituting approximately 40% of the grape's mass. While grape pomace is recognized as a potential source of tannic acid, its widespread utilization remains limited. As a result, large quantities accumulate near wineries, posing environmental and disposal challenges [23]. However, recent innovations have shown promise in transforming this waste into valuable resources. For instance, grape pomace extracts can be utilized in green synthesis processes to produce IONPs. These NPs exhibit favorable properties such as controlled size and enhanced biocompatibility, offering not only valuable products but also mitigating the environmental burden posed by grape pomace waste accumulation. This dual benefit underscores the potential of innovative approaches in sustainable waste management and resource utilization [24].

Pucci and colleagues mentioned in their study that among various metal ions, iron (Fe^{3+}) is particularly favored for complexation with tannic acid (Fig. 3). This preference arises from the strong interaction between tannic acid and iron, the ability of iron to form multiple bonds, and its relatively low toxicity compared to other metals. These tannic acid-iron complexes, in general, hold promise for various applications in medicine, such as cancer treatment, diagnostic imaging, and wound healing [25].

Research using Fourier Transform Infrared Spectroscopy (FTIR) spectroscopy has repeatedly demonstrated that plants contain various reducing sugars as illustrated in Table 1 which are responsible for the synthesis of NPs by reducing the metal salts and also stabilizing them naturally. For instance [27] highlight in their study that *C. citratus* extract serves as a reducing and capping agent, primarily using hydroxyl and carbonyl groups to reduce iron. The FeO-NPs were functionalized in one step, achieving properties similar to traditional methods. The biomolecule-coated surface increases biocompatibility. Similarly [28] mentioned in their research that Green synthesis of IONPs by *pheonix dactylifera* leaf extract presents the phenolic compounds act as reducing and capping agents.

Through the green synthesis method, various plant extracts have been used to create IONPs. A key advantage of using plant extracts is that water serves as the solvent, making the process safe and suitable for numerous biological applications. The reduction of iron salts by these extracts results in noticeable changes in color and pH, which act as markers for nanoparticle synthesis [34]. For instance, Oolong green tea extract has been utilized to biosynthesize iron NPs, offering a cost-effective and locally available material. The polyphenols in Oolong tea extract stabilize zero-valent IONPs at room temperature without requiring surfactants or polymers [35]. A variety of plant-derived polyphenols and the general concept of synthesis of metal oxide from the reduction process by polyphenols is given below in (Fig. 4).

1.3 Exploring the role of bioactive components as an anti-cancer agent

Polyphenols, abundant in plant extracts, not only serve as reducing and capping agents in the synthesis of nanoparticles but also contribute significant biological effects [36]. These plant-based antioxidants are gaining attention due to their potential dual role: aiding in nanoparticle synthesis and offering therapeutic benefits in cancer treatment (Patra et al. 2021). Dietary polyphenols are increasingly being recognized for their role in cancer prevention, primarily by influencing molecular pathways linked to cell death and inflammation. These compounds have shown promise in enhancing the efficacy of conventional anticancer therapies through synergistic mechanisms [37]. Research has identified several

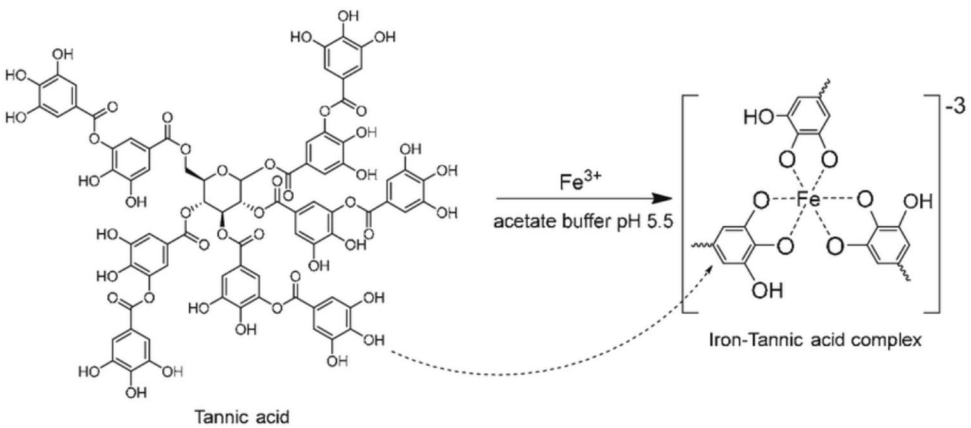

Fig. 3 Illustration of the complex formation between tannic acid and $Fe.^{3+}$ ions. Tannic acid, depicted on the left, contains multiple hydroxyl (–OH) groups that can chelate with iron ions [26]

Table 1 Summary of FTIR results for different plant extracts, indicating characteristic peaks, functional groups, and corresponding polyphenolic compounds

Plant extract source	Peak (cm^{-1})	Functional groups	Corresponding polyphenolic compound	Nanoparticle	References
Cinnamomum tamala leaves	3280	O–H stretching	Eugenol-like compounds	Fe_3O_4	[29]
	1620	C = O stretching	Flavonoids, tannins		
	2922	C–H stretching	Phenolic compounds, flavonoids		
	1059	C–O stretching vibration	Flavonoids, catechins		
Nigella sativa seed extract	3384.04	H_2O stretching vibration	Organic molecules from N. sativa extract	IONPs	[30]
	1722.80	H_2O bending vibration	N/A		
	1054.53	unknown	N/A		
	582.29	Fe–O stretching	N/A		
Psidium guajava L. Leaves Extract	572	FeO stretching	FeO bonding	Fe_3O_4	[31]
	1745	C = O stretching	Carboxylic acid coordination		
	3345	O–H stretching	Alcohol and phenol compounds		
	1687	C = O stretching	ketones, esters, and acids		
	3575	O–H stretching	Alcohol and phenol compounds		
brown Egyptian propolis extract	3309	–OH stretching	Phenolic hydroxyl group	PEG-IONPs	[32]
	2923	C–H bond stretching	C–H		
	1706	C = O stretching	C = O		
	1156	Aromatic C–O bond stretching	Aromatic C–O		
Aqueous leaves extract of Mentha Pulegium L	3455	O – H group stretching vibration	O – H	IONPs	[33]
	1744	C = C, C – C, C – O stretching	Aromatics cycles		
	1218	C – H and C – O stretching	Alcohols, carboxylic acids, ester, ether groups		
	510	Fe – O stretching	Fe – O		

Polyphenols are identified as key reducing and capping agents in nanoparticle synthesis

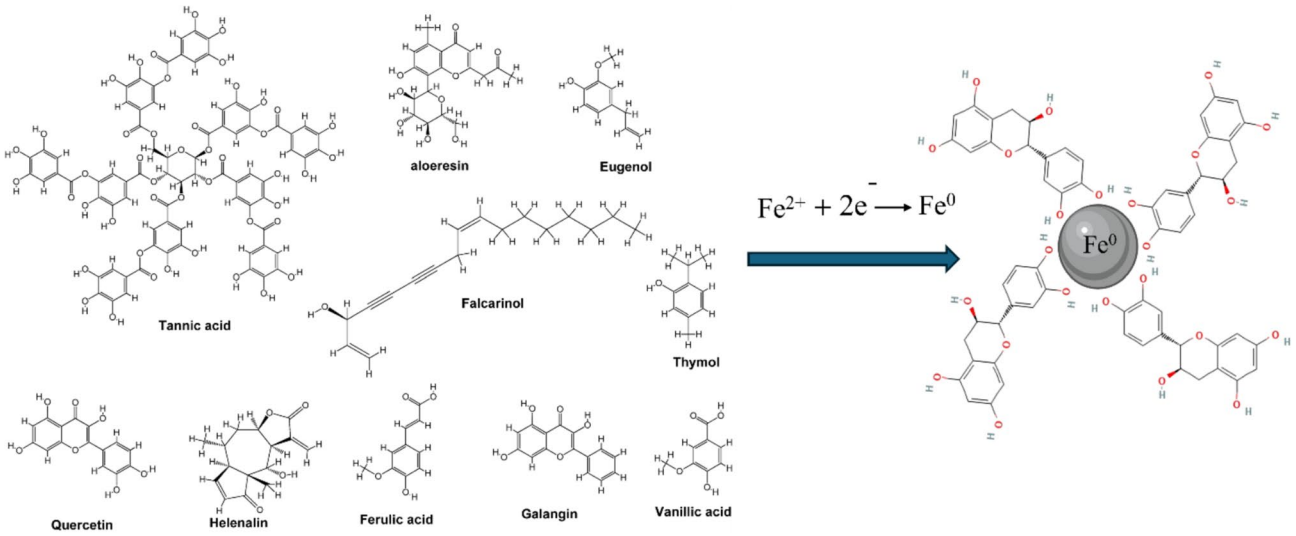

Fig. 4 The image displays the chemical structures of different polyphenols. These polyphenols act as reducing agents, facilitating the reduction of Fe^{2+} ions to Fe^0. The right side of the figure illustrates the general mechanism of how polyphenols reduce iron ions, resulting in the formation of IONPs stabilized and functionalized by these natural compounds

mechanisms through which polyphenols exert their anti-cancer properties. One key mechanism is their antioxidant capacity, which allows them to neutralize free radicals unstable molecules that can damage cells and contribute to carcinogenesis [38], Cell Cycle Regulation: Polyphenols may influence how cancer cells grow and divide, potentially slowing or stopping their proliferation [39], Apoptosis Induction: They may trigger programmed cell death (apoptosis) in cancer cells, essentially eliminating them [40], Anti-inflammatory Effects: Chronic inflammation can be a risk factor for cancer. Polyphenols may have anti-inflammatory properties that could help reduce this risk [41]. Furthermore, polyphenols directly neutralize free radicals [42]. Collectively, these properties underline the dual role of polyphenols in cancer management, both as therapeutic agents with anticancer potential and as reducing agents in the green synthesis of nanoparticles (Fig. 5) and the polyphenols listed in Table 2 are abundant in plant extracts used for nanoparticle synthesis, underscoring their relevance to both the synthesis process and their inherent anticancer properties.

Polyphenols serve a dual purpose in this approach: firstly, acting as reducing and capping agents in the eco-friendly synthesis of IONPs, and secondly, potentially contribute their own therapeutic effects in cancer management [50].

1.4 IONPs synthesis by the green method

The green synthesis of IONPs offers an eco-friendly and sustainable alternative to traditional chemical methods. Plant extracts play a vital role in this method by serving as reducing and capping agents as previously mentioned. Figure 6 shows the reduction of metal ions (such as Fe^{3+} or Fe^{2+}) to nanoparticles through the action of phytochemicals from plant extracts. These plant biomolecules, including polyphenols, flavonoids, and terpenoids, act as reducing agents by donating electrons, converting Fe^{3+} or Fe^{2+} ions into magnetite (Fe_3O_4) nanoparticles, the growth and stabilization stages, where the nanoparticles form and stabilize. During this process, the biomolecules function as capping agents, preventing nanoparticle aggregation, ensuring uniform size distribution, and enhancing biocompatibility [51].

In a typical procedure, plant materials, such as tea leaves, lemongrass, or Aloe vera, are first cleaned and prepared as an extract using deionized water. The iron precursor, usually an iron salt like $FeCl_3$ or $FeCl_2$, is dissolved in water. The plant extract is gradually added to the iron solution under continuous stirring, and the pH is adjusted using a base, such as sodium hydroxide (NaOH). The formation of IONPs is indicated by a color change, typically darkening as the nanoparticles form. After a specific reaction time, the nanoparticles are separated via centrifugation, washed, and dried at a mild temperature. The plant extract biomolecules such as polyphenols, flavonoids, terpenoids, and alkaloids are essential in reducing and stabilizing IONPs. These compounds act as reducing agents by donating electrons to Fe^{3+} or Fe^{2+} ions, converting them into Fe_3O_4 (magnetite), which forms the core of the nanoparticles [52].

Recent studies have demonstrated the effectiveness of various plant extracts in the green synthesis of IONPs, highlighting the role of natural biomolecules in reducing and stabilizing iron ions. For example, Hibiscus plant extract has been

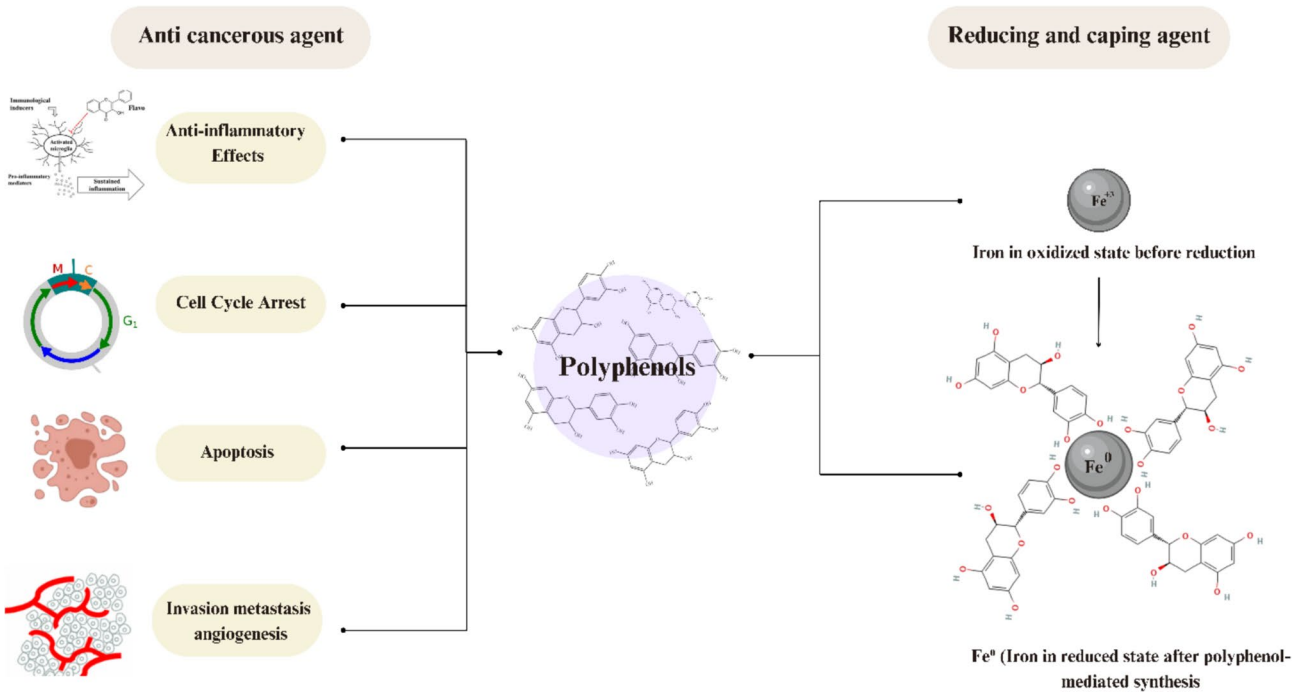

Fig. 5 Role of polyphenols in IONP synthesis and anti-cancer activity

successfully used for the green synthesis of hematite (α-Fe_2O_3) nanoparticles. Structural analysis confirmed the successful synthesis of hematite nanoparticles with an average size of 20 nm [53]. Similarly, *Hibiscus sabdariffa* calyces extract was employed as a reducing and capping agent for biosynthesized IONPs [54]. Moreover, the gel of *Aloe vera* contains phenolic compounds and flavonoids that aid in the synthesis of IONPs with high antioxidant potential. These nanoparticles have demonstrated strong biocompatibility, making them promising candidates for hyperthermia-based cancer treatments [55]. Additionally, *Moringa oleifera* extract, which is rich in alkaloids and polyphenols, has been employed in the green synthesis of IONPs. The alkaloids in the extract function as both reducing and capping agents, enhancing the stability and biocompatibility of the nanoparticles [56]. Together, these examples underscore the versatility and efficacy of plant extracts in producing biocompatible IONPs for various biomedical applications.

1.5 Application of bio-synthesized IONPs in cancer therapy

Bio-synthesized IONPs have emerged as promising tools in cancer therapy due to their versatile applications mentioned in the Fig. 7. These nanoparticles can be used in various cancer treatment methods, offering both therapeutic and diagnostic benefits. Below are some of the key applications of bio-synthesized IONPs in cancer therapy.

1.6 Photothermal therapy (PTT)

Photothermal therapy (PTT) utilizing bio-synthesized IONPs has shown great promise in cancer treatment due to their effective near-infrared (NIR) light absorption and heat generation, which causes localized tumor cell destruction. These bio-synthesized IONPs not only have lower toxicity and better biocompatibility than traditional agents but also enhance targeting efficacy by remaining longer in the reticuloendothelial system [57]. When combined with other therapeutic approaches, such as chemotherapy or radiation, PTT provides a novel and potent treatment option, particularly for prostate cancer (PCa) and castration-resistant prostate cancer (CRPC) [58].

1.7 Photodynamic therapy (PDT)

Photodynamic Therapy (PDT) utilizes photosensitizers to generate ROS upon light exposure, effectively targeting and destroying cancer cells. Recent advancements in bio-synthesized IONPs have shown promise in enhancing the

Table 2 Polyphenols act as dual anti-cancerous agent and reducing agent for IONPs synthesis

Natural source	Polyphenol	Cancer Risk Reduction	Role in IONPS synthesis	References
Soybeans and soy products	Isoflavone	This subclass of polyphenols showed the strongest association with a reduce risk of lung cancer in both prospective and case–control studies. Interestingly, the benefit seemed limited to never-smokers	Isoflavones can serve as reducing agents in IONP synthesis, helping in the eco-friendly formation of nanoparticles	[43, 44]
Soybeans	Soy isoflavones	No clear evidence for preventing breast cancer in adults. Possible benefit for reducing breast cancer risk if consumed early in life (needs further research)	Soy isoflavones contribute to the stability of IONPs by preventing oxidation during green synthesis processes	[45]
Berries	Anthocyanidins (flavonoid subclass	Inverse association with Gastric Cancer risk (women only in some studies	Anthocyanidins serve as reducing and antioxidant agents, improving nanoparticle stability and preventing aggregation	[46]
Tea	Tea Catechins (a specific type of polyphenol	Convincing evidence for lower risk of oral cancer and Esophagus cancer	Catechins act as reducing agents in IONP synthesis and contribute to antioxidant activity, enhancing biocompatibility	[47, 48]
Turmeric	Curcumin	May inhibit colon cancer by reducing inflammatory responses and signaling pathway activation	Curcumin is widely used in green synthesis due to its role as a reducing and stabilizing agent for IONPs	[39]
Cocoa beans	Cocoa Polyphenols	Prevent and/or inhibit the genesis and advancement of various forms of malignancies, including prostate cancer, liver cancer, colon cancer, leukemia, and others	Cocoa polyphenols contribute to the capping and stabilization of IONPs, reducing toxicity and enhancing antioxidant activity	[38, 49]

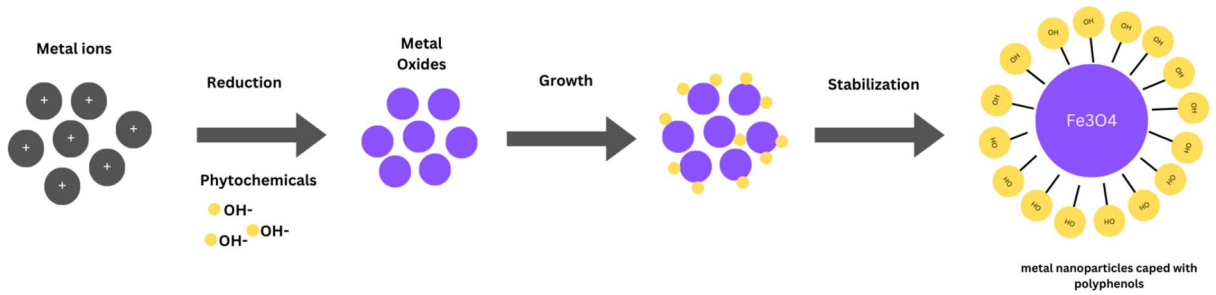

Fig. 6 Illustration of general steps of green synthesis method

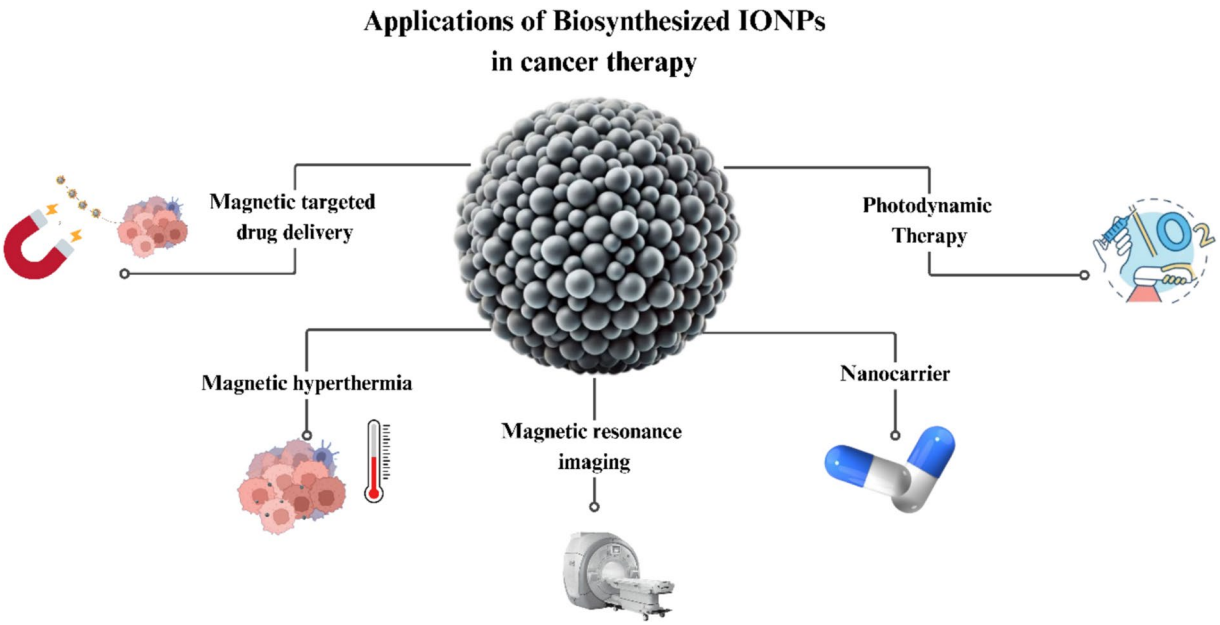

Fig. 7 Different approaches that exploit biosynthesized magnetic IONPs for cancer therapy

efficacy of PDT by acting as potent photosensitizers, thereby increasing ROS production that induces cancer cell death [59]. Bio-synthesized IONPs can improve the accumulation of photosensitizers in tumor tissues, enhancing the selectivity and effectiveness of PDT [60].

The combination of IONPs with traditional photosensitizers can overcome limitations such as poor solubility and low targetability, thus improving therapeutic outcomes. The integration of IONPs in PDT has shown promising results in preclinical studies, indicating potential for improved treatment strategies in oncology [61] for more studies refer to Table 3.

1.8 Magnetic hyperthermia

Magnetic hyperthermia employs external magnetic fields to heat magnetic nanoparticles, focusing on tumor cells while sparing healthy tissue. Bio-synthesized IONPs are ideal for this due to their magnetic properties and biocompatibility. When exposed to an alternating magnetic field, IONPs generate localized heat 42–46 °C that induces apoptosis in cancer cells. Their effectiveness is influenced by the specific absorption rate (SAR), optimized through nanoparticle design. IONPs' stability and ability to uniformly distribute heat enhance treatment outcomes. Combining magnetic hyperthermia with chemotherapy offers a promising, non-invasive cancer treatment [62].

Table 3 Characteristics and Applications of Green-Synthesized Iron Oxide Nanoparticles (IONPs) from Various Plant Sources [66]

Plant Name	Part of the plant used	Ion precursor	Size	Shape	Magnetization	Application
Green tea	Leaves	$FeCl_2 \cdot 4H_2O/FeCl_3.6H_2O$	85.44 nm	Semi-spherical	9.4924 emu/g	Antioxidant activity
Aloe vera	Leaves	$FeCl_2 \cdot 4H_2O/FeCl_3.6\ H_2O$	7.38 nm	Semi-spherical	37.718 emu/g	Antioxidant activity
pine leaves	Leaves	$FeCl_3.6H_2O$	12–37 nm	Spherical	N/A	Antibacterial/anticancer activity
Stevia rebaudiana Bertoni	Leaves	$(Fe\ (NO_3)_3$	20 nm	spherical	5.35 emu/g	Antioxidant activity
Artemisia absinthium	Leaves & Stems	$Fe(Cl)_3 \cdot 6H_2O\ /FeSO_4 \cdot 7H_2O$	Less than 10 nm	spherical	N/A	Magnetic hyperthermia
Garcinia mangostana	Fruit Peels	$Fe(Cl)_3.6H_2O\ /Fe(Cl)_2.4H_2O$	13.42 nm	spherical	73.15 emu/g	Magnetic hyperthermia
Gardenia resinifera	Leaves	$FeCl_3.6H_2O$	5 nm	spherical	8.5 emu/g	Magnetic hyperthermia
Pimenta dioica	Leaves	$Fe(Cl)_3.6H_2O/Fe(Cl)_2.4H_2O$	15 nm	spherical	N/A	Photothermal therapy
Punica granatum	Fruit Peels	$Fe(Cl)_3.6H_2O/Fe(Cl)_2.4H_2O$	14.38 nm	spherical	69 emu/g	MRI/Magnetic Hyperthermia
Psoralea corylifolia	seeds	$Fe(Cl)_3.6H_2O$	39 nm	spherical	N/A	Anticancer activity
Graptophyllum pictum	Leaves	$FeSO_4.7H_2O$	24 nm	FCC shape	N/A	Targeted drug delivery
Ficus hispida	Leaves	$FeSO_4.7H_2O/FeCl_3.6H_2O$	10.96 nm	spherical	100 emu/g	Photocatalysis

1.9 Magnetic resonance imaging (MRI)

MRI utilizing IONPs as contrast agents has shown significant promise in enhancing tumor visibility. Bio-synthesized IONPs, in particular, leverage their magnetic properties to improve the contrast between healthy and cancerous tissues, facilitating better tumor detection. The superparamagnetic nature of IONPs allows for stable and biocompatible formulations, which are crucial for effective MRI applications [63, 64].

1.10 Drug delivery

Bio-synthesized IONPs can also be used as carriers for delivering drugs directly to cancer cells. These nanoparticles can be loaded with anticancer drugs and directed to the tumor site, where they release the drugs in a controlled manner. This targeted drug delivery system improves the effectiveness of the treatment and reduces side effects by minimizing the exposure of healthy cells to the drug [65].

Previous studies have extensively investigated the synthesis and properties of IONPs derived from various plant sources. Table 3 presents a summary of these nanoparticles, their characteristics, and their applications, highlighting the significant potential of plant-based synthesis methods. The data underscores the versatility and eco-friendliness of these methods, further emphasized in this current review [66].

1.11 Targeted delivery of IONPs

Targeted delivery of iron oxide nanoparticles (IONPs) is a key strategy for enhancing cancer treatment efficacy by ensuring that therapeutic agents accumulate specifically at tumor sites. [67].IONPs can be directed to the tumor via multiple mechanisms, each with its own advantages. These approaches are discussed below, highlighting their potential to improve treatment outcomes through localized delivery and minimizing damage to healthy tissues. Various methods such as local administration, passive targeting using the Enhanced Permeability and Retention (EPR) effect, active targeting, and magnetic targeting are utilized to optimize IONPs' effectiveness in cancer therapy (Fig. 8).

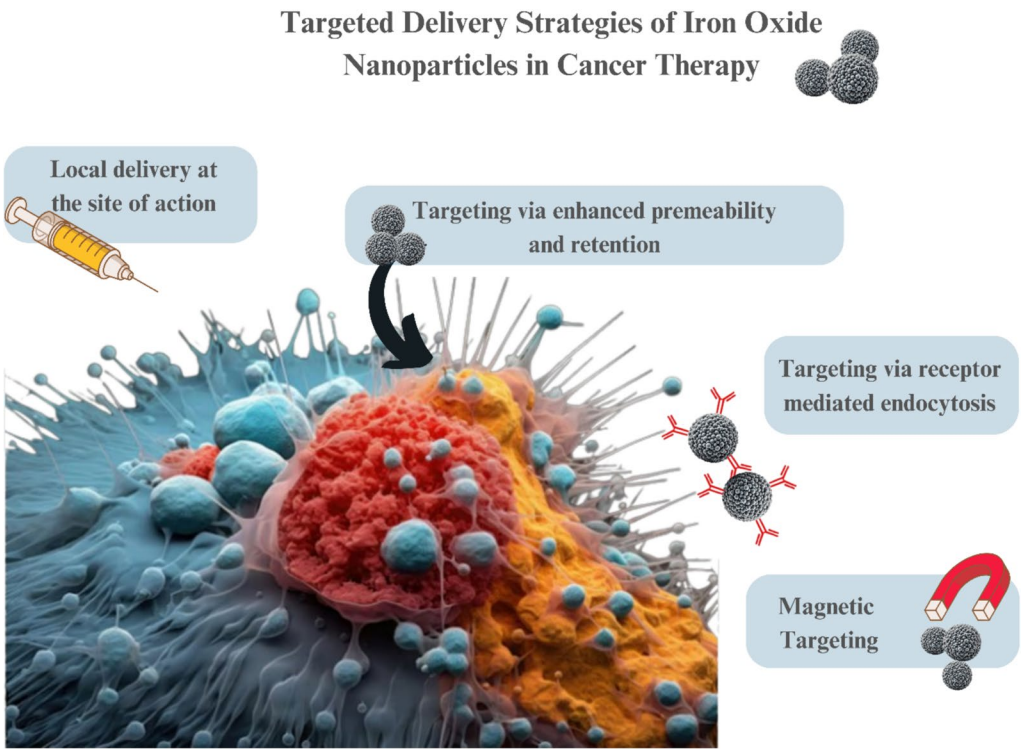

Fig. 8 Targeted delivery strategies of IONPs in cancer therapy

1.12 Local delivery at the site of action

Administering the IONPs solution directly at the tumor site (e.g., through intracranial or intraperitoneal injection). Intracranial delivery, for instance, offers a convenient means to target IONPs to brain tumors like gliomas without needing to enhance drug lipophilicity for crossing the blood–brain barrier (BBB) using invasive catheters. However, this approach is associated with significant clinical morbidity, patient discomfort, and potential for surgical errors. Additionally, the tight junctions between brain cells pose a physiological challenge, often leading to fluid stagnation or outflow following administration [9].

1.13 Passive target delivery

Malignant tumors present unique challenges, often characterized by irregular vascular structures and poor lymphatic drainage. These features create opportunities for passive targeted delivery using nanocarriers, leveraging the Enhanced Permeability and Retention (EPR) effect. This effect allows NPs to passively accumulate in the tumor microenvironment due to the leaky blood vessels and limited lymphatic drainage in the tumor [2]. Encapsulating small molecules within nanosized carriers helps improve their pharmacokinetic profile, extending circulation time and enhancing localization at the tumor site [68]. Synthesized IONPs are particularly promising for passive targeted cancer therapy. However, the size of these NPs is crucial; IONPs ranging between 10 and 100 nm provide the optimal balance for effective tumor targeting via EPR-mediated delivery [11].

1.14 Active target delivery

Beyond passive accumulation, IONPs can be actively directed towards specific cells. This strategy, known as active targeting, relies on the attachment of targeting molecules to the surface of the nanocarrier. Targeting molecules encompass a variety of substances including antibodies, ligands, peptides, nucleic acids, and other compounds that specifically attach to receptors that are excessively expressed on the surface of tumour cells [69].These targeting molecules act like recognition tags, allowing the nanocarrier to bind to specific receptors present on the surface of the target cells. This binding, facilitated by ligand-receptor interactions, ensures the nanocarrier reaches its intended destination with high accuracy [2].

1.15 Magnetic targeting

IONPs due to their inherent magnetic property can be used in targeted delivery by applying external fields. Their superparamagnetism allows their tiny magnetic moments to align in an external magnetic field, enabling them to be guided and concentrated in specific areas of the body [70]. Magnetic targeting offers a more precise approach. An external magnetic field can be applied to guide IONPs loaded with medications towards a tumor site, minimizing exposure of healthy tissues to the therapeutic agents. This targeted approach leads to a higher drug concentration in the specific area, ultimately reducing overall side effects [71, 72]. Studies have shown promise for this approach in treating prostate cancer, where IONPs loaded with docetaxel (DTX) can be delivered directly to the tumor for improved treatment efficacy (Imran et al., 2020).

1.16 Biocompatibility and anti-tumor activity of bio-synthesized IONPs

IONPs are commonly considered to be biocompatible. However, the majority of chemical synthesis processes utilize hazardous chemicals such as hydrazine or potassium bitartrate, which may persist as minute amounts in the end NPs product. Biological synthesis provides a method to create IONPs without using these toxic compounds [73]. The bio-synthesized IONPs were shown to effectively inhibit the growth of different types of tumour cells, including leukaemia (Jurkat cells), breast cancer (MCF-7 cells), cervical cancer (HeLa cells), and liver cancer (HepG2 cells), as demonstrated by in vitro cytotoxicity evaluations [74, 75]. To clarify the effectiveness of this, research has highlighted the importance of the inherent covering of IONPs, for instance, biomolecules from rosemary extracts containing polyphenols, which show anti-cancer properties. The presence of polyphenolic coating successfully inhibited the

Table 4 Summarizing research findings on the biocompatibility and cytotoxic activity of green synthesized IONPs

Plant extract used	Nanoparticles	Cell line used	Concentration (µg/ml)	Evaluation Method	Findings	References
Nigella sativa seed extract	IONPs	Vero cells	12.5–200	MTT	Green-synthesized IONPs showed negligible toxicity on normal cell lines across different doses	[30]
Spinacia oleracea leaves extract	PEG-IONPs, and PEG-IONPs-DOX	Triple-Negative Breast Cancer	0.1–1	MTT	Cytotoxicity was concentration-dependent for all treatments, with the highest concentration (1 µg/ml) showing the strongest effect. PEGylation of IONPs significantly enhanced cytotoxicity at higher concentrations (1 µg/ml): PEG-IONPs exhibited 93% cytotoxicity compared to 58% for uncoated IONPs. At lower concentrations (< 1 µg/ml), uncoated IONPs showed higher cytotoxicity than PEGylated IONPs	[77]
Pimenta dioica	IONPs	Human cervical cancer cells (HeLa)	20–1000	MTT	Cell viability remained above 88% up to 200 µg/ml, 82% at 500 µg/ml, and around 68% at 1000 µg/ml These findings indicate that green synthesized SPIONs are biocompatible and safe for cells even at high concentrations	[34]
Commiphora berryi latex	IONPs, silymarin and silymarin-loaded IONPs	lung (A-549) and liver cancer (HepG2) cells	5–100	MTT	The IC50 values for A-549 cells were 28, 23, and 18 µg/mL for IONPs, silymarin, and silymarin-loaded IONPs, respectively. For HepG2 cells, the IC50 values were 43, 31, and 21 µg/mL for IONPs, silymarin, and silymarin-loaded IONPs, respectively. These results indicate that silymarin-loaded IONPs exhibit the highest cytotoxicity against both lung and liver cancer cells	[78]

Table 4 (continued)

Plant extract used	Nanoparticles	Cell line used	Concentration (µg/ml)	Evaluation Method	Findings	References
Aloe vera and flaxseed	IONPs	MCF-7 cell lines (breast cancer)	0.58–150	MTT assay	Aloe vera/IONPs are non-toxic below 100 µg/ml, and flaxseed/IONPs show no significant toxicity up to 4.7 µg/ml in MCF-7 cells. Higher concentrations may cause membrane breakdown. Anticancer effects increase with concentration up to 4.7 µg/ml, suggesting potential cancer treatment benefits using aloe vera and flaxseed IONPs	[79]
Bark of Prosopis farcta	IONPs	brain glioblastoma cells (U87)	1–500	MTT assay	The green synthesized Fe_2O_3 NPs demonstrated no toxicity against the U87 cell line, making them a suitable candidate for use as a drug delivery agent in cancer treatment	[80]
P. granatum (pomegranate) fruit	5-FU and IONP@5-FU	CCD112 normal and HCT116 colorectal cancer cell lines	0–125	MTS assay	5-FU alone eliminated both cell types at a minimum concentration of 7.81 µg/mL. The IONP@5-FU formulation caused minimal damage to healthy cells and effectively targeted cancer cells, with 15.62 µg/mL eliminating 29% of cancer cells and 11% of healthy cells	[81]
Punica Granatum Fruit Peel Extract	IONPs	HCT11, MCF7, HeLa, CCD112 colon normal and HEK-293 embryonic kidney normal	0–250	MTS assay	IONPs exhibited minimal cytotoxicity against HCT116, MCF7, HeLa, and A549 cancer cells, even at the highest tested concentration. Additionally, the IONPs were non-toxic to human normal cells (CCD112 and HEK293)	[82]

Table 4 (continued)

Plant extract used	Nanoparticles	Cell line used	Concentration (µg/ml)	Evaluation Method	Findings	References
Borassus flabellifer tender seeds	IONPs	NIH 3T3 cells(normal cells)	50–500	MTT assay	The viability percentage was above 80% in all cases, indicating high biocompatibility of the nanoparticles with fibroblast cells. Similar non-toxicity results for iron oxide nanoparticles with NIH 3T3 fibroblast cells were reported	[83]
Juglans regia green h	IONPs	3 T3 (Mouse Embryonic fibroblast cell lines) and HT-29)	1–1000	MTT assay	The J. regia green husk-coated iron oxide nanoparticles showed no significant toxicity up to 1000 µg/ml on normal cell lines, indicating good tolerance by 3T3 cells. Similarly, these nanoparticles had no toxic effect on cancerous HT-29 cell lines at high concentrations	[84]
Artemisia absinthium L	IONPs	keratinocyte cell line (HaCaT), human melanoma cell line–A375, human epidermoid carcinoma cell line–A431 cells	150–500	*Alamar Blue Assay*	The study found that cell viability decreased with longer incubation times and higher concentrations of test compounds for HaCaT, A375, and A431 cell lines. HaCaT cells remained viable above 80% even at high concentrations, indicating no significant cytotoxicity. A375 cells were more sensitive, with Fe_2O_3 NPs causing the greatest reduction in viability (50.42% at 72 h). A431 cells showed higher resistance compared to A375 cells. Wormwood extracts and Fe2O3 NPs had a stronger antitumor effect and did not affect HaCaT cells significantly, indicating they are not cytotoxic to healthy cells	[85]

Table 4 (continued)

Plant extract used	Nanoparticles	Cell line used	Concentration (µg/ml)	Evaluation Method	Findings	References
Musa paradisiaca peel	IONPS, ION@PEG, ION@PEG@DOX	Hela cells	25–200	*MTT assay*	Hela cell viability after 48 h with different nanocomposite concentrations. At 200 µg/ml, cell viability was 55.5% with IONPs, 76.7% with ION@PEG, and 45.5% with ION@PEG@DOX. At 25 µg/ml, viability was 76.9% with IONPs, 86.1% with IONPs@PEG, and 62.5% with IONPs@PEG@DOX. ION@PEG showed higher viability, suggesting PEG reduces cell damage and supports doxorubicin delivery	[86]
Spinacia oleracea leaves	IONPs, PEG-IONPs, PEG-IONPs-DOX and free DOX	Triple negative breast cancer cell line(MDA-MB-231)	N/A	*MTT assay*	The study found that PEG-coated IONPs and PEG-IONPs-DOX are more effective at killing cancer cells than uncoated IONPs and free DOX. At 1 µg/mL, PEG-IONPs achieved 93% cytotoxicity, and PEG-IONPs-DOX caused complete cell death (100%). PEG-IONPs-DOX was about 22 times more effective than free DOX, potentially allowing for lower doses and fewer side effects	[77]

growth of C26 colon cancer cells. This indicates that Rosemary-FeNPs possess significant cytotoxicity, as evidenced by their IC50 value of 20.98 µg/ml, compared to the extracts alone (47.87 µg/ml) [76] more studies are thoroughly reviewed and summarized in the following Table 4.

The graph (Fig. 9) illustrates the cytotoxic effects of various nanoparticle treatments IONPs, PEG-IONPs, and drug-loaded IONPs on both cancerous and non-cancerous cell lines, as presented in Table [4]. The data reveals that PEG-IONPs and drug-loaded IONPs demonstrate significantly higher cytotoxicity towards cancerous cells compared to IONPs alone. Drug-loaded IONPs, in particular, show the highest efficacy in killing cancer cells, underscoring the potential of functionalized nanoparticles in targeted cancer therapy. Conversely, IONPs exhibit minimal toxicity toward non-cancerous cells, which suggests their suitability as a safer therapeutic option with reduced side effects. PEGylation, while enhancing the therapeutic impact on cancer cells, also helps maintain low toxicity to healthy cells, a critical factor for improving the safety profile of cancer treatments.

This comparison underscores the potential of green-synthesized nanoparticle-based treatments for enhancing the precision and efficacy of cancer therapies while minimizing harm to healthy tissues. The graph effectively highlights the advantages of functionalizing nanoparticles with PEG or drug molecules, which can lead to more efficient tumor targeting and improved therapeutic outcomes.

1.17 Challenges associated with IONPs translation and strategies to overcome

Despite these advancements, several challenges need to be addressed to fully realize the potential of green-synthesized IONPs as mentioned in Fig. 10.

1.18 Toxicity

One of the major concerns with IONPs is their potential toxicity, especially at higher concentrations. It is crucial to understand the toxicity of magnetic nanoparticles (MNPs), as it is influenced by various factors such as their size, shape, structure, surface modifications, concentration, dosage, biodistribution, bioavailability, solubility, immunogenicity, and pharmacokinetics [87]. Excess iron accumulation in tissues can lead to oxidative stress, cellular damage, and organ dysfunction. As previously mentioned, and demonstrated in the graph, PEGylated IONPs exhibit significantly lower cytotoxicity towards normal cells compared to uncoated IONPs, underscoring the importance of surface modification strategies. PEGylation, or coating IONPs with biocompatible polymers, effectively reduces particle aggregation and minimizes the release of free iron ions into the bloodstream. Additionally, adjusting the size and dosage of IONPs can further minimize

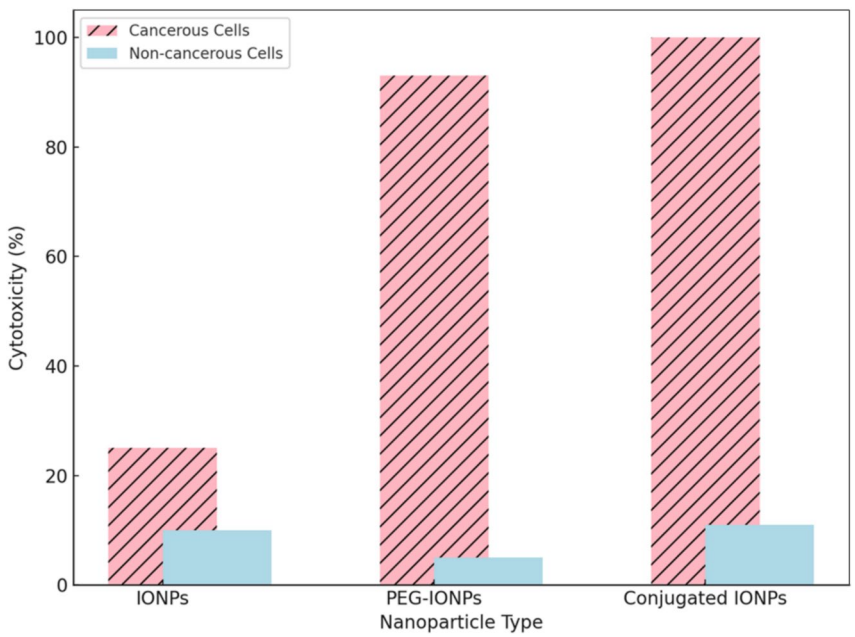

Fig. 9 A bar graph depicts the cytotoxicity of green-synthesized IONPs towards cancerous and non-cancerous cells

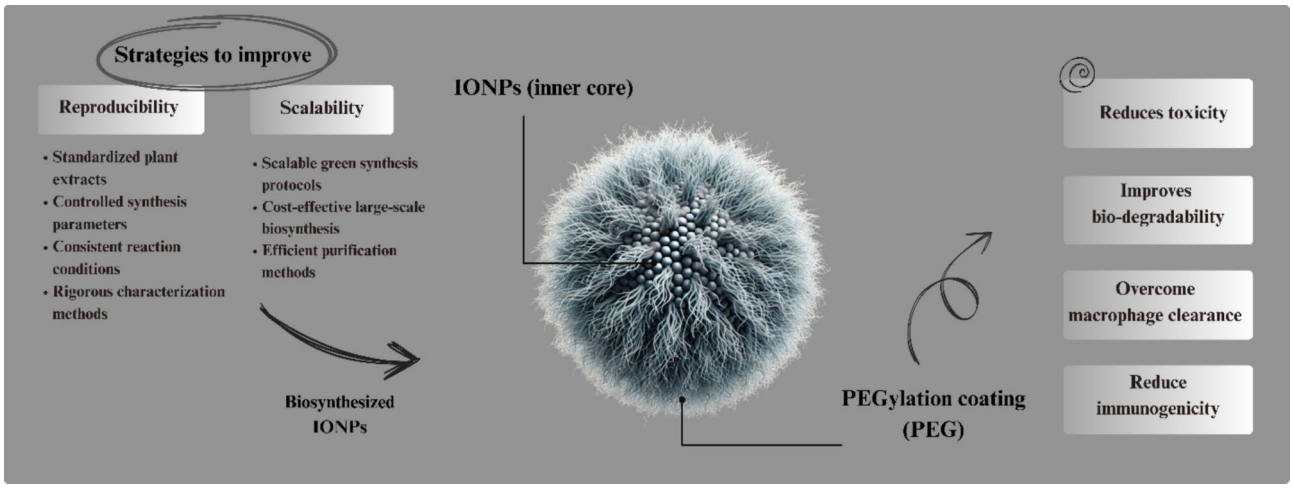

Fig. 10 Challenges associated with IONPs translation and strategies to overcome

cytotoxicity, while functionalizing nanoparticles with targeting ligands ensures more specific accumulation in tumor tissues, reducing off-target effects on healthy cells [88, 89].

1.19 Degradability

IONPs, particularly larger or poorly coated particles, may show slow or incomplete biodegradability, which can lead to long-term accumulation in the body. Similar to how PEGylation reduces toxicity by enhancing biocompatibility, surface modifications can also improve the degradability of IONPs. In particular, using biodegradable polymer materials such as PEG, dextran or chitosan can promote enzymatic or biological degradation, ensuring that the nanoparticles are safely broken down in vivo [90].

1.20 Overcoming macrophage clearance and immunogenicity

One of the major limitations of IONPs is their susceptibility to immunogenicity the ability to provoke an immune response. When foreign nanoparticles are introduced into the body, they can trigger recognition by the immune system, leading to inflammation or rapid clearance. This process often begins with opsonization, where proteins in the bloodstream bind to the surface of the nanoparticles. Opsonization tags the nanoparticles for recognition by the mononuclear phagocyte system (MPS), especially macrophages in the liver and spleen, which rapidly clears them from circulation [91]. This immune recognition limits the therapeutic efficacy of IONPs by reducing the time they spend in the bloodstream, preventing them from reaching their target tissues. To overcome this challenge, surface modification strategies, such as PEGylation, have been highly effective. PEGylation involves coating IONPs with PEG, forming a hydrophilic protective layer around the nanoparticles [92]. As depicted in Fig. 8, this layer repels opsonization proteins, preventing immune recognition and reducing macrophage uptake. Furthermore, PEGylation helps reduce the immunogenicity of IONPs by shielding the nanoparticles from immune surveillance, PEGylation decreases the likelihood of triggering an immune response [93].

1.21 Reproducibility and scalability

Scaling up the production of IONPs from lab to industrial or clinical levels presents several challenges. Maintaining uniformity in nanoparticle size, stability, and surface functionalization during large-scale production can be difficult. However, green synthesis methods offer a more sustainable and scalable alternative to traditional techniques. By utilizing biogenic sources like plant extracts, green synthesis reduces the reliance on expensive chemicals, making the process more cost-effective and easier to scale. Additionally, green synthesis operates under simpler conditions, such as lower temperatures and pressures, facilitating larger-scale production without requiring significant infrastructure changes. This method also aligns with environmental sustainability goals by minimizing waste and avoiding harmful chemicals, which eases scaling while meeting regulatory standards [94].

Reproducibility, however, remains a key challenge due to variations in raw biogenic materials, which can affect nanoparticle consistency. As suggested by Fernandes and coworkers, addressing this issue involves optimizing production parameters, such as plant extract concentrations and reaction conditions, to standardize outcomes. Furthermore, naturally occurring compounds in green synthesis can act as capping agents, helping to prevent aggregation and ensuring uniform nanoparticle size and shape. Regular monitoring and quality control measures, like electron microscopy, can further improve consistency across batches. By applying these strategies, green synthesis can overcome reproducibility challenges and enhance the reliability of nanoparticle production [95].

2 Conclusion

In comparison to chemically synthesized nanoparticles, biosynthesized IONPs offer distinct advantages in cancer therapy, making them a novel alternative. Unlike traditional methods that rely on toxic chemicals, biosynthesized IONPs are produced using plant extracts, significantly enhancing their biocompatibility and safety profile. Unique findings from this study demonstrate that biosynthesized IONPs exhibit higher stability, lower cytotoxicity, and better targeted delivery to tumor sites. These properties position them as a sustainable and effective option for cancer theranostics, offering a promising advancement over conventional nanoparticles. The use of plant-based extracts not only reduces environmental impact but also enhances biocompatibility and safety. IONPs' multifunctionality, spanning drug delivery, magnetic hyperthermia, and diagnostic imaging, positions them as crucial tools in personalized cancer therapy. Despite their potential, challenges such as reproducibility, toxicity, and scalability remain. Future research should focus on optimizing synthesis methods and addressing these limitations to fully translate biosynthesized IONPs into clinical practice.

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Data availability This manuscript does not report data generation or analysis.

Declarations

Ethics approval and consent to participate Not applicable.

Competing interests The authors declare no competing interests.

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