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Sustainable synthesis of iron oxide nanoparticles using phytochemicals: mechanisms, functionalization strategies, applications and future perspectives

Abstract

The green synthesis of iron oxide nanoparticles (IONPs) using phytochemicals has garnered significant attention due to its eco-friendly, biocompatible, and cost-effective nature. This review highlights the chemical diversity of plant-derived compounds such as flavonoids, terpenoids, alkaloids, and polyphenols and their multifunctional roles as reducing, stabilizing, and capping agents in nanoparticle synthesis. Advancements in green extraction methods, including microwave-assisted, ultrasound, and supercritical fluid extraction, have enhanced the yield and bioactivity of phytochemicals for IONP synthesis. Furthermore, the paper explores the influence of these bioactives on nanoparticle formation, crystallinity, and stability. Novel biofabrication approaches utilizing microalgae, *in-vitro* cultures, and green biomaterials are also reviewed. Mechanistic insights into redox pathways, functional group interactions, and in situ molecular dynamics are discussed, supported by emerging trends in AI/ML-based process optimization and microreactor technologies. Functionalization of phyto-IONPs with polymers, biomolecules, and targeting ligands has expanded their applications in cancer therapy, magnetic hyperthermia, drug delivery, catalysis, energy storage, and bioinks. Emphasis is also placed on toxicity studies and the environmental impact of phytogenic nanomaterials. Collectively, this review identifies critical gaps in mechanistic understanding, scale-up processes, and regulatory frameworks, while proposing future directions for integrating green-synthesized IONPs into biomedical and industrial platforms.

Keywords: iron oxide nanoparticles, phytochemicals, functionalization, biomedical engineering, applications

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Agilandeswari Mohan,[1,2] Shakthivel Rajendran,[1] Naveen Palani,[2,3] Rabiya Riffath Syed Altaf,[2,3] Keren Celestina Mendonce,[2,4] TG Nithya,[1] Puruchothaman Venkatesan,[1] Sangavi Nagendran,[1] Parthasarathy Surya,[5] Mohankumar Srinivasan,[1] Rajesh Kannan Ramar,[6] Nandhini Sundaresan,[7] Suriyaprakash Rajadesingu[2]

[1]Department of Biochemistry, Faculty of Science and Humanities, SRM Institute of Science and Technology, India

[2]Centre for Research in Environment, Sustainability Advocacy and Climate Change (REACH), Directorate of Research, SRM Institute of Science and Technology, India

[3]Department of Physics and Nanotechnology, SRM Institute of Science and Technology, India

[4]Department of Biotechnology, Faculty of Science and Humanities, SRM Institute of Science and Technology, India

[5]Department of Research Analytics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, India

[6]Plantaxome Global Innovations, India

[7]Department of Pharmacognosy, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), India

Correspondence: Suriyaprakash Rajadesingu, Centre for Research in Environment, Sustainability Advocacy and Climate CHange (REACH), Directorate of Research, SRM Institute of Science and Technology, Kattankulathur 603203, Chengalpattu District, Tamil Nadu, India, Tel +91 9942 186 885

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Introduction

The rapid advancement of nanotechnology has heightened the demand for sustainable, cost-effective, and biocompatible approaches to nanoparticle synthesis. Among the various nanomaterials, iron oxide nanoparticles (IONPs) have garnered significant attention due to their unique magnetic properties, high surface area, and broad applicability in medicine, environmental remediation, catalysis, and biosensing.[1–3] Traditionally, IONPs have been synthesized via physical and chemical methods that often involve hazardous reagents, elevated temperatures, and high energy input, posing serious risks to environmental and human health.[4] To overcome these limitations, the green synthesis of IONPs has emerged as a promising alternative, leveraging naturally derived phytochemicals from plant sources.[5,6] These bioactive molecules including flavonoids, terpenoids, phenolic acids, alkaloids, and tannins act as both reducing and stabilizing agents, facilitating the formation of nanoparticles under mild, environmentally benign conditions.[7] These phytochemicals contain functional groups such as hydroxyl, carbonyl, and amine moieties, which enable controlled nucleation and stabilization of IONPs, thereby improving their colloidal stability, biocompatibility, and surface reactivity.[8,9]

Recent advancements have expanded the scope of green synthesis through innovative extraction techniques (e.g., ultrasound-assisted and supercritical fluid extraction), enabling higher yields and purities of phytoconstituents. Additionally, biofabrication approaches using microalgae, callus cultures, and green biomaterials have opened new avenues for nanoparticle synthesis beyond traditional plant extracts.[10,11] Despite these advancements, challenges remain in scaling up production, standardizing phytochemical content, and ensuring reproducibility across batches. Integrating in-situ monitoring techniques such as UV-Vis spectroscopy, FTIR, and XRD with computational tools like density functional theory (DFT) and molecular dynamics simulations has enhanced our understanding of reaction mechanisms. Moreover, the application of artificial intelligence (AI) and machine learning (ML) for optimizing reaction parameters and employing microreactor technologies for continuous flow synthesis are emerging as powerful tools in the field.[12] Functionalization strategies such as surface coating with biopolymers, ligands, or drugs have significantly expanded the biomedical potential of phytogenic IONPs, particularly in targeted drug delivery, magnetic hyperthermia, and imaging. Concurrently, their integration into catalytic systems, energy storage platforms, biosensors, and 3D-bioprinted scaffolds underscores the versatility and scalability of green-synthesized IONPs.[13]

This review provides a comprehensive overview of phytochemical-assisted green synthesis of IONPs, emphasizing recent trends in biofabrication methods, mechanistic insights, functionalization strategies, and advanced applications. It also addresses toxicity assessments, sustainability metrics, and future challenges, aiming to bridge the gap between lab-scale synthesis and real-world applications. By synthesizing knowledge from recent studies, this review highlights the potential of phytogenic IONPs as a cornerstone of green nanotechnology and sustainable material science.

Phytochemicals and their role in green synthesis of IONPs

Phytochemicals act as strong reducers in the synthesis of nanoparticles which are particularly important in the green synthesis of metal and metal oxide nanoparticles. In this regard, phytochemicals act both as the reducing agents of metal salts, for example, Fe^{3+} or Ag^{+}, converting them directly into their nanoparticles iron oxide nanoparticles or silver nanoparticles, respectively without employing toxic reagents at high energy processes. Chemosensitization by plant extracts involves the presence of polyphenols and flavonoid moieties that contain electron-donating groups to effect this reduction.[10] At the same time these compounds serve as stabilizers so that nanoparticles do not cluster together and also help to maintain stable particle size. This green synthesis approach is well-documented in enabling production of nanoparticles for medical, electronic and environmental purposes. Another great contribution of phytochemicals is their application in the biocatalysis field of the green chemistry triad. USP affords plant derived enzymes and secondary metabolites for the green synthesis of drugs in the modern world. Such natural promoters lower the need to perform energy-intensive reactions and employ toxic reagents, suggesting more efficient and green approaches to construction a medication as shown in Figure 1. As an example, the enzymes that can be derived from plant sources include lipases as well as amylases in the formulation of bioactive compounds.[13] In addition, alkaloids, terpenoids, and flavonoids are described to be antimicrobial, anti-inflammatory and even anticancer in action. The use of these natural compounds for biocatalytic reactions enhances the prospects for decreasing the ecological impact of producing pharmaceuticals.[7] Antioxidants are obtained from polyphenols and flavonoids which gives them the potential to be integrated in the application of degradation of organic materials since they have antioxidant properties. At the chemical level their performance in antioxidant activity is effective in shielding against oxidation in reactions and processes.[4] Further, the residues resulting from extraction or production of phytochemicals can be utilized as higher value co-products as shown in Table 1. For instance, plant residues can be effectively used for bioenergy, in composting and as a source of additives in food and cosmetic products which minimizes waste and optimize use of resources.[12]

Table 1 Comprehensive overview of phytochemicals utilized in the green synthesis of nanoparticles

Phytochemical	Source	Chemical structure	Green chemistry application	Biodegradability	Toxicity	Industrial use	Environmental impact	Reference
Alkaloids	Plants	Heterocyclic nitrogen compounds	Natural pesticides	High	Low to moderate	Pharmaceuticals	Low Pollution	15
Flavonoids	Fruits, vegetables	Polyphenolic structure	Antioxidants, UV absorbers	High	Low	Cosmetics, food	Biodegradable	16
Terpenes	Citrus peels, pine trees	Hydrocarbon-based compounds	Green solvents, biofuels	High	Low	Cleaning agents, perfumes	Renewable resource	17
Polyphenols	Tea, berries, cocoa	Multiple phenol groups	Antioxidants, preservatives	High	Low	Food industry, medicine	Low waste production	18
Saponins	Soybeans, quinoa	Glycosides with steroid/lipid core	Natural detergents	High	Low	Soaps, pharmaceuticals	Eco-friendly surfactants	19
Lignans	Flaxseeds, sesame seeds	Polyphenolic dimers	Biodegradable plastics	High	Low	Biopolymers, medicine	Reduced synthetic waste	20
Tannins	Oak bark, tea leaves	Polyphenols	Natural dyes, leather tanning	High	Low	Textile, leather industry	Non-toxic alternative	21
Carotenoids	Carrots, tomatoes	Terpenoid-based pigments	Natural colorants, UV protectants	High	Low	Food coloring, cosmetics	Sustainable & non-toxic	22
Coumarins	Citrus fruits, cinnamon	Benzopyrone structure	UV absorbers, pharmaceuticals	High	Moderate	Medicine, fragrances	Low environmental harm	23
Resveratrol	Grapes, red wine	Stilbene derivative	Antioxidants, anti-aging agents	High	Low	Cosmetics, supplements	Biodegradable & natural	23,24

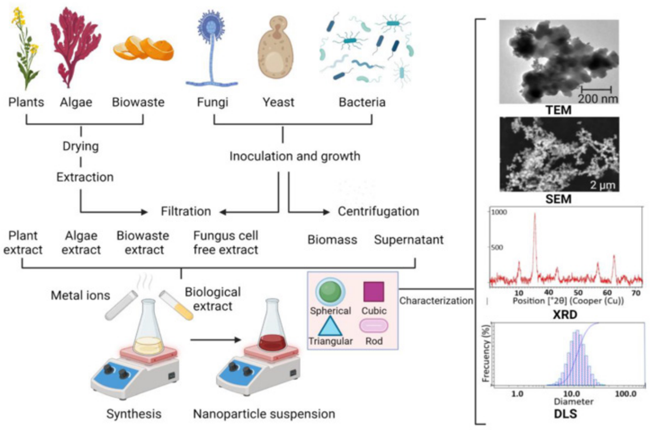

Figure 1 Capping and stabilizing agents involved in the green synthesis of iron oxide nanoparticles and their influence on different nanoparticle formations.[14]

Chemical diversity and functional roles of plant-derived compounds

Phytochemicals are POPs, natural occurring molecules in plants that have multiple uses in nutrition, medicine and in the ecosystem. These are unlike the vitamins or minerals that are other basic elements in plant metabolism and immune reactions and are specific in assisting plants in defence activities, plant growth regulation and specific protection against some physical conditions.[25] In the last few years, phytochemicals have garnered significant attention about their therapeutic uses and applicability in medicine, food processing technology, agriculture and ecology. Phytochemicals are primarily categorized into two broad groups: primary products and secondary products.[26] The primary metabolites have some effect in the growth and development of the plant while the second group of compounds consists of alkaloids, flavonoids, phenolic acids, terpenoids, saponins and are reported to have most of the desired bioactivity of plants as shown in Figure 2. These are normal physical products existing in plants and they are generated as reactions to certain stimuli such as ultraviolet light, insects and microbes.[27]

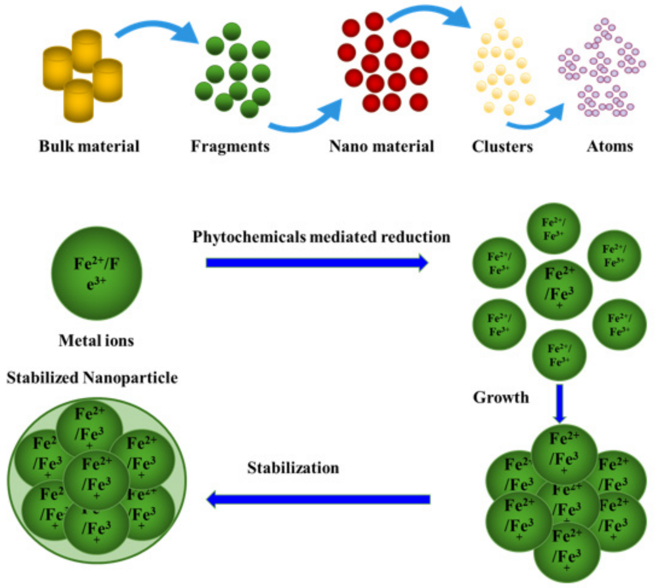

Figure 2 Phytochemicals such as flavonoids, terpenoids, phenolic acids, and alkaloids act as reducing and stabilizing agents, facilitating the conversion of metal ions to nanoparticles through redox reactions and surface capping.

Multifunctional role of flavonoids in phytochemistry

It is a category of bioactive polyphenolic compounds that are considered to be responsible for the color, taste and odor of plant foods. They are present mainly in fruits, vegetables, flowers as well as in herbs, and are established to contain a very high antioxidant, anti-inflammatory properties as well as anticancer properties.[28]

These compounds have a major function of defense against UV radiation, bacteria, viruses and other types of stress. Examples: Flavonoids: Quercetin, catechins (green tea), anthocyanin (berries), kaempferol, rutin. Pharmacological Effects: Antioxidant: flavones, flavonols and isoflavones, quench reactive oxygen species which cause oxidative damage. Anti-inflammatory: It can help lessen inflammation and may benefit in conditions such as arthritis. Anticancer: Some of the flavonoids can prevent the proliferation of cancer cells. Cardioprotective: Today, quercetin and other flavonoids are attributed to the promotion of heart health through the reduction of blood pressure cholesterol levels. Role in Plants: Flavonoids help deter UV radiation and pathogens, as well as to attract pollinators because of its vivid colour and smell. Neuroprotective: Polyphenol compounds like quercetin and epigallocatechin gallate (EGCG) in green tea has potential to slow neurodegenerative disorders including; Alzheimer's and Parkinson's disease through reduction of oxidative stress and inflammation in the brain. Antiviral: Some flavonoids, luteolin and kaempferol, clobber antiviral abilities, and may be used in HIV and the simple cold remedy attempts.[29] Biochemical constituents such as flavonoids like anthocyanins that are found in berries have been proven to lower the chances of heart diseases since they offer a protective coat to the blood vessels, improve blood pressure as well as blood lipid levels as shown in Figure 3. Flavonoids are used in functional food and drinks like fruit juices, tea, and nutritional supplements for their health promoting qualities. They are employed in the biotechnological industries to extract natural food dyes for confectioneries, drinks and creams owing to their bright colors.[29,30]

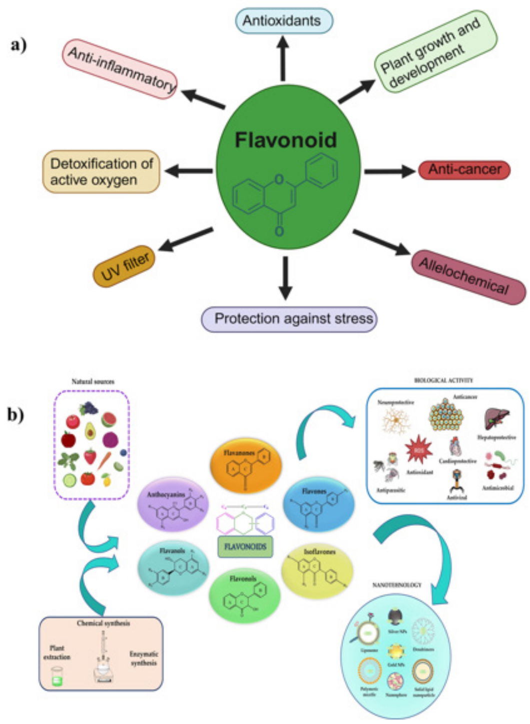

Figure 3 Functional roles of secondary metabolites in biomedical applications, **(a)** Classification of different secondary metabolites along with their specific

biomedical applications such as antimicrobial, anticancer, antioxidant, and anti-inflammatory activities. **(b)** Natural sources of these metabolites with corresponding biological activities, both chemical and biological (green) synthesis approaches for their integration into nanomaterial fabrication.[31,32]

Pharmacological and therapeutic potential of plant-derived terpenoids

Terpenoids (or isoprenoids) are a vast class of naturally occurring organic compounds based on the isoprene unit. Coumarins are a significant group of plant secondary metabolites which are also involved in plant defense and have anticoagulant activity. It is also used to cure common ailments including inflammation, microbial infections, and some forms of cancers. Examples: Pharmacological activities: Essential Oil Components: Menthol (peppermint), limonene (citrus fruits), beta carotene (carrots), and lavender oil, eucalyptus oil, and thyme oil.[31,32] Anti-inflammatory: Beta-caryophyllene, a terpenoid compound in the composition of preparations for the treatment of inflammation.[33] Anticancer: While some terpenoids have gained attention due to their anticancer properties limonene and taxol to be specific. Antioxidant: Other carotenoids such as Beta carotene and lutein have anti-oxidation properties, or inhibit oxidation. Role in Plants: Some terpenoids work as defense structures since their odour and taste repel herbivores and pathogens. They also entice pollinators for plant reproduction These they also entice pollinators for plant reproduction. Anti-cancer: Examples are taxol derived from the Pacific Yew tree and others known as terpenoids since they perform a very important function of halting the growth of cancer cells and inducing apoptotic cell death.[34] Antifungal and Antibacterial: For this reason, Terpenoids such as eugenol derived from cloves and Thymol derived from thyme have wide spectrum antimicrobial effects and used in treating bacterial and fungal infections. Immune-boosting: Most terpenoids for instance the curcumin found in turmeric improves the body's immunity making it less susceptible to a variety of diseases. Cosmetic and Aromatherapy Applications: It should be noted that the largest group, the terpenoids, especially the volatiles in the essential oils, are popular in aromatherapy for the purpose of relaxation, mood adjustment, or alleviation of stress. They are also used in cosmetics, perfumes and body product preparations such as skin and hair care products because of good smells.[34,35]

Advancements in green extraction methods for bioactive compounds

Phytochemicals are naturally occurring biologically active compounds that exist in plants and are known to have many health promotion and disease prevention benefits. These compounds are mostly documented in medicinal plants, edible plants, food wastes, marine algae and any of the fungi. All of these sources have sources of phytochemicals that are different from the rest and that have various health benefits.[36] Plant sources of bioactive compounds including flavonoids, polyphenol, alkaloid, and tannin which are contained in medicinal plants have the potential to act as reducing and stabilizing agents in the green synthesis of IONPs. For example, iron oxide nanoparticles synthesis from *Lawsonia inermis* (Henna) extract has been reported earlier. Interest in nanoparticles, especially in iron oxide nanoparticles (IONPs), has been increasing due to their multifunctional characteristics.[37] The failure of pathogenic microorganisms to respond to antibiotics has created pressure towards the development of alternate antimicrobial materials, of which nanotechnology is part. Plant-mediated green synthesis of nanoparticles have advantage over chemical and physical methods by exhibiting non-toxic, renewable resources from plants, bacteria, fungi, and agro- wastes leading to low energy consumption.[38]

Several mushrooms used in food preparation (including shiitake and reishi) contain immunostimulating substances like polysaccharides (glucans) and triterpenoids. More so, with regard to fungi, lichens for instance, organic extra products that have activity against microorganisms have been identified in these fungi. This research focus on fungi as a potential source of medicine is emerging because of the variation in phytochemicals. Mushrooms contain water and have low calorie content; that is, 50–70 calories per 100 grams of the portion size. It contains proteins at the level of 1.5 – 3.6% of the fresh weight and all essential amino acids, carbohydrates 4.7 – 6.9%, dietary fiber 2.7 – 3.9 %, and useful polysaccharides. Moreover, they have little fats (0.4 – 0.9%), desirable omega 6 and omega 3 fatty acids. These are potassium, phosphorus, magnesium, and the trace metals, zinc, copper, and selenium. They include B-complex, vitamin C, and only a little of D2, E.[40]

Wild mushrooms are edible fungi which have been cultured to be eaten by human beings in Poland and many other European and Asian countries. Means of preservation disrupt the nutrient value, with freezer storage retaining the maximum value of the nutrients. Micro fungi is a kind of non-vascular plant that people in China, Japan and the Himalayas usually eat, their nutrient compositions are as follows: carbohydrates 53.2~79.08%, fiber and protein 5.95~16.2%. Algae are used in food and medicine, they contain protein (from 20 to 70% depending on species, average of 46%), dietary fiber (23.5 -- 64% dry weight), and bioactive compounds.[39]

Macroalgae also has sterols which include fucosterol serving the functions of treating diabetes and hypertension.[41]

Plants still provide many natural medications where most of the natural drug comes from seed bearing flowering plants. It comprises morphine, quinine, caffeine, volatile oils and others. Ethnobotanists are carrying out efforts to identify, describe and record indigenous current and past uses of plants in a bid to counteract the loss of this information.[42]

Influence of bioactive plant constituents on nanoparticle formation and stability

In this green synthesis process of IONPs, phytochemicals act as green reducing, stabilizing, and capping agents of the plant origin. These bioactive compounds substitute the toxic chemical agents that are normally employed in nanoparticle synthesis, thus, the synthesized products are ecologically safe and biocompatible. Besides promoting the formation of nanoparticles, their participation also helps to stabilize the created nanoparticles and improve its functional characteristics for further use.[21]

When nanoparticles are produced, they typically aggregate owing to high surface energy. The phytochemicals help to act as stabilizing and capping agents so as to arrest the tendency of the nanostructured particles to form agglomerates on the solution. This occurs through functional group interactions between phytochemicals and surfaces of nanoparticles randomly. As green synthesis precursors and reductants, phytochemicals are responsible for the reduction of iron ions, stabilization, and functionalization of the synthesized nanoparticles. Reductants that can reduce metal ions into nanoparticles without forming large aggregates, they are green substitutes for chemical reagents. Diversity of phytochsemicals in plants has led to a larger variety of receptor arrangement and, therefore, the nanoparticles offer great potential for use in medicine and other fields requiring advanced catalytic activity and environmental remedial mechanisms. Further studies should be devoted to the investigation of suitable plant sources with the highest yield and further elucidation of the synthesis parameters to improve nanoparticle properties and obtain reproducible results.[43]

Green nanotechnology is specifically concerned with the ways to manufacture nanoparticles without using hazardous substances and energy. The most sustainable technique revolves around the preparation of iron oxide nanoparticles (Fe_3O_4-NPs) through phytochemicals from plant extracts. Such natural compounds as polyphenols, flavonoids, alkaloids, terpenoids, proteins for the preparation of which were used, act as reducing and stabilizing agents. During synthesis, phytochemicals act as reducing agents to convert iron salts (Fe^{2+} or Fe^{3+}) to nanoscale iron oxide and as stabilizing agents to avoid agglomeration. The availability of antioxidants in plant extracts also improves the stability and biocompatibility mechanical properties of Fe_3O_4-NPS for biomedical as well as environmental applications. It reveals that green synthesis is more effective than the conventional chemical methods as it has low toxicity, cost and environmental impact.[44] Recent synthesis of iron oxide nanoparticles using different plant extracts have shown that these nanoparticles have excellent properties in drug delivery, antibacterial properties and heavy metal adsorption, making them good candidates for green nanotechnology. Therefore green nanotechnology incorporates the concern of the environment in the process of preparation of nanoparticles by reducing the use of toxic reagents. Plant derived phytochemicals are used as reducing and stabilizing in the green synthesis of IONPs. These chemical compounds such as polyphenols, flavonoids, alkaloids and protein help to reduce Fe ions to nanoparticles and at the same time prevents their agglomeration. For example, *Hibiscus rosa-sinensis* flower extracts have been used to synthesize Fe_3O_4 nanoparticles in which the phytochemistry present within the flower extract plays both the role of reductant and stabilizing agent for the resultant nanoparticles. As a result of this method being eco-friendly, the biocompatibilities of the nanoparticles are also improved which makes them suitable for use in many biomedical applications.[45]

It is therefore possible to fine-tune the properties of the nanoparticles that are being synthesized by carefully choosing the plant source of phytochemicals. For instance, aqueous extracts of *Moringa oleifera* leaves containing bioactive compounds such as polyphenols, have been used to synthesise iron oxide nanoparticles due to its high reduction and stabilising potential. These plant-mediated synthesis approaches are economic and eco-friendly, which presents an environmentally friendly strategy in contrast to other chemical synthesis processes. Furthermore, presence in plant extracts can provide other functional properties of the nanoparticles, due to the presence of phytochemicals.[46]

The synthesis of iron oxide nanoparticles by microwave irradiation is a technique that is rapid and energy efficient. The use of microwave radiation in this approach ensures more uniform heating which cuts down on reaction time and, i.e., improves the formation of nanoparticles. Unlike traditional heating,[47] conduction, and convection, microwave irradiation affects the reactants themselves, guaranteeing optimum energy transfer and shorter synthesis time. Green microwave-assisted synthesis differs from conventional methods, and plant extracts, and natural polymers act as reducing and stabilizing agents. The compounds from these extracts improve the reduction of metal ions into nanoparticles besides offering protection from aggregation. The interaction of microwave irradiation in the reaction also helps to improve homogeneous reaction and therefore the dispersion of the nanoparticles with better size and shape regulation.[24,48] There are some advantages that adorn this method, for instance, the time taken for the reaction to occur is relatively short, energy used in the process is low and lastly the characteristics of the nanoparticles are easily manipulated. In addition, the process is mass compatible and can be used on a commercial scale when necessary. However, some challenges like overheating, sample penetration depth restriction, and the variation of reaction conditions that may affect the properties of synthesized nanoparticles remain to be solved to favor the development of nanoparticle synthesis techniques for an industrial outlook. In the green synthesis process, phytochemicals are primarily responsible for the reduction as well as the stabilization of iron oxide nanoparticles.[1,8]

Biofabrication of nanomaterials using microalgae, in-vitro plant cultures, and green biomaterials

"Use of Microalgae, Plant Tissue Cultures, and Sustainable Biomaterials" With the increasing demand for green and sustainable nanomaterial synthesis, methods involving alternative biological systems, such as microalgae, plant tissue cultures and sustainable materials are becoming more applicable. The reason why the microalgae are an ideal platform is their rapid reproduction, few requirements for nutrients, and wide range of chemical profile. Other species of *Chlorella vulgaris* and *Spirulina platensis* produce large quantities of bioactive molecules, including proteins, polysaccharides, and polyphenols, which serve as useful reducing and stabilizing agents in the nanoparticles synthesis. One of the main benefits of microalgae is their ability to have cultivation in wastewater or non-arable lands, leading to greener and economically favoured production. Besides, leaning on extract from microalgae makes it possible to produce biogenic nanoparticles in large volumes suitable for use in antimicrobial coatings, drug delivery breakthroughs, and remediation initiatives.[42]

Cell cultures, such as callus, cell suspension, and hairy root cultures, provide a reproducible approach to produce nanoparticles that exceed standard processes based on whole plant extracts. *In vitro* systems, including plant tissue cultures, facilitate year-round production of phytochemicals of constant quality, avoiding the pains of natural fluctuation in green synthesis.[49] Investigations show that cultures of *Catharanthus roseus*, *Azadirachta indica*, and *Withania somnifera* develop stable and well characterized IONPs at tissue culture conditions. Use of tissue cultures in controlled laboratory conditions makes it possible to investigate metabolic pathways relevant to Nanoparticles systematically; thus, it aids developing metabolic engineering techniques to amplify the abundance of phytochemicals and IONP efficiency.[44]

As environmentally-friendly options for reduction and stabilization, renewable biomaterials from agricultural waste materials and biodegradable polymers are on the rise. Banana peels, tea waste, coconut coir, and cellulose derivatives are plentiful in polyphenols and flavonoids while aiding process for waste valorization and the goals for a circular economy. These biomaterials fulfill two functions as templates and capping agents for construction of IONPs with customized surface features and functions as shown in Table 2. Remarkable magnetic and antimicrobial properties have been reported on iron oxide nanoparticles synthesised by citrus peel extract or rice husk hydrolysate.[3] The combination of such biodegradable biomaterials with environmentally friendly solvents, and reducing energy usage, ultimately decreases the ecological footprint of nanomaterials preparation. The presence of microalgae, plant tissue cultures, and sustainable biomaterials in the processes of production for Phyto-IONPs enhances environmentally-stewardly production as well as consistency, financial viability and scalability. These bioresources are a clear advance in the field of green nanotechnology and promote a holistic approach to material science which supports sustainable, resource-efficient and circular economic practices.[6]

Table 2 Green synthesis of iron oxide nanoparticles using various biological sources, showing iron precursors, reducing and capping agents, particle sizes, and shapes

Biological source	Iron precursor	Reducing agent	Capping agent	Particle size (nm)	Shape	Application	Environmental impact	Reference
Plant extracts	$FeCl_3$, $FeSO_4$	Polyphenols, flavonoids	Proteins, polysaccharides	May-50	Spherical, cubic	Drug delivery, catalysis	Biodegradable, low toxicity	21
Bacteria	$Fe(NO_3)_3$	Enzymes, biomolecules	Exopolysaccharides	10-100	Spherical, irregular	Biomedicine, MRI imaging	Eco-friendly, renewable	50
Fungi	$FeCl_3$, $Fe_2(SO_4)_3$	Secondary metabolites	Proteins, pigments	Oct-80	Spherical, rod	Antimicrobial, sensors	Sustainable, non-toxic	50,51
Algae	$FeSO_4$, $Fe(NO3)_3$	Polysaccharides, phenolics	Polysaccharides	May-40	Spherical	Water Purification, Drug Delivery	Biocompatible, low waste	39
Fruit extracts	$FeCl_3$, $FeSO_4$	Vitamin c, organic acids	Flavonoids	May-30	Spherical, hexagonal	Antioxidants, biomedical	Green alternative, safe	52
Honey	$Fe(NO_3)_3$	Sugars, proteins	Glucose, amino acids	Oct-50	Spherical	Wound healing, coatings	Sustainable, low toxicity	53
Waste biomass	$FeCl_3$, Fe_2O_3	Organic residues	Lignin, proteins	20-100	Irregular	Heavy metal removal, catalysis	Utilizes waste, reduces pollution	54
Essential oils	$FeSO_4$, $FeCl_3$	Terpenoids, phenolics	Lipids, alkaloids	May-50	Spherical, rod	Antibacterial, cosmetics	Biodegradable, renewable	55

Mechanism and process optimization in phyto-mediated IONP synthesis

Phyto-mediated synthesis of the iron oxide nanoparticles (IONPs) is an environmentally friendly process that utilizes the reducing and stabilizing characteristics of plant mediated phytochemicals. In this process the biomolecules such as flavonoids, phenolic acids, alkaloids, terpenoids and carbohydrates take dual roles. They deposit ferric or ferrous ions (Fe^{3+} and Fe^{2+}) as iron oxide nanoparticles while capping the deposited particle surface from agglomeration.[56] Bio-reduction of iron salts i.e. ferric chloride or ferrous sulfate to magnetite (Fe_3O_4) or hematite (Fe_2O_3) forms precede the process of the mechanism. After reduction nucleation causes the formation of nanoparticle seeds that grow into well-defined nanostructures as shown in Figure 4. This growth process is affected by several parameters, all which include the concentration of plant extract, temperature, pH and reaction time. The binding of functional groups such as hydroxyl, carboxyl and Amine moieties found in the phytochemicals to the surface of the nanoparticle plays a significant role in the maintenance, potentiation and stabilization of colloidal stability as well as bio-compatibility. Phyto-mediated synthesis is not free from challenges, even with its benefits.[57] Environmental or seasonal aspects cause a biochemical variability of plant extracts that creates reproducibility problems. Additionally, there lacks standardized protocols for large scale production, preventing the adoption by the industry. The level of understanding the underlying mechanisms at the molecular level is still insignificant and more research has to be done using the advanced characterization tools like FTIR, XPS and in situ spectroscopy. Other research to encourage the adoption of green nanotechnology should therefore focus on how green chemistry metrics such as atom economy E-factor can be used to judge the environmental sustainability of the process. Further optimization and mechanistic studies will be critical towards maximization of the complete potential of plant-based generation of iron oxide nanoparticles.

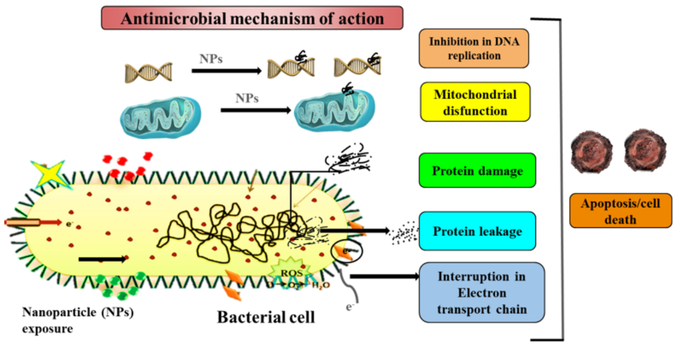

Figure 4 Antimicrobial mechanism of action of nanoparticles on bacterial cells, highlighting their physicochemical properties and interactions that lead to cell membrane disruption, oxidative stress, protein denaturation, and DNA damage.

Redox mechanisms and functional group interactions

Redox mechanism is pivotal in the nanoparticle development in the green synthesis of iron oxide nanoparticles where the redox is driven by phytochemicals. Reduction of iron ions (Fe^{3+} or Fe^{2+}) to lower oxidation states contains a redox process that results in nucleation and growth of IONPs. Phytochemicals, notably polyphenols, flavonoids, tannins, and ascorbic acid, serve as electron donors because they themselves suffer from oxidative reactions to reduce the metal ions.[58] For instance, flavonoids and phenolic acids give electrons through their hydroxyl (-OH) groups, to convert Fe^{3+} to either Fe^{2+} or directly to Fe_3O_4 or Fe_2O_3 depending on the environment. These redox-active compounds are converted into quinones or other oxidized forms in the reaction, calling attention to their identity as natural reducing agents. At the same time, the stabilization of nanoparticles is maintained by strong intermolecular interactions between functional groups of phytochemicals with the surface of the nanoparticles as shown in Figure 5. Hydroxyl (-OH), carboxyl (-COOH) and amine ($-NH_2$)

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groups are especially significant because they form coordination bonds, hydrogen bonding and or electrostatic interactions with iron atoms located at the nanoparticle surface.[59] Such a capping mechanism avoids aggregation and increases stability and dispersion of the nanoparticle in aqueous media. Further, these functional groups affect the surface charge and hydrophilicity as well as the ability to undergo further functionalization of the nanoparticles. Infrared spectroscopy FTIR and X-ray photoelectron spectroscopy XPSs frequently show shifts of peaks related to these functional groups indicating the presence of the chemical interaction with the surface of the nanoparticle. Therefore, the combination of redox mechanisms and functional group interactions do not only control nanoparticle formation but likewise influence their physicochemical properties and possible biomedical or environmental applications.[60]

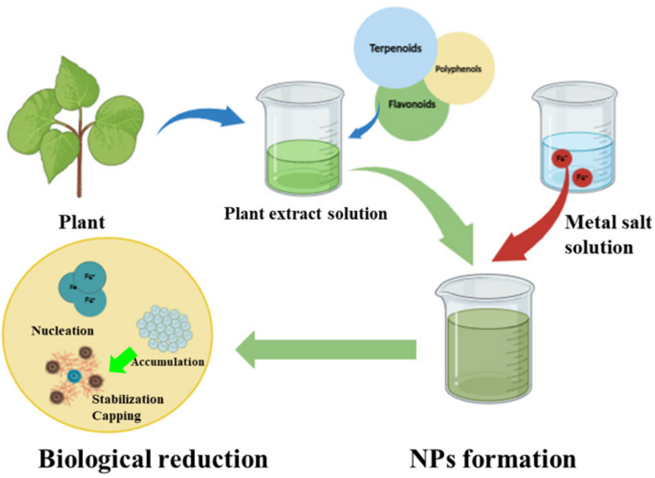

Figure 5 Illustration of plant extract-mediated nanoparticles interacting with a biological system.

In situ monitoring and molecular modeling

In situ monitoring and molecular modeling are powerful tools that have been developed to better understand the phyto-mediated synthesis of iron oxide nanoparticles (IONPs). In situ analytical techniques (UV-Visible spectroscopy, FTIR, XRD) give real-time and also give information about reaction kinetics, nucleation and growth process. UV-Vis allows following changes in absorbance that correlate with the nanoparticle formation process, and FTIR – allows observing functional group interaction between phytochemicals and metal ions in real time.[61] Even after synthesis techniques such as dynamic light scattering (DLS) and transmission electron microscopy (TEM) can even be used, but when used for real time measurements these provide important data on size evolution and the distribution of particles. These approaches allow finding of ideal synthesis time points, eliminate trial and error, and define mechanistic pathways, particularly in more complicated plant extraction systems where a few biomolecules are effective at the same time. In Complementing experimental tools, molecular modelling and simulation strategies including Density Functional Theory (DFT), molecular docking and molecular dynamics simulations (MD) provide atomistic information on redox interaction and binding affinities of phytochemicals with iron precursors and nanoparticle surfaces.[62]

DFT calculations, for example, can be used to calculate the electronic structure and the energy transfer that accompany reduction while MD simulations can explain the stability and orientation of the phytochemicals at the nanoparticle interface. These computational models show how particular functional groups (such as hydroxyls in quercetin or carboxyls in Gallic acid) bind to iron atoms to form stable complexes that control both efficiency of the reduction process and surface capping. Combined, in situ monitoring as well as molecular modeling connects the gap between observation of experiments and mechanistic understanding and provides a more predictive and rational design approach for green nanoparticle synthesis. Molecular modeling and computational simulations have become valuable complementary approaches allowing one to support experimental observations and predict driving mechanisms of the intermolecular interactions at the molecular level.[63] Density Functional Theory (DFT) calculations are especially valuable for the elucidation of the electronic system and redox potential of phytochemicals that take part in the synthesis. From these simulations it becomes apparent how the plant-derived molecules Gallic acid, quercetin or ascorbic acids are able to donate electrons for the iron ions, and how their functional groups orient and attach to the nanoparticle surface. Molecular docking techniques enable one to predict binding sites and interaction energy of phytochemicals to iron ions or crystal facets of iron oxide nanoparticles, providing insights into the preferential attachment of capping agents.[64] Further using molecular dynamics (MD) simulations, stability of nanoparticle-biomolecule complexes is investigated under the different pH and temperature conditions that simulate the real world synthesis environments. These computational strategies not only explain the thermodynamic feasibility of redox reactions but also determine the nature of nanoparticle morphology and surface properties in dependence to the chemical structure of capping agents.[65]

AI/ML-based optimization and microreactor technologies

Recent developments of green nanotechnology have introduced artificial intelligence (AI) and machine learning (ML) as strong calculating tools to optimize the synthesis of iron oxide nanoparticles (IONPs) from phytochemicals. Historically, synthesis parameters (such as temperature, pH, precursor concentration, volume of the extract and reaction time) have been optimised via trial-and-error or classical on-the-go statistical methods. However, such approaches are typically cumbersome and restrictive in their usefulness in capturing the nature of such nonlinear relations between variables.[66] AI/ML (artificial intelligence/machine learning) include support vectors machine (SVM), random forest regression, artificial neural Network (ANN), and genetic algorithms, as data-driven alternatives capable of learning from experimental datasets and using them to predict outcomes such as nanoparticle size, stability, and yield; accurately. These models can reveal hidden patterns and weigh each synthesis parameter to help identify the best set of conditions for specific functional goals, i.e., synthesis of highly crystalline, monodisperse, or surface-functionalized nanoparticles.[67] Moreover, using large databases of previous experimental results or simulations, ML algorithms can be trained to provide predictive frameworks for new plant based systems therefore minimizing the need for numerous similar lab experiments. Microreactor technologies miniature continuous flow systems are shaking up the production of nanoparticles because they provide finer control over reaction conditions than do traditional batch reactors.[68] Microreactors enable fast mixing, control of temperature and uniformity of heat distribution, essential for the reproducible efficiency of homogeneous nanoparticle formation. When linked to AI/ML algorithms, these systems can function as self-optimizing platforms enabling real-time input of parameters of particle characteristics (determined by inline sensors such as UV-Vis or DLS) into the models, thus automating the alteration of flow rates, reactant ratios or temperature. This leads to adaptive synthesis

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protocols that adaptively respond to changing compositions of plant extracts, which is particularly valuable given the intrinsic variation in phytochemical profiles across and within species of plant or during the seasonal harvest. In addition, microreactors ensure that there is minimal use of reagents, waste produced, and reaction time, hence a good fit to green chemistry and sustainability philosophies.[69]

Combined, AI/ML and microreactor-based synthesis constitute a next-generation paradigm for green nanoparticle production as digital and automation tools increase efficiency, reproducibility and scalability of production. With an increasing degree of integration and accessibility of such systems, tremendous opportunities for standardizing phyto-mediated nano particle synthesis and its translation from lab scale innovation to industrial-scale application emerge. Further research in this field can be expected to concentrate on creating resilient AI models based on entire databases of green synthesis reactions, and on increasing the adoption of smart microfluidic systems that perform autonomous decision-making during real-time synthesis processes.[70]

Optimization of synthesis parameters in plant-mediated nanoparticle fabrication

Phyto-mediated synthesis of iron oxide nanoparticles (IONPs) is highly sensitive to adaptive adjustments of multiple key synthesis parameters including pH, temperature, extract-to-precursor concentration ratio and reaction time. Each of these variables directly shapes the size, morphology, crystallinity, stability and functional behavior in the case of nanoparticles.[71] Significant role of pH is seen in dictating the reduction potential of phytochemicals as well as the surface charge of nanoparticles. Acidic environments usually limit the rate of reduction reaction and produce larger or aggregated particles, because of inadequate nucleation whereas alkaline conditions favor nucleation and thus small particles, which are well distributed. Also pH influences the ionization state of functional groups in phytochemicals (e.g. hydroxyl & carboxylic groups) that regulate their binding affinity to the surface of the nanoparticle and this in return affects the capping efficiency, as well as the colloidal stability.[72] Temperature, another important element, affects the kinetics of the redox reaction and the crystallization of nanoparticles. Increased temperatures normally increase metal ion reduction and nanoparticle formation rates, which can enhance crystallinity and narrow the size distribution. However, too high temperatures may denature bio active compounds in the plant extract or cause uncontrolled growth and agglomeration.[73] The amount of concentration of a plant extract and iron precursor control the balance between reducing/capping agents and available metal ions. An increased extract concentration may increase reduction and capping efficiencies but this may however result in excessive organic coating or particle aggregation. On the other hand, low quantities of phytochemicals may leave the reduction incomplete or even cause unstable particles as shown in Table 3. Optimization of the precursor-to-extract ratio is necessary in order to obtain a stable nucleation-growth regime and well-covered, monodisperse nanoparticles. The duration of reaction controls the level of nanoparticle growth and maturity.[74] Lower processing time may result in incomplete nucleation or decreased crystallinity while excessive reaction times may increase the particle agglomeration or secondary growth. In addition, the aging or maturation period after synthesis also affects stability and structure of the final product. Through an organized optimization of these parameters individually and cooperatively, researchers will be able to tailor the physical and chemical properties of IONPs for various applications including targeted drug delivery, magnetic resonance imaging, or environmental remediation. This understanding is also necessary for the attainment of reproducibility, scalability and green chemistry principles consistency in nanoparticle synthesis protocols.[75]

Table 3 Phytochemical sources and their main bioactive compounds involved in nanoparticle synthesis

Phytochemical source	Main phytochemicals	Role in synthesis	Stabilization mechanism	Application	Advantages	Challenges	Reference
Green tea extract	Polyphenols, Catechins	Reduction & capping	Hydrogen bonding, electrostatic interaction	Drug delivery	Biocompatible, antioxidant properties	Batch-to-batch variation	76
Turmeric (*Curcuma longa*)	Curcumin, Tannins	Reduction	Hydrophobic Interactions	MRI Contrast Agent	Anti-inflammatory, Low toxicity	Low aqueous solubility	77
Aloe Vera	Flavonoids, Saponins	Reduction & stabilization	Surface coating	Hyperthermia treatment	Enhances cell compatibility	Stability issues	78
Neem (*Azadirachta indica*)	Alkaloids, Tannins	Reduction	Covalent bonding	Antibacterial Coatings	Strong Antimicrobial Effect	Possible cytotoxicity	79
Pomegranate peel	Polyphenols, flavonoids	Reducing agent	Electrostatic interactions	Cancer therapy	High antioxidant activity	Extraction variability	80
Clove extract	Eugenol, tannins	Reduction & stabilization	Hydrogen bonding	Mri imaging	Strong antibacterial effect	Requires purification	81
Moringa leaf extract	Phenolic compounds, terpenoids	Reducing & capping agent	Surface functionalization	Biosensors	High bioavailability	Solvent interaction issues	82
Ginger extract	Gingerol, shogaol	Reduction	Encapsulation & coating	Targeted drug delivery	High stability	Solvent compatibility issues	83
Cinnamon extract	Cinnamaldehyde, polyphenols	Reduction & capping	Covalent bonding	Antifungal, antitumor	Strong redox activity	Aggregation tendency	84
Black pepper extract	Piperine, alkaloids	Stabilization	Hydrophobic interactions	Enhanced drug bioavailability	Improves drug absorption	Requires proper functionalization	85

Surface engineering and advanced applications of phyto-IONPs

Surface engineering of phyto-synthesized iron oxide nanoparticles (Phyto-IONPs) is a very vital step in the enhancement of stability, biocompatibility, functionality and application of PhE-IONPs in different situations.[76–85] Although phytochemicals from plant extracts naturally provide an organic coating that provides primary stabilization, there is a need for extra surface modification methods that are used to better engineer the nanoparticle interface for given uses.[86] Techniques that have proved to enhance circulation time in biomedical applications and decrease nonspecific interaction include polymer grafting, ligand exchange and coating with biocompatible agents such as Polyethylene glycol (PEG), chitosan, dextran or silica etc. Such surface modifications also enable attachment of functional groups (e.g., carboxyl, amine, or thiol groups) providing the capability to target the delivery of the drugs or imaging agents through covalent coupling with antibodies, peptides, or aptamers.[87] Furthermore, surface engineering can also increase dispersibility in various media, tune their magnetic properties and avoid oxidation to less stable forms of magnetite (Fe_3O_4): hematite (Fe_2O_3). The functional diversity attained through the process of surface engineering has diversified the advanced applications of Phyto-IONPs to various interdisciplinary domains. In the field of biomedicine, these nanoparticles are widely investigated for targeted drug delivery, hyperthermia therapy, enhancement of MRI contrast and biosensing, due to their magnetic reactivity, low toxicity and bio-origins. For example, the so-called PEGylated phyto-IONPs have been employed as effective MRI contrast agents with improved blood retention and decreased clearance. Folate- or antibody-conjugated IONPs facilitate the introduction of chemotherapeutic agents to diseased tissues in cancer therapy, by targeting tumor cells specifically, with minimal systemic toxicity.[88] The phytochemical coating in antimicrobial applications also tends to show synergistic antibacterial or antifungal properties of its own, increasing the therapeutic value of the nanoparticles without the addition of other drugs. Phyto-IONPs with surface modification are also used for environmental remediation, like heavy metal extraction and wastewater purification, where functional coatings increase the binding affinity to different types of pollutants. In catalysis, they act as green catalysts of redox and organic transformation reactions because of their surface-active sites and their green synthesis background.[89]

Functionalization with polymers, biomolecules, and targeting ligands

The functionalization of iron oxide nanoparticles is important in the optimization of their potential in biomedical, environmental, and diagnostic areas. When such nanoparticles are synthesized using phytochemicals, they generally acquire surface functional groups including hydroxyl, carboxyl and carbonyl thus offering the ability to give better surface modification hence eliminating the need for use of harsh chemicals. Functionalization by using polymers, biomolecules, and targeting ligands enhances the stability, dispersibility, biocompatibility and specificity toward the target of nanoparticles.[90] Stabilization of IONPs and their interaction with biological systems are well attained through the use of polymers. Polyethylene glycol (PEG), chitosan, dextran and polyvinyl alcohol (PVA) that are natural & synthetic polymers have been used.

In particular, PEGylation is reported to reduce protein adsorption and prolong *in vivo* circulation time of nanoparticles and therefore PEG coated IONPs are highly desirable for drug delivery and imaging. Chitosan is also a biodegradable, biocompatible polymer with a positively charged surface that favors cellular uptake, and its drug attachment is enabled by ionic interaction as shown in Figure 6. Dextran coated IONPs are widely utilized in the case of magnetic resonance imaging (MRI) as a contrast agent because of their biocompatibility and functional hydroxyl groups that permit further conjugation.[91] Ions of the metal iron oxide are commonly used with proteins, peptides, and nucleic acids in order to enhance the biological border of IONPs. Coating the nanoparticles, for example, with albumin or transferrin, can improve biocompatibility and lead to a targeting of specific cellular receptors. Other peptide chain structures such as RGD or TAT induce receptor mediated endocytosis which will increase cellular internalization. Additionally several nucleic acids including DNA and siRNA can be hooked up for purposes of gene delivery or biosensing, with magnetic properties of the IONPs making the tracking and separation straightforward.[92]

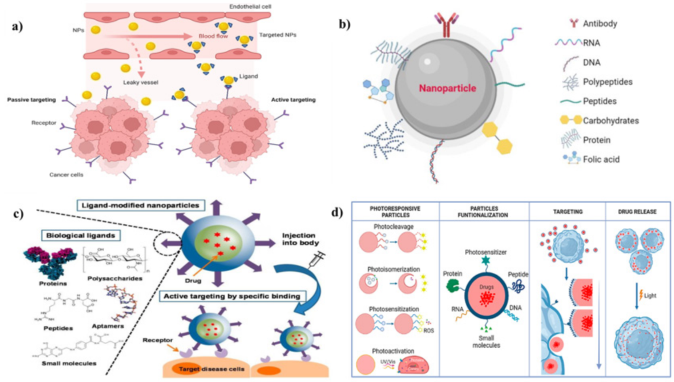

Figure 6 Functionalization of nanoparticles for targeted drug delivery: **(a)** Passive versus active targeting mechanisms in cancer therapy, **(b)** Biomolecules used for nanoparticle functionalization, **(c)** Biological ligands enabling active targeting, and **(d)** Photosensitive polymeric nanocarriers illustrating drug release mechanisms.[90,93–95]

Specificability of targeting ligands provides site-specific functionality in that nanoparticles are guided to specific cells or tissues. The prevalence of any targeting ligand is most commonly due to the high affinities of the targeting ligand for its specific targeting molecules, the folate receptor in this case is often overexpressed on low expression to high expression levels on many of the cancer cells.[93–95] Further, antibodies and aptamers are highly specific – because they recognize and bind to unique biomarkers on a cell surface. Sheer size of molecules like galactose and mannose have been used to target hepatocytes and macrophages, respectively, which simplified the design of nanoparticles for specific therapeutic or diagnostic uses.[96]

Therapeutic and diagnostic potential of phytogenic nanomaterials

Phytochemical based iron oxide nanoparticles (IONPs) have been found to be very useful in biomedical applications not only because they are non-cytotoxic, but also because they have magnetic properties. Owing to the size and composition such nanoparticles can be used for therapeutic and diagnostic treatments, and in drug delivery, Magnetic Resonance Imaging (MRI), and hyperthermia therapies. The green synthesis of IONPs using plant extract phytochemicals not only improves their stability but also minimizes toxic effects which makes them more suitable for clinical applications.[97]

Plant-based nanoparticles as emerging carriers for targeted drug delivery

Biochemical phytochemicals used for the preparation of IONPs have shown promise of this drug delivery system because it is biocompatible, possesses stability, and has magnetic properties. Various types of these nanoparticles find practical application as drug delivery systems, as they allow the transport of required substances directly to the targeted area in the organism.[98] Due to their superparamagnetic characteristic, they accrue to the influence of external magnetic field for regulation of drug delivery and are non-toxic to the systemic tissues.The solubility and bioavailability of the drug are stated to be another strength of phytochemical mediated IONPs in drug delivery.[99] Most drugs, especially hydrophobic ones experience solubility issues and are therefore could easily be trapped and do not easily circulate in the body. Given that curcumin, paclitaxel, and other drugs of interest are hydrophobic, functionalized IONPs can encapsulate these drugs and enhance their solubility thereby circulating them in the bloodstream for a longer period. Besides, use of phytochemicals such as flavonoids and polyphenols on the nanoparticle surface improves biocompatibility and keeps the nanoparticles from being cleared rapidly from the body by the immune system.[100] Cancer therapy is one area where TD is especially advantageous. When the drug–loaded nanoparticles are directed to the tumor area, the drug is released systematically thus sparing the healthy tissues. The resultant targeted reportedly enhances treatment outcomes and reduces a lot of side effects of chemotherapy. Similarly, magnetic guidance does not involve the use of any invasive methods for controlling the nanoparticles and provides maximum targeting at the site of need. IONPs carry and deliver multiple drugs at the same time, including chemotherapeutic agents and gene therapy molecules that work jointly to increase the efficiency of the treatment. These nanoparticles provide for time dependent drug release characteristics and thus serve to enhance efficiency of drug delivery.[101]

Besides, their sensitivity to the changes in pH or temperature allows them to become appropriate candidates for Personalized Medicine as far as drug delivery is concerned. Targeted drug delivery through phytochemical mediated iron oxide nanoparticles prove to be incredibly efficient, selective and bio compatible. By improving drug solubility, delivering drugs to specific tissues or organs, and providing stimuli-sensitive drug release, nanoparticles have become a widely-used asset in contemporary pharmacotherapy. In the following research, developing new functionalization methods and nanocarrier materials will extend their therapeutic application to other diseases, such as cancer, neurodegenerative diseases, and infectious diseases.[102]

Enhanced magnetic resonance imaging applications

IONPs, stabilized by phytochemicals, have lately emerged as valuable MRI contrast agents. MRI is one of the noninvasive imaging techniques of dissection that offers topographical resolution of gentle tissues in humans.[103]

However, a major limitation of MRI is that its use is closely linked with contrast agents, which increase the clarity of the internal framework. Gadodiamide gadolinium based contrast agents known for their effectiveness are, however, associated with risks of toxicity and residual retention in the body. Instead, biocompatible and environmentally friendly green synthesized iron oxide nanoparticles become the better candidate for improving the MRI contraction. Superparamagnetism of IONPs along with nanoscale makes it highly efficient in changing relaxation time of protons in body fluids. These nanoparticles reduce T2, hence provide negative contrast for MRI images. Self mobilizing agents also enhance the contrast between the normal and pathological tissues especially tumours, inflammation and neuroscience disorders.[104] The synthesis of IONPs using phytochemicals further has advantages in MRI applications. These flavonoids, polyphenols, and alkaloids present on the nanoparticle indeed improve stability and biocompatibility. These compounds serve a dual function of natural capping agents, demining toxicities while at the same time facilitating against nanoparticle accumulation. Furthermore, due to the functional groups inherent to the phytochemicals structure, additional surface alterations are possible for the conjugation of targeting moieties, including antibodies, peptides, or folic acid for targeted imaging. This enhances the imaging accuracy by making the nanoparticles home on tissues or tumors of interest within the body. The other benefit of phytochemical-mediated IONPs in MRI is that they have a longer circulation time within the bloodstream. It also explained how the phytochemicals in the foliage add a layer of organic coatings to the nanoparticles to slow down the body's attempt to clear the particles thereby prolonging the imaging time needed to improve the contrast of the image.[105] Moreover, these nanoparticles can be design for dual imaging modality and can act as therapeutic vector for drug delivery or hyperthermia treatment apart from being working as MRI contrast agents phytochemical mediated iron oxide nanoparticles provide a green safest and novel option. Due to their magnetic properties, stability and targeted imaging ability, early disease diagnostic tools and speciality medicine. By using more time and efforts on research and development of clinical applications of these nanomaterials, it may be possible to see important changes in the specificity of the biomedical imaging, and, at the same time, reduce or eliminate negative impacts.[106]

Advances in magnetic hyperthermia for cancer therapy using biogenic nanoparticles

Hyperthermia is a novel method of cancer treatment where temperature is increased to constructive temperature to eliminate the cancer cells.[107] Magnetic nanoparticles particularly, iron oxide nanoparticles have been largely considered in MH due to superparamagnetic nature, biocompatibility coupled with specific ability to produce localized heat under an applied AMF. These nanoparticles are most often surface modified and then administered, with the help of passive targeting, to the tumor area, where they can respond to the AMF and produce heat due to magnetic relaxation. Huge localized heat damages proteins, disrupts cell membranes and stimulates apoptosis, causing tumors' cells death in case of IONPs usage.[108] Incidentally, magnetite Fe_3O_4 and maghemite γ-Fe_2O_3 are the most preferred FEMA materials for hyperthermia treatment. Both types show superparamagnetic properties and are capable of producing heat from AMF exposure suitable for biomedical applications. Low-frequency AMF application is well addressed by magnetite nanoparticles that are usually synthesized employing green methods using plant extracts to minimize and control their sizes. Maghemite nanoparticles, in contrast, exhibit a robust magnetic behavior as well as stability which participates in clinical applications. Several factors affect hyperthermia treatment with IONPs The use of IONPs helps the treatment with hyperthermia in the following ways. The particle size is a critical factor in deciding the linearity of the magnetic properties and the efficiency for generating heat, the smaller nanoparticles having a size of about 10-20 nm are chosen as they display superior biological distribution and permeation into the tumors. IONPs accumulate at the tumor site, the heating efficiency also depends on the concentration, and appropriate concentration of IONPs can produce enough heat but no systemic toxicity. Moreover, the frequency and the amplitude of the AMF are critical to regulating heat generation: while the lower frequency ranging 100-500 kHz is optimal in the clinical use. The targeting efficiency of IONPs is also considered, as it can be increased by preparing the nanoparticles for specific ligands that will react with specific markers on the tumor cells.[109]

Hyperthermia with IONPs includes the usage of non-invasive procedures, capability of identifying cancer cells targets, and it can boost the effect of other treatments such as chemotherapy and radiation therapy. The hyperthermia does not produce cancer cell resistance as chemotherapy does, which makes it a good option for managing recurrent and resistant cancer. However, there are some concerns which are still issues with the clinical applicability of this technique are as follows; nanoparticles may aggregate, the most effective targeting strategies remain to be established, accurate system adjustment of the magnetic field to reach deeper tissues is still under process. To provide comprehensive information for future studies, there is a need to conduct work in harmony with the synthesis of IONPs with fine tunable size, stability, and uniformity in their size distribution, conjugation functional immobilization to amplify their targeting ability and to minimize their toxicity.

Advances in catalytic applications and energy storage

Iron oxide nanoparticles have attracted much interest in catalysis and energy storage because of their chemical, magnetic and electronic characteristics. The large surface area, variability of oxidation states, and intrinsic stability of metal oxides make them superb catalysts and excellent materials for use in energy-storage systems. In catalysis, IONPs find use as a catalyst or a support catalyst in the reactions such as redox reactions, hydrogenation and degradation of some organic pollutants. In energy storage applications, IONPs make a significant contribution to the improvement of batteries, supercapacitors, and fuel cells and their use in the creation of renewable energy systems.[110,111]

Iron oxide nanoparticles in catalysis are used as heterogeneous catalysts employed in many industrial as well as environmental processes. Such redox-active species with Fe^{2+}/Fe^{3+} redox potentials are ideal candidates for redox processes, for instance, in the reduction of organic contaminants in water treatment and efficient conversion of hydrocarbons in fuel processing. Fe_3O_4 and γ-Fe_2O_3 are the most preferred materials for catalytic activities because of their high catalytic activity and ability to be recycled. The ability to easily remove IONPs from a reaction mixture and reuse them eliminates the need to synthesize new material with every reaction and also prevents the release of small metal particles that are toxic to the environment.[112] When IONPs are functionalized with metal or metal oxide nanoparticles including Pt, Pd or CeO_2, the functional IONPs exhibit higher catalytic activity for energy conversion processes, for example, ORR and HER. Iron oxide nanoparticles also find their important applications in energy storage, where they enhance the performance of lithium-ion batteries (LIBs), sodium-ion batteries (SIBs) and supercapacitors. Because of its high theoretical capacitance, Fe_3O_4 and Fe_2O_3 have been examined as anode materials for rechargeable batteries. They offer marvelous charge storage facilities because of multiple oxidation states, which always facilitate the transfer of electrons. However, they include problems like the volume variation in the course of charge-discharge cycles and low conductivity of $LiCoO_2$. To avoid these problems, researchers are using a functionalization approach in which IONPs are dispersed in carbon-containing materials such as graphene, CNTs and conductive polymers. Moreover, iron oxide based nanomaterials are employed in electrode application of supercapacitors due to high capacitance as well as enhanced cycling stability. Another important potential field of application of IONPs as components of energy storage is in fuel cells, in OER and ORR processes.[25] The noble metal catalysts have been found expensive, and researchers have looked towards cheaper iron oxide based catalysts in fuel cell technology. IONPs have the potential for being used in sustainable energy solutions owing to the high stability, catalytic activity and earth abundance of the nanoparticles. In addition, IONPs are used in thermochemical energy storage where the nanoparticles are used to reversibly convert heat to chemical energy and vice versa. However, challenges persist in order to enhance the performance of iron oxide nanoparticles in catalytic and energy storage applications. Concentration of particles, low electronic conductivity, and the tendency of the electrode structure to degrade under the cycling process require a solution. Experimental studies are now under way on modifying core surface; nanostructuring and exploiting core–shell and hybrid composites to improve the electro chemistry and catalytic properties of IONPs. IONs functionalized with advanced materials like Metal Organic Frameworks (MOFs) and 2D Nanomaterials can pave the way for the future generation of energy storage and conversion.[55]

There is still an active international agenda concerning water pollution and emerging research for cheaper, effective, and evidently safe methods. For the reasons of large surface area, magnetism and conjugation, the IONPs with phytochemical assistance have been considered as potential materials for water treatment applications. Due to their ability to adsorb pollutants such as heavy metals, organic matter and microorganism, these nanoparticles are very effective. Permanency of its magnetic property makes the filter easy for collection and reuse; a filter of such type is thus better than conventional filter. The overall use of these IONPs can also be boosted significantly if the surface of these materials is conjugated with phytochemicals in a manner that seeks out specific pollutants. For example, when enhancing specific adsorption of IONPs on heavy metals: arsenic, lead or cadmium, tannins or flavonoids can be used to improve water desalination from polluted sources. IONPs can also be applied as magnetic based filters which would increase the prospect of improved recycling thus lowering the incidents of replacement of the filter. Water purification is an important factor in enabling the provision of equal and safe drinking water basins as a result of pollution. While the filtration chemical treatments and coagulation processions have drawbacks by costs, speed, and environmental harm. More recently, researchers have considered iron oxide nanoparticles (IONPs), which are characterized by large surface area, magnetization, and ability to be functionalized. Such properties qualify IONPs to desorb different pollutants, including heavy metals, organic pollutants, and pathogens from water. Examples of purification mechanisms applied by IONPs include adsorption, magnetic separation, as well as catalytic action.[113]

It is because of this large surface area it is possible to effect adsorption of contaminants that can later be separated using a magnetic rack. The following magnetic properties allow the easy collection of the nanoparticles after purification necessary for efficient treatment of water: Furthermore, the IONPs can be modified with different ligands or a shell layer to improve the selectivity of the process for specific contaminants, including heavy metals such as lead, arsenic, and mercury, and dye and pharmaceutical waste, including dyes and pharmaceuticals. They can also support the reactions in advanced oxidation processes (AOPs), where Aeroxides stimulate the formation of hydroxyl radicals that break up atoms of analysed organic compounds and also help disinfect water by decreasing its pathogen content. Both magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) nanoparticles are the iron oxide nanoparticles predominantly recommended for water purification.[114] Low-frequency AMF applications exhibit efficiency, especially when magnetite nanoparticles are used, and they have good magnetic properties that can be easily separated after use. They also have large surface areas and can be further well applied for adsorption of various pollutants and their removal efficiency can also be well improved on the basis of modification. Maghemite nanoparticles are unusually stable and have strong magnetic responses to enhance the separation and adsorption of maximum capacities. The efficiency of IONPs in water purification depends on the particle size of IONPs, functionalization of IONP surface, magnetic field strength, as well as the pH and the temperature of water.[115]

At the same time the smaller nanoparticles are generally characterized by a greater surface to volume ratio increasing adhesion potential, however, shrinking below a certain size tends to cause aggregation. Substituting with chemical groups in the polymer works well to enhance selectivity to the type of pollutant being removed with carboxyl or amine groups. The degree of magnetic field affects the nanoparticle retrieval process, while pH and temperature directly influence adsorption capacity. The main benefits of incorporating IONPs in water purification include high absorbability; magnetical separability; specificity; low cost; renewability and antibacterial capabilities. Due to their versatility in MS, they can adsorb a given range of contaminants, and thus, be recovered by applying magnetic fields, making them an effective replacement for conventional purification techniques.[116] Moreover, their ability for selective targeting by functionalization enhances the effectiveness of separation operations and lowers secondary pollution probability. Furthermore, IONPs are effective against the microbial load due to the proven antimicrobial characteristic. However, there is still some drawback, for example, when the nanoparticles treated water, one problem that needs to be overcome is the tendency of the nanoparticles in the water to aggregate which decreases the efficiency of the treatment. Efforts are in progress to find ways of stabilizing the products to avoid aggregation of the particles and enhance dispersion.[117]

Advancements in the integration of green nanoparticles into bioinks and flexible devices

The incorporation of phytochemically synthesized iron oxide nanoparticles (IONPs) into the tail of modern materials like bioinks and flexible electronic devices is a step over the sustainability road in nanotechnology. In the world of bioprinting, more and more IONPs are being introduced into bioinks to add magnetic responsiveness, contribute to mechanical strengthening and also provide real time imaging or therapeutic functions. These magnetic bioinks which may contain other biopolymers such as alginate; gelatin or collagen may be 3D printed into complex structures for use in tissue engineering, regenerative medicine, and drug screening platforms.[118] The use of artificially synthesized via the green approach IONPs guarantees biocompatibility and lowers cytotoxicity, which is important for maintaining cell viability throughout, and after the printing process. In addition to biomedical applications, IONPs are also implemented in flexible substrates; namely biodegradable polymers, conductive hydrogels and elastomers to form the next generation of wearable sensors, energy storage devices and soft robotics. The flexibility of these devices also benefits from the superparamagnetic property, environmental-safety, and functional-surface-chemistry of phytogenic IONPs for multifunctionality, e.g., magnetically controlled actuation, environmental sensing, and wireless communication. The natural surface coatings from plant-derived phytochemicals also enable the mixing of nanoparticles and organic matrices without further toxic surfactant or modifier. In general, the combination of green-synthesized IONPs to bioinks and flexible materials provides a sustainable and innovative pathway to the production of smart, responsive, and eco- friendly technology. The use of plant based synthesis routes considerably improves the environmental sustainability of these applications.[119] Unlike the customary IONPs that are synthesized using harmful chemicals, phytochemically synthesized nanoparticles are comparatively non-toxic and environmentally benign, therefore, provide a good fit for use in close contact with the human skin or biological tissues. In addition, the ease with which phytochemical residue permits surface functionalization opens the possibility for additional sensing elements, biorecognition molecules or therapeutic agents to be introduced, thus increasing the scope of applications of these hybrid materials.[120] The integration of phytochemical-mediated iron oxide nanoparticles into bioinks and flexible devices represents the convergence of green nanotechnology and the state-of-the-art milieu of material science. Such an approach will not only facilitate the development of sustainable development but it will allow one to design multifunctional platforms for next-generation biomedical devices, environmental sensors, and smart wearable systems. Future research directing efforts towards optimizing nanoparticle concentration, dispersion stability and long-term biocompatibility will be vital in making the full potential of these new green engineered hybrid materials evident.[121]

Safety, environmental sustainability, and future perspectives of phytogenic nanomaterials

Iron oxide nanoparticles (IONPs) obtained through phytochemical route are often considered as safer options to their chemically synthesized counterparts; however, deep insight of their toxicological characters are important to make judicious use of such nanoparticles. The green approach to synthesis generally minimizes the use of hazardous reagents; and these nanoparticles, which are usually capped with bioactive phytochemicals, may enhance biocompatibility.[122] The biological effects of ION Ps are however dictated by various factors such as size, shape, surface charge, concentration, exposure route as well as time period as shown in Figure 7. What is more, even plant-derived IONPs can cause oxidative, inflammatory or cytotoxic reactions at higher doses or longer exposures. Studies have found out that the smaller nanoparticles of higher surface area may produce the reactive oxygen species (ROS) which can cause the possible DNA damages, lipid peroxidation and mitochondrial dysfunctions of certain cell types. Therefore, strict *in vitro* and *in vivo* toxicological investigations are crucial making biosafety possible. Environmentally, the green synthesis of IONPs has significant advantages because it facilitates the removal of toxic chemicals and solvents in nanoparticle synthesis.[123]

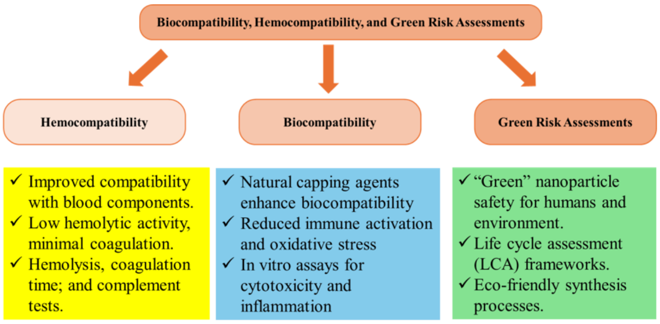

Figure 7 Green assessment of biologically synthesized nanoparticles interacting with biological systems.

The use of biodegradable plant extracts as reducing and stabilizing agents reduces ecological footprint and favors the sustainable development principles. However, the fate, transport and transformation of IONPs in the environment, particularly in soil and aquatic systems are poorly investigated. This long term builds up and interactions with microorganism, plant and non target organisms may have undesired ecological impacts. Thus, environmental risk assessments such as bioaccumulations studies and ecotoxicity analysis are necessary to assess the safety of broad spread application especially in the context of agriculture, wastewater treatment and biosensor systems.[124] To mitigate potential toxicity, future research should focus on controlled synthesis parameters that produce uniform and stable nanoparticles with predictable biological behavior. Surface modification through natural polymers, proteins, or biomimetic coatings can further reduce toxicity and improve biocompatibility as shown in Table 4. The adoption of predictive models, such as quantitative structure-activity relationship (QSAR) modeling and high-throughput screening methods, may accelerate safety assessments and regulatory approval. Moreover, the use of advanced analytical tools like omics technologies and real-time imaging can help decipher the nano–bio interactions at molecular levels, contributing to safer nanodesign.[125]

Table 4 Key factors influencing nanoparticle synthesis: their optimal ranges, effects on nanoparticle properties, and specific roles in the green synthesis reaction

Parameter	Effect on synthesis	Optimal range	Nanoparticle properties affected	Role in reaction	Advantages	Challenges	Reference
Iron precursor type	Determines composition, purity	$FeCl_3$, $FeSO_4$, $Fe(NO_3)_3$	Size, crystallinity	Provides Fe ions for nucleation	High purity	Solubility issues	126
Phytochemical concentration	Controls reduction & stabilization	Moderate concentration	Size, stability, morphology	Acts as reducing & capping agent	Eco-friendly, Biocompatible	Batch variability	127
pH Level	Influences reduction rate & stability	7–11	Size, surface charge	Affects ionization of phytochemicals	Controls agglomeration	Aggressive pH affects stability	128
Reaction temperature	Controls nucleation & growth rate	50–90°C	Size, crystallinity	Higher temp increases reaction rate	Enhances crystallinity	Requires energy input	129
Reaction time	Affects yield & size	30–180 min	Size, dispersity	Longer times promote uniform growth	Better control over size	Extended time may cause aggregation	43
Agitation speed	Enhances uniform mixing	200–1000 rpm	Dispersity, shape	Prevents aggregation	Uniform shape	High speed can induce shear stress	130
Ionic strength	Influences particle stability	Controlled salt addition	Stability, zeta potential	Regulates surface charge	Prevents aggregation	High concentration causes precipitation	1,30,131
Capping agent type	Controls stabilization efficiency	Polyphenols, Proteins	Surface functionalization	Enhances stability	Improves biocompatibility	Extraction purity issues	132
Solvent type	Affects reaction kinetics	Water, Ethanol	Yield, stability	Medium for Reaction	Green solvents preferred	Toxic solvents may be harmful	133
Post-synthesis processing	Controls final properties	Centrifugation, Drying	Purity, dispersibility	Removes By-products	Increases stability	Cost & time intensive	134

In-vitro and *in-vivo* toxicity models

Toxicity analysis of iron oxide nanoparticles prepared through phytochemical procedures is the major one performed by both *in-vitro* and *in-vivo* measurements to determine their safety, biocompatibility, and environmental/biological risks. Human ker cell lines through wild culture are used for the establishment of such as breast carcinoma, leukaemia and lymphoma.[126–134] Important assays monitor cytotoxicity through follow up of cell viability (methodology includes M However, despite being cheap and quickening results, *in vitro* models are inadequate substitutes for accounting for the comprehensive response observed in living organisms.[135] In the actual response to their manageable genetics, easy to keep, physiological closeness to humans, zebrafish and Drosophila models have become major tools for evaluating nanoparticle toxicity. Because of their optical clarity, rapid development and fully understood organogenesis, zebrafish embryos are particularly suited for studying nano toxic impacts. Real-time monitoring for IONP exposure allows us to monitor morphological abnormalities, delayed hatching, cardiotoxic-effect, neurotoxic-impairment, and change in behavior. Several reports have proved that high concentrations and surface-charged IONPs affect the growth of zebrafish larvae, produce oxidative stress and alter their gene expression. Furthermore, Drosophila serves as a useful *in vivo* biological model to evaluate the long-term effect of IONPs on the lifespan, reproduction health, mobility and neural behavior.[136]

The rapid life cycle and possibility to use transgenic Drosophila make this model an excellent candidate for high throughput research and understanding how nanoparticles interact in a living organism. Since the phytochemicals enveloping green-synthesized IONPs have the capacity to perform complex interactions with biological systems as shown in Figure 8, zebrafish and Drosophila offer unique advantages for the evaluation of nanoparticle biosafety. Such approaches permit tracking dose-specific, targeted, and lasting effects that *in vitro* experiments often fail to notice. Furthermore, internalization and circulating localization of nanoparticles in tissues can be followed by fluorescence based monitoring and imaging techniques. Toxicity testing *in vitro* and *in vivo* gives a strong rationale to decide the safety of phytogenic iron oxide nanoparticles, which will guide their development for application purposes in medicine, environmental sustainability and industry.[137]

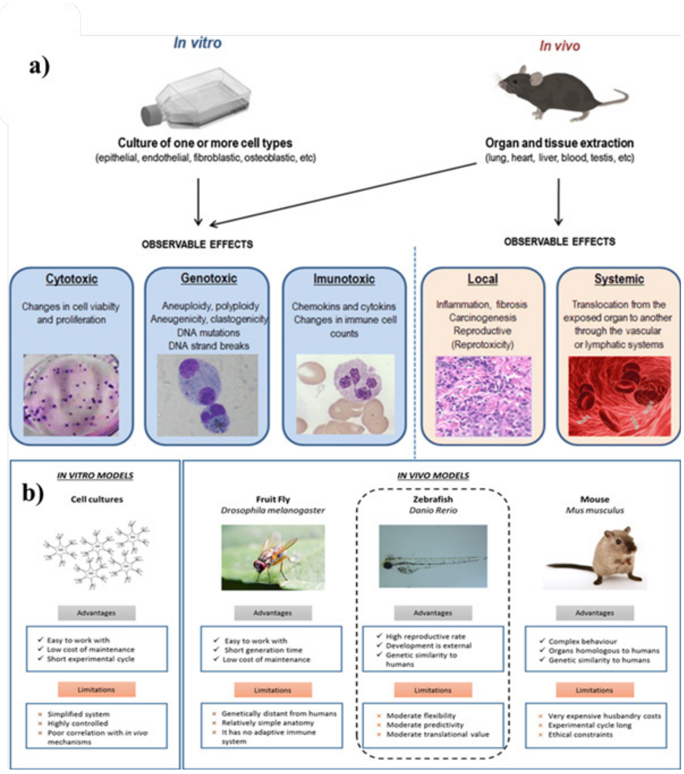

Figure 8 Overview of *in vitro* and *in vivo* toxicological approaches, **(a)** Used to evaluate the adverse effects of substances such as carbon-based nanomaterials (CNMs), **(b)** *In vitro* models offer rapid and cost-effective screening, *in vivo* models, such as zebrafish, provide more comprehensive insights into developmental and neurotoxic impacts.[138,139]

Toxicological evaluation and biocompatibility of green-synthesized nanoparticles

Biocompatibility and hemocompatibility are critical parameters in evaluating the potential of phytochemically synthesized iron oxide nanoparticles (IONPs) for biomedical applications.[138,139] A biocompatible material is a substance that is able to perform its task in a host without inciting local or systemic adverse reactions.[140]

Phytogenic IONPs synthesized with plant extracts also often have inherent biocompatibility, because these natural capping agents – flavonoids, polyphenols, and terpenoids – can help to reduce immune-mobilization and oxidative stress. Oxidant and inflammation suppressant phytochemicals present on the surface of these nanoparticles are crucial for retaining their stability and strengthening their interaction with biologic environments. However, it is vital to review biocompatibility by a sequence of *in vitro* tests, using relevant human cell lines, to assess the presence of cytotoxic, or inflammatory effects. The cell-binding of IONPs is of paramount importance in intravenous use as adverse occurrences like coagulation, hemolysis, platelet aggregation, or immune reactions might arise because of interactions with components from the blood. It was found out that the natural coatings found on green synthesized IONPs contribute to their enhanced hemocompatibility by inhibiting formation of developed protein corona and reducing non-specific interconnection.[25]

Examples of such tests are blood hemolysis assays, coagulation time assay analysis and complement activation assays that are regularly performed in order to determine the hemocompatibility of materials. According to the studies, phytogenic IONPs are characterized by a low extent of hemolytic activity and insufficient influence on normal blood physiology and thus may be considered promising for drug delivery, imaging, and theranostics.[141]

Since biocompatibility is a necessity, green-risk evaluations are also becoming a necessity when one wants to ascertain the impact of nanomaterials on the environment and safety. Other than evaluating the toxicity of nanoparticles, these assessments also address the ecological and lifecycle repercussions of their synthesis and their application.[142] A "green" nanoparticulate material is to protect human beings and ecosystems from harm, and be produced using environmentally benign processes and must pose low risk when disposed of or broken down. The life cycle assessments (LCAs) are currently widely used to calculate the ecological and resource costs relating to the synthesis of environmentally friendly nanomaterials.[143] Moreover, application of frameworks such as Green Chemistry Principles, the NanoRisk Framework, and Safe-by-Design (SbD) is used to identify hazards from the onset and guide safer nanoparticles' production. The use of green risk assessment practices in developing of phytogenic IONPs guarantees compliance not only with technical requirements, but also with the ethical and regulatory requirements for green nanotechnology.[144]

Conclusion

The green synthesis of iron oxide nanoparticles (IONPs) using phytochemicals offers a sustainable, biocompatible, and eco-conscious alternative to conventional chemical and physical methods. This review comprehensively addresses the multifunctional role of phytochemicals particularly flavonoids and terpenoids in reducing, capping, and stabilizing IONPs. Their inherent bioactivity, combined with advancements in green extraction techniques, has significantly improved the efficiency and biocompatibility of nanoparticle synthesis. Furthermore, the integration of plant-based systems, microalgae, and *in-vitro* cultures provides a versatile platform for biofabrication with enhanced control over nanoparticle morphology and functionality. Despite these advancements, several key challenges persist. A major research gap lies in the incomplete understanding of the precise redox mechanisms and biomolecular interactions during nanoparticle formation. The lack of standardized protocols for synthesis and characterization contributes to batch-to-batch variability and hinders reproducibility across studies. Additionally, while *in-vitro* studies are abundant, there is a scarcity of in-depth *in-vivo* toxicity assessments and long-term biocompatibility evaluations, which are crucial for clinical translation. Emerging technologies such as in situ monitoring, molecular modeling, and AI/ML-based predictive optimization offer promising avenues to bridge these gaps by enabling real-time process control and deeper mechanistic insights. Moreover, the development of microreactor systems could facilitate the scaling-up of phyto-mediated synthesis while maintaining product consistency and reducing environmental impact. To fully harness the therapeutic and industrial potential of phytogenic IONPs, future research must prioritize standardization, mechanistic elucidation, biosafety validation, and regulatory harmonization. The convergence of green nanotechnology with artificial intelligence, omics technologies, and sustainable engineering will be pivotal in advancing the next generation of smart, safe, and scalable nanomaterials for multidisciplinary applications.

Author contributions

Agilandeswari Mohan: Writing – original draft, Methodology, **Shakthivel Rajendran**: Writing – review & editing, Software, **Naveen Palani**: Formal analysis, Software, **Rabiya Riffath Syed Altaf**: Resource, Visualization, **Keren Celestina Mendonce**: Formal analysis, Resource, **T.G.Nithya -** Visualization, **Puruchothaman Venkatesan**: Resource, Visualization, **Sangavi Nagendran:** Resource, Validation**, Parthasarathy Surya**: Resource, Validation, **Mohankumar Srinivasan** - Resource, Validation, **Rajesh Kannan Ramar** - Resource, Validation, **Nandhini Sundaresan**: Resource, Validation, **Suriyaprakash Rajadesingu**: Validation, Visualization, Supervision.

Consent for publication

I hereby give my consent for the publication of the manuscript.

Ethical approval

Not applicable.

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Conflicts of interest

The author declares that there are no conflicts of interest.

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