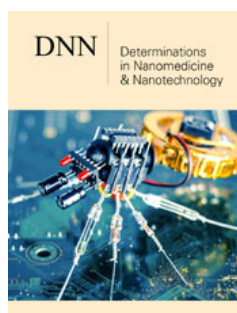


Iron Oxide Nanoparticles for Biomedical Applications: Synthesis Strategies, Structure-Function Insights, and the Road to Clinical Translation

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***Corresponding author:** Naveed Ahmad, College of Civil and Transportation Engineering, Shenzhen University, China

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Naveed Ahmad^{1*}, Muhammad Naeem Tabassam², Muhammad Shahbaz¹ and Amir Shahzad³

¹College of Civil and Transportation Engineering, Shenzhen University, China

²College of Physics and Optoelectronics Engineering, Shenzhen University, China

³School of Integrated Circuits, Shenzhen University, China

Abstract

Iron Oxide Nanoparticles (IONPs) - Chiefly Magnetite (Fe_3O_4) and Maghemite ($\gamma\text{-Fe}_2\text{O}_3$) - remain among the most clinically advanced inorganic nanomaterials owing to their tunable superparamagnetism, low intrinsic toxicity relative to other metal oxides, and amenability to surface functionalization. This mini-review synthesizes current understanding of IONP synthesis routes (co-precipitation, thermal decomposition, hydrothermal, and green/biogenic methods), the structure-property relationships that govern their magnetic and catalytic behaviour, and their principal biomedical applications in drug delivery, antimicrobial therapy, Magnetic Resonance Imaging (MRI), and magnetic hyperthermia. Persistent translational bottlenecks - colloidal instability, batch-to-batch variability, and an incomplete biosafety picture at the sub-10nm scale - are critically examined. We conclude by outlining a forward-looking research agenda centred on green-synthesized, multi-functional, stimuli-responsive IONP platforms designed to close the gap between laboratory promise and regulatory approval.

Keywords: Iron oxide nanoparticles; Magnetite; Superparamagnetism; Drug delivery; Antimicrobial resistance; Magnetic hyperthermia and Theranostics

Introduction

Nanomedicine has matured from a conceptual promise into a field with several clinically approved inorganic platforms, and iron oxide nanoparticles occupy a privileged position within it [1,2]. Their superparamagnetic behaviour below approximately 20nm allows IONPs to be magnetized only in the presence of an external field, avoiding the permanent agglomeration that limits ferromagnetic carriers, while their iron-based composition offers a biodegradation pathway that converges with the body's native iron-handling machinery [3]. This combination has already yielded FDA- and EMA-cleared products for iron-deficiency anaemia and MRI contrast, and has driven exploratory clinical use in magnetic hyperthermia for recurrent glioblastoma [4]. Yet the same physicochemical features that make IONPs attractive-high surface-to-volume ratio, catalytic (peroxidase-mimetic) reactivity, and magnetic responsiveness-also introduce a size-and coating-dependent toxicity profile that has stalled several candidates in preclinical stages [5]. This mini-review consolidates the most recent (2022-2026) literature on IONP synthesis, characterization, and biomedical deployment, building on the comprehensive 2024 synthesis of preparation methods and

biomedical applications by Meng et al. [6], with an emphasis on identifying the specific engineering gaps that a doctoral research programme is best positioned to close.

Synthesis Strategies

IONP synthesis routes are broadly grouped into physical, chemical (co-precipitation, thermal decomposition, hydrothermal/solvothermal, sol-gel, sonochemical) and biological (green/biogenic) methods, each imposing a distinct trade-off between size control, crystallinity, scalability, and biocompatibility [3,7]. Co-precipitation of $\text{Fe}^{2+}/\text{Fe}^{3+}$ salts under alkaline conditions remains the most widely used route for biomedical IONPs because it is aqueous, low-cost, and readily scaled, though it yields comparatively broad size

distributions [3]. Thermal decomposition of Iron Precursors (e.g., $\text{Fe}(\text{acac})_3$, Iron Oleate) in high-boiling organic solvents produces highly monodisperse, crystalline nanoparticles but requires post-synthetic ligand exchange for aqueous dispersibility [3,7]. Green synthesis using plant extracts (e.g., *Eucalyptus globulus*, *Thevetia peruviana*, *Iris kashmiriana*) or microbial systems has expanded rapidly since 2023, exploiting phytochemical reducing agents to yield IONPs with intrinsic antioxidant and antibacterial character while avoiding hazardous reagents [8-11], though reproducibility across plant batches remains an unresolved limitation of this route [8]. Table 1 summarizes the comparative performance of these approaches against the criteria most relevant to biomedical translation.

Table 1: Comparative overview of principal synthesis strategies for iron oxide nanoparticles.

Method	Typical Size	Size Distribution	Key Advantage	Key Limitation	Ref.
Co-precipitation	5-20nm	Broad	Aqueous, scalable, low-cost	Limited size/shape control	[3]
Thermal decomposition	4-15nm	Narrow (monodisperse)	High crystallinity, uniform size	Organic-phase synthesis; needs ligand exchange	[3,6]
Hydrothermal/solvothermal	10-100nm	Moderate	Good crystallinity, tunable morphology	High temperature/pressure equipment	[6]
Green/biogenic synthesis	10-40nm	Moderate-broad	Eco-friendly; intrinsic bioactivity	Batch-to-batch reproducibility	[7-10]

Structure-Property Relationships and Characterization

Biomedical performance of IONPs is dictated by a small set of interlinked physicochemical parameters: core size and crystallinity (governing saturation magnetization and superparamagnetic threshold), phase purity (magnetite vs. maghemite vs. hematite, each with different magnetic and catalytic character), and surface chemistry (governing colloidal stability, protein corona formation, and circulation half-life) [2,12]. X-ray diffraction and Raman spectroscopy remain the primary tools for phase identification, FTIR and XPS for surface functional group and coating verification, TEM/HRTEM for core morphology, and vibrating-sample magnetometry for quantifying saturation magnetization and coercivity [3,12]. A recurring finding across recent reports is that IONPs below roughly 5nm exhibit disproportionately elevated Reactive-Oxygen-Species (ROS) generation relative to their 10-20nm counterparts, a size-dependency with direct implications for both antimicrobial efficacy and off-target toxicity [5,13].

Biomedical Applications

Drug delivery and theranostics

Surface-functionalized IONPs (dextran, PEG, silica, or polymeric shells) serve as magnetically guided carriers capable of image-guided drug delivery, combining diagnostic and therapeutic functions in a single theranostic platform [2,14]. Ligand-modified systems - folate-, dopamine/HSA-, and heparin-conjugated IONPs

- have shown enhanced tumour accumulation via the enhanced permeability and retention effect and receptor-mediated targeting in preclinical models [4], although only ferumoxytol-class formulations have progressed to routine clinical use, and current approvals remain restricted to anaemia and off-label MRI indications rather than oncologic drug delivery [4]. Nanocomposite IONP architectures extend this platform further, improving dual/multimodal MRI diagnostic accuracy and enabling exogenous- and endogenous-stimuli-triggered (pH-, redox-, or field-responsive) drug release from a single carrier [15].

Antimicrobial applications

Against the backdrop of accelerating antimicrobial resistance, IONPs have emerged as a metal-oxide alternative to conventional antibiotics, acting primarily through ROS generation, membrane disruption, and interference with bacterial iron homeostasis [5,16]. Antibacterial potency is modulated by particle size, shape, surface charge and superparamagnetism, and can be further enhanced through external magnetic-field application or doping with secondary metals (Ag, Zn, Cu) [5]. Green-synthesized IONPs from *Streptomyces* sp., *Thevetia peruviana*, and related biological sources have independently reproduced this antibacterial activity while adding antibiofilm and enzyme-inhibitory properties, suggesting a multifunctional route toward wound-care and anti-infective formulations [10,11,13]. Nonetheless, a 2025 comprehensive review notes that comparative head-to-head data against standard-of-care antibiotics on multidrug-resistant clinical isolates remains scarce - precisely the translational gap this field must close [17].

Magnetic resonance imaging

As T2/T2*-weighted contrast agents, superparamagnetic IONPs (SPIONs) shorten transverse relaxation times to generate negative (dark) contrast in liver, lymph node, vascular and inflammatory imaging, and are increasingly combined with magnetic particle imaging for improved quantitative sensitivity [2,18]. Brain-targeted formulations exploiting transferrin- or RVG-peptide functionalization have extended SPION-based imaging toward blood-brain-barrier-crossing diagnostic and drug-delivery applications [19].

Magnetic hyperthermia

Under an alternating magnetic field, SPIONs dissipate heat via Néel and Brownian relaxation, enabling localized tumour ablation; this mechanism underlies the only IONP formulation (Nanotherm®) currently approved as a class III device for recurrent glioblastoma in Europe, with prostate- and pancreatic-cancer trials advancing under FDA guidance [4,20]. Specific absorption rate - the key figure of merit for heating efficiency - depends strongly on core size, size distribution and coating, and remains the principal engineering lever for improving clinical performance [20,21] (Figure 1).

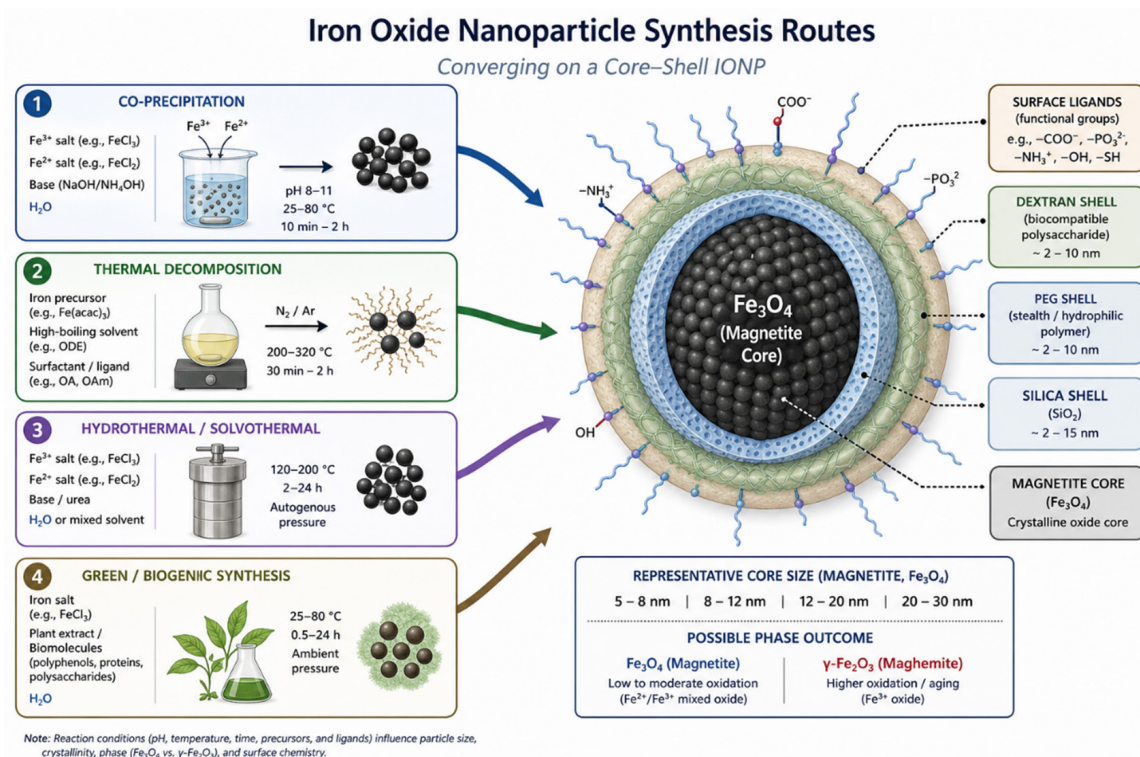


Figure 1: illustrates the four principal synthesis families discussed in Section 2 and their convergence on a functionalized core-shell architecture.

Toxicity, Biosafety, and Translational Challenges

Biosafety data remain the principal rate-limiting factor for clinical translation. Ultrasmall IONPs (<5nm) have been shown to induce acute oxidative stress and hydroxyl-radical generation in multiple organs, particularly the heart, in a size- and dose-dependent manner [5,22], while several formerly marketed SPION agents have been withdrawn over toxicity and hypersensitivity concerns, underscoring that biocompatibility cannot be assumed from iron's status as an essential nutrient [18]. Coating chemistry substantially modulates this risk profile: dextran- and PEG-coated particles generally show improved biocompatibility over bare or citrate-stabilized cores, and antioxidant-functionalized IONPs have been reported to actively mitigate oxidative injury while retaining diagnostic utility [13]. This principle extends to vascular safety specifically: hydroxyethyl starch-coated IONPs were recently shown to avoid cytotoxicity, inflammatory activation, autophagic stress,

and ferroptotic injury in human microvascular endothelial cells under both basal and inflammatory (LPS-challenged) conditions, reinforcing coating selection as a primary, tunable safety lever ahead of *in vivo* testing [23]. A parallel translational barrier is manufacturing reproducibility - green-synthesized batches in particular show extract-to-extract variability in size, yield and surface chemistry that complicates regulatory characterization [9,17].

Future Perspective

Three converging research directions are, in our assessment, best positioned to move IONPs from bench to bedside over the next research cycle.

1. Standardized green synthesis: systematic, statistically designed studies correlating specific phytochemical classes (not merely plant species) with resulting IONP size, phase

purity, and antimicrobial potency, to convert an empirically reproducible but mechanistically opaque route into a controllable one [8,10].

2. Multidrug-resistance-targeted antimicrobial platforms: head-to-head evaluation of doped and green-synthesized IONPs against clinical multidrug-resistant isolates under standardized MIC/MBC protocols, directly addressing the comparative-data gap identified in Section 4.2 [24].
3. Stimuli-responsive theranostic integration: pH- or redox-

responsive coatings that couple MRI/hyperthermia readout with on-demand drug release, extending the single-modality platforms currently in preclinical use toward genuinely closed-loop image-guided therapy [14,19].

Pursued together, these directions would directly address the two bottlenecks - reproducibility and biosafety characterization - that most reviews identify as the proximate cause of the persistent gap between IONP publication volume and clinical approval [18,24] (Figure 2) (Table 2).

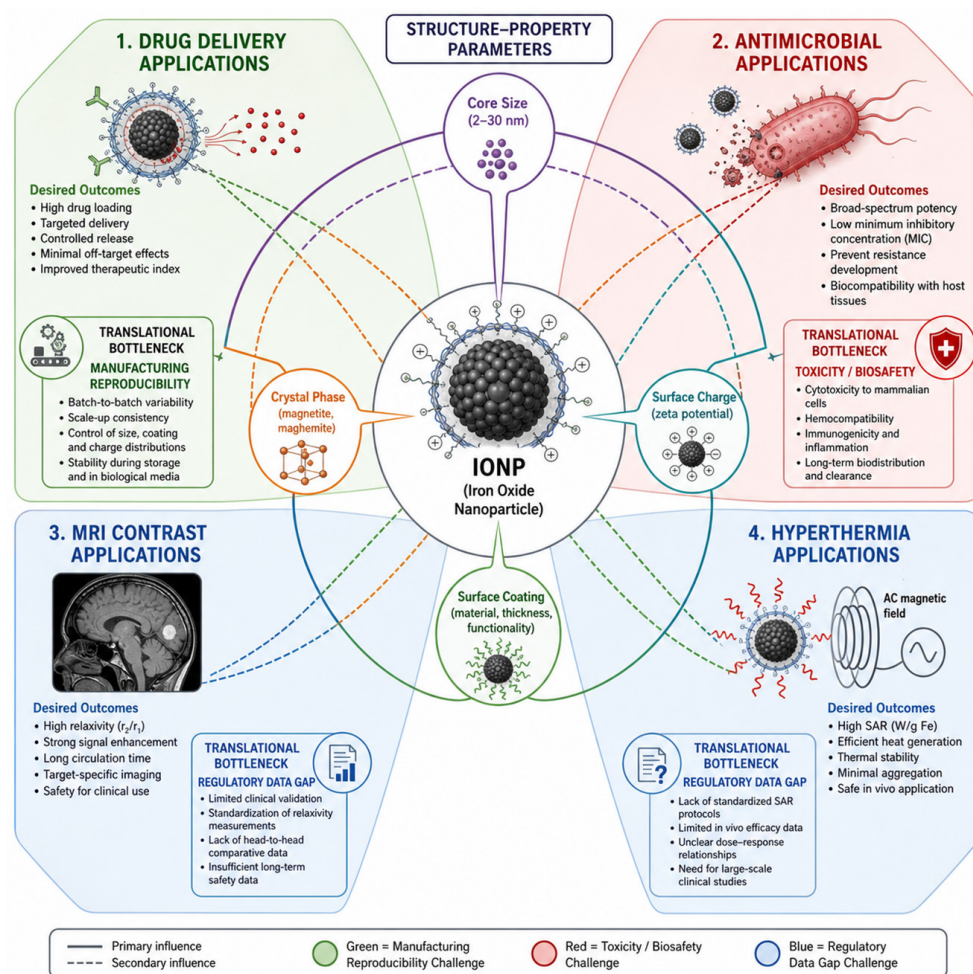


Figure 2: Maps each application in Section 4 to its principal translational bottleneck discussed in Section 5, providing a visual summary of the future-perspective priorities in Section 6.

Table 2: Summary of principal biomedical applications, underlying mechanism, key advantage, and dominant translational challenge for iron oxide nanoparticles.

Application	Primary Mechanism	Key Advantage	Dominant Challenge	Ref.
Drug delivery / theranostics	Magnetic guidance + EPR-mediated tumour accumulation	Combines imaging and therapy in one platform	Few systems beyond ferumoxytol reach clinic	[2,4,14]
Antimicrobial therapy	ROS generation, membrane disruption, iron-homeostasis interference	Active against multidrug-resistant strains in vitro	Lack of standardized MDR-isolate comparative data	[5,14,24]
MRI contrast	T2/T2*-weighted relaxivity shortening	Established clinical/regulatory precedent	Restricted indication scope vs. Gd agents	[2,18,19]
Magnetic hyperthermia	Néel/Brownian relaxation heat dissipation under AMF	Localized, non-invasive tumour ablation	Low SAR and high intratumoral dose requirement	[4,20,21]

Conclusion

Iron oxide nanoparticles combine clinical precedent with substantial unrealized potential across drug delivery, antimicrobial therapy, MRI, and hyperthermia. The literature reviewed here indicates that further gains will come less from discovering new applications and more from disciplined engineering of existing platforms - standardizing green synthesis, generating comparative antimicrobial-resistance data, and building stimuli-responsive multifunctionality - to resolve the reproducibility and biosafety gaps that currently separate promising preclinical results from regulatory approval.

References

- Arias LS, Pessan JP, Vieira APM, Lima TMT, Delbem ACB, et al. (2018) Iron oxide nanoparticles for biomedical applications: A perspective on synthesis, drugs, antimicrobial activity, and toxicity. *Antibiotics* 7(2): 46.
- Dadfar SM, Roemhild K, Drude NI, Von Stillfried S, Knüchel R, et al. (2019) Iron oxide nanoparticles: Diagnostic, therapeutic and theranostic applications. *Adv Drug Deliv Rev* 138: 302-325.
- Salehrozveh M, Dehghani P, Mijakovic I (2024) Synthesis, functionalization, and biomedical applications of iron oxide nanoparticles (IONPs). *J Funct Biomater* 15(11): 340.
- Kalber TL, Ordridge KL, Southern P, Loebinger MR, Kyrtatos PG, et al. (2016) Hyperthermia treatment of tumors by mesenchymal stem cell-delivered superparamagnetic iron oxide nanoparticles. *Int J Nanomedicine* 11: 1973-1983.
- Zhang TG, Miao CY (2024) Iron oxide nanoparticles as promising antibacterial agents of new generation. *Nanomaterials* 14(15): 1311.
- Meng YQ, Shi YN, Zhu YP, Liu YQ, Gu LW, et al. (2024) Recent trends in preparation and biomedical applications of iron oxide nanoparticles. *J Nanobiotechnology* 22: 24.
- Jijo H, Shamlath A, Abraham A, Xavier PAF, Chahal S, et al. (2025) Harnessing the potential of iron oxide nanoparticles: A comprehensive review on their synthesis, functionalization and pharmaceutical innovations. *Next Nanotechnol* 8: 100270.
- Hasan YR, Wong FWF, Ashari SE, Halim M, Mohamad R (2025) Iron oxide nanoparticles: Biosynthesis, peroxidase-like activity, and biosafety. *Appl Microbiol Biotechnol* 109(1): 202.
- Attea SA, Ghareeb MA, Kelany AK, Elhakim HKA, Allemailem KS, et al. (2024) Biosynthesis of iron oxide nanoparticles by marine *Streptomyces* sp. SMGL39 with antibiofilm activity: *In vitro* and *in silico* study. *Molecules* 29(19): 4784.
- Rauf A, Ahmad Z, Ajaj R, Haiyuan Zhang, Muhammad Ibrahim, et al. (2025) Green synthesis: An eco-friendly route for the synthesis of iron oxide nanoparticles using aqueous extract of *Thevetia peruviana* and their biological activities. *Sci Rep* 15: 18316.
- AL-Salman HNK, Qasim QA, Abbas BA, Hussein AJ, Jabir MS (2025) Insights into the pharmaceutical properties of green fabricated iron oxide nanoparticles. *Sci Rep* 15: 27621.
- Lee J, Lee JH, Lee SY, Park SA, Kim JH, et al. (2023) Antioxidant iron oxide nanoparticles: their biocompatibility and bioactive properties. *Int J Mol Sci* 24(21): 15901.
- Wu L, Wen W, Wang X, Huang D, Cao J, et al. (2022) Ultrasmall iron oxide nanoparticles cause significant toxicity by specifically inducing acute oxidative stress to multiple organs. *Part Fibre Toxicol* 19(1): 24.
- Nughwal A, Bharti R, Thakur A, Monika Verma, Renu Sharma, et al. (2025) Green synthesis of iron oxide nanoparticles from Mexican prickly poppy (*Argemone mexicana*): Assessing antioxidant activity for potential therapeutic use. *RSC Adv* 15(13): 10287-10297.
- Yang Y, Liu Y, Song L, Cui X, Zhou J et al. (2023) Iron oxide nanoparticle-based nanocomposites in biomedical application. *Trends Biotechnol* 41(12): 1471-1487.
- Saba I, Batoo KM, Wani K, Verma R, Hameed S (2024) Exploration of metal-doped iron oxide nanoparticles as an antimicrobial agent: A comprehensive review. *Cureus* 16(9): e69556.
- Ghazi R, Ibrahim TK, Nasir JA, Gai S, Ali G, et al. (2025) Iron oxide based magnetic nanoparticles for hyperthermia, MRI and drug delivery applications: A review. *RSC Adv* 15(15): 11587-11616.
- Zhao Z, Muyao Li, Jie Zeng, Linlin Huo, Kun Liu, et al. (2021) Recent advances in engineering iron oxide nanoparticles for effective magnetic resonance imaging. *Bioact Mater* 12: 214-245.
- Qiao R, Changkui Fu, Helen Forgham, Ibrahim Javed, Xumin Huang, et al. (2023) Magnetic iron oxide nanoparticles for brain imaging and drug delivery. *Adv Drug Deliv Rev* 197: 114822.
- Pucci C, Degl'Innocenti A, Belenli Gümüş M, Ciofani G (2022) Superparamagnetic iron oxide nanoparticles for magnetic hyperthermia: Recent advancements, molecular effects, and future directions in the omics era. *Biomater Sci* 10(9): 2103-2121.
- Mao Z, Li X, Wang P, Yan H (2022) Iron oxide nanoparticles for biomedical applications: An updated patent review (2015-2021). *Expert Opin Ther Pat* 32(9): 939-952.
- Rukhsar M, Zubair Ahmad, Abdur Rauf, Hassan Zeb, Mujeeb Ur-Rehman, et al. (2022) An overview of iron oxide (Fe_3O_4) nanoparticles: From synthetic strategies, characterization to antibacterial and anticancer applications. *Crystals* 12(12): 1809.
- Ali A, Hira Zafar, Muhammad Zia, Ihsan Ul Haq, Abdul Rehman Phull, et al. (2016) Synthesis, characterization, applications, and challenges of iron oxide nanoparticles. *Nanotechnol Sci Appl* 9: 49-67.
- Thrapsanioti LN, Kuskov AN, Berdiaki A, Luss AL, Vlaskina ER, et al. (2026) Tailored iron oxide nanoparticles for biomedical applications: hydroxyethyl starch coating enhances endothelial biocompatibility. *Nanomedicine* 71: 102880.
- Yang Y, Liu Y, Song L, Cui X, Zhou J et al. (2023) Iron oxide nanoparticle-based nanocomposites in biomedical application. *Trends Biotechnol* 41(12): 1471-1487.