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Biogenic Synthesis of Titanium Dioxide Nanoparticles Using Plant Extracts: Mechanistic Insights and Photocatalytic Therapeutic Applications

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Abstract - Titanium dioxide (TiO_2) nanoparticles have emerged as the most photocatalytically active metal oxide in nanomedicine, yet their biogenic synthesis via plant extracts remains significantly under-studied compared to zinc oxide nanoparticles. This review presents a mechanistic analysis of TiO_2 green synthesis, focusing on how phytochemical composition governs particle nucleation, phase selection between anatase and rutile polymorphs, and ultimate bioactivity. The central argument is that TiO_2's photodynamic therapy (PDT) potential is unmatched among metal oxide nanoparticles: its band gap of 3.0–3.2 eV enables the generation of singlet oxygen ($^1O_2$), hydroxyl radicals (•OH), and superoxide anions ($O_2^{\bullet-}$) under UV and visible light, enabling targeted destruction of cancer cells and pathogens. We systematically review antimicrobial, anticancer, anti-inflammatory, and wound healing applications of biogenic TiO_2, compare the synthesis challenges inherent to TiO_2 relative to ZnO, critically evaluate the current toxicity profile and limitations for clinical translation, and introduce new perspectives on doping strategies, combination therapies, environmental remediation, and regulatory pathways..

***Key Words*:** *Titanium dioxide nanoparticles, green synthesis, photocatalysis, antimicrobial, anticancer, plant extract.*

1. INTRODUCTION

Nanotechnology has fundamentally expanded the therapeutic toolkit of modern medicine, with metal oxide nanoparticles occupying a central position owing to their tunable optical, electronic, and surface properties [1]. Among all metal oxides examined for biomedical application, titanium dioxide (TiO_2) holds a unique distinction: it is the most photocatalytically active stable oxide known, with a reactive oxygen species (ROS) generation capacity under UV irradiation that surpasses zinc oxide (ZnO), iron oxide, and cerium oxide under comparable conditions [2]. This photocatalytic supremacy derives from TiO_2's intrinsic band gap of 3.0–3.2 eV, its exceptional chemical stability in biological environments, and the capacity to functionalise its surface chemistry to target specific cellular compartments [3].

The biosynthesis of metal oxide nanoparticles using plant extracts has attracted significant scientific interest as a sustainable, non-toxic alternative to chemical and physical fabrication routes [4]. For ZnO, green synthesis protocols are now well-established because the zinc precursor (typically zinc acetate or zinc nitrate) undergoes facile hydrolysis and precipitation at modest temperatures, and the phytochemicals in plant extracts serve simultaneously as reducing and capping agents [5]. TiO_2 synthesis presents a substantially more complex challenge: titanium precursors (principally titanium tetraisopropoxide, TTIP, and titanium tetrachloride, $TiCl_4$) are highly reactive with water, prone to rapid uncontrolled hydrolysis, and require precise pH, temperature, and calcination conditions to yield phase-pure, crystalline nanoparticles [6]. Understanding how plant-derived polyphenols, flavonoids, and terpenoids overcome these challenges is the mechanistic problem at the heart of biogenic TiO_2 synthesis.

Equally important is the polymorph question. TiO_2 exists in three major crystalline phases: anatase, rutile, and brookite. Of these, anatase is the most photocatalytically active owing to its lower electron–hole recombination rate and higher surface area [7]. Rutile, while more thermodynamically stable, has a narrower band gap (3.0 eV vs 3.2 eV for anatase) that extends light absorption slightly into the visible spectrum, and the commercially dominant P25 TiO_2 (Degussa) achieves high catalytic activity through a synergistic anatase–rutile mixture [7,8]. Plant extract composition critically determines which phase

predominates in biogenic synthesis, a relationship that has received insufficient systematic attention.

This review addresses six interconnected objectives: (i) a mechanistic comparison of TiO_2 and ZnO biogenic synthesis highlighting the unique challenges and solutions offered by plant phytochemistry; (ii) an analysis of how plant extract composition governs anatase versus rutile phase selection; (iii) a systematic review of photocatalytic antimicrobial, anticancer, anti-inflammatory, and wound healing applications; (iv) a critical evaluation of the toxicity profile and current barriers to clinical translation; (v) an exploration of doping strategies and visible-light-active TiO_2 formulations; and (vi) emerging applications in environmental remediation and theranostics, and a regulatory pathway analysis for clinical advancement.

2. THE CASE FOR TiO_2: PHOTOCATALYTIC SUPERIORITY

2.1 Band Gap Engineering and ROS Generation

The therapeutic power of TiO_2 nanoparticles is fundamentally photonic in origin. Upon absorption of a photon with energy equal to or exceeding the band gap (≥3.2 eV for anatase, ≥3.0 eV for rutile), an electron is promoted from the valence band to the conduction band, generating an electron–hole pair (e^-/h^+) [2,9]. In aqueous biological environments, these charge carriers react with water and dissolved oxygen through a cascade that produces three principal cytotoxic species: hydroxyl radicals (•OH), superoxide anion radicals ($O_2^{\bullet-}$), and singlet oxygen ($^1O_2$) [9]. The hydroxyl radical is among the most oxidising species known in chemistry, with a standard reduction potential of +2.80 V versus NHE, enabling indiscriminate oxidative attack on lipids, proteins, and nucleic acids within its diffusion-limited radius of action [3,10].

What distinguishes TiO_2 from competing metal oxides for photodynamic therapy (PDT) is the spatial and temporal controllability of this ROS generation. Illumination can be applied focally via fibre optic probes, spatially restricted to tumour-localised nanoparticles, and switched on or off instantaneously, enabling what has been termed 'activatable nanotherapy' [11]. ZnO, while also photocatalytically active, dissolves progressively in biological media through zinc ion release, confounding ROS attribution and raising systemic toxicity concerns [12]. TiO_2's exceptional chemical stability and resistance to acid–base dissolution means that its therapeutic function is retained in the low-pH microenvironment of solid tumours and phagolysosomes, environments that rapidly corrode ZnO [5,12].

The electron–hole pair lifetime in TiO_2 is critically influenced by the crystalline phase and particle morphology. In anatase, the conduction band minimum sits approximately 0.2 eV higher than in rutile, providing a greater thermodynamic driving force for single-electron oxygen reduction to superoxide. Nano-scale TiO_2 further extends electron–hole lifetime through quantum confinement effects in particles below approximately 10 nm, where discrete energy levels retard charge carrier recombination and enhance photon utilisation efficiency [9,10]. The synergistic anatase–rutile heterojunction present in P25 TiO_2 exploits this principle industrially: electron transfer from rutile to anatase across the phase boundary traps electrons in anatase and holes in rutile, spatially separating charge carriers and extending their lifetime by an order of magnitude [7,8].

2.2 Surface Chemistry and Drug Delivery Potential

TiO_2 nanoparticles possess a hydroxyl-rich surface (Ti–OH groups) that renders them inherently amenable to functionalisation via silane coupling agents, phosphonate ligands, and carboxylic acid tethers [13]. This tunable surface chemistry supports loading of chemotherapeutic drugs such as doxorubicin, cisplatin, and curcumin, with photocatalytic ROS generation providing an additional light-activated drug release mechanism [14]. The combination of passive enhanced permeability and retention (EPR) effect-driven tumour accumulation, surface drug loading, and on-demand photocatalytic cytotoxicity constitutes a multi-modal therapeutic platform that ZnO, iron oxide, and silver nanoparticles do not replicate in the same integrated manner [14,15].

Recent advances in TiO_2 surface engineering have introduced mesoporous TiO_2 nanostructures with surface areas exceeding 200 m^2/g, providing drug loading capacities of 15–40% by weight for hydrophobic therapeutics. The Ti–OH surface groups also facilitate conjugation of targeting ligands, including folic acid (targeting folate receptor-overexpressing cancers), transferrin (exploiting the transferrin receptor pathway upregulated in tumour cells), and antibody fragments for tumour-specific antigen recognition [13,14]. This multiplicity of functionalisation strategies, combined with TiO_2's

inherent photocatalytic activity, enables theranostic platforms where the same nanoparticle serves concurrently as an imaging contrast agent, a drug carrier, and a photocatalytic therapeutic.

2.3 Comparison with Competing Metal Oxide Nanoparticles

A comparative evaluation of TiO_2 against other photocatalytically active metal oxides used in nanomedicine reveals distinct advantages and limitations. ZnO nanoparticles exhibit comparable band gap energies (3.37 eV) and similarly efficient ROS generation under UV irradiation; however, their progressive dissolution in biological fluids at pH values below 7.0 releases cytotoxic Zn^{2+} ions that confound therapeutic attribution and elevate systemic toxicity [5,12]. Iron oxide nanoparticles (Fe_3O_4, γ-Fe_2O_3) are the most clinically advanced metal oxide nanomedicine, with FDA-approved formulations for MRI contrast enhancement and iron deficiency treatment, but their ROS generation capacity is Fenton reaction-dependent and substantially lower than TiO_2 under controlled illumination conditions [1,3]. Cerium oxide nanoparticles exhibit paradoxical antioxidant behaviour through Ce^{3+}/Ce_4^{+} redox cycling, making them valuable cytoprotective agents but inappropriate for ROS-mediated therapeutic applications requiring sustained oxidative damage [1].

3. BIOGENIC SYNTHESIS: CHALLENGES, MECHANISMS, AND PHYTOCHEMISTRY

3.1 Why TiO_2 Green Synthesis Is Harder Than ZnO

The contrast between ZnO and TiO_2 green synthesis illuminates the unique mechanistic demands placed on plant phytochemistry. ZnO synthesis proceeds through the precipitation of zinc hydroxide followed by dehydration — a reaction that is thermodynamically spontaneous at room temperature and atmospheric pressure [5]. The phytochemicals in plant extracts accelerate nucleation, prevent agglomeration through steric stabilisation, and cap the nanoparticle surface. Calcination at 300–400°C removes organic residues and improves crystallinity [4,5].

TiO_2 synthesis is categorically more demanding for three reasons. First, titanium precursors (TTIP, $TiCl_4$) undergo violent, uncontrolled hydrolysis upon contact with water, producing amorphous titanium hydroxide ($Ti(OH)_4$) that requires precise control of hydrolysis rate and condensation conditions to yield organised TiO_2 structures [6,16]. Second, amorphous TiO_2 is photocatalytically inactive; crystallisation into the anatase phase requires calcination at temperatures typically between 400–500°C, and rutile formation occurs at 600–900°C [7]. Third, the phase outcome is sensitive to pH, temperature, ionic strength, and the specific organic ligands present during synthesis — variables that plant extract composition directly controls [16,17].

Plant extracts overcome these challenges through a multi-functional phytochemical role. Polyphenols and flavonoids such as quercetin, catechins (particularly epigallocatechin gallate, EGCG), and rosmarinic acid coordinate to titanium centres through their hydroxyl and carbonyl groups, acting as bidentate ligands that slow and control hydrolysis [18]. This ligand-controlled hydrolysis produces more uniform $Ti(OH)_4$ nuclei. Terpenoids and saponins provide steric bulk at the nanoparticle surface, preventing agglomeration during the condensation step. The organic matrix formed by these phytochemicals also influences the calcination pathway: electron-dense aromatic systems appear to favour the anatase phase by templating the anatase crystal structure during the gel-to-crystalline transition [17,18].

3.2 Anatase vs Rutile Phase Selection by Plant Extracts

Phase-selective synthesis of TiO_2 is arguably the most mechanistically significant variable in biogenic nanoparticle production, because anatase is substantially more photocatalytically active than rutile due to its lower charge carrier recombination rate, higher conduction band edge position (enabling stronger reductive chemistry), and greater surface hydroxyl density [7,19].

Multiple studies have demonstrated that plant extract composition directly determines the anatase–rutile ratio. Extracts rich in polyphenolic antioxidants — Camellia sinensis (green tea), Ocimum tenuiflorum (tulsi), and Azadirachta indica (neem) — consistently produce phase-pure or predominantly anatase TiO_2, with XRD patterns confirming the characteristic anatase peaks at $2\theta = 25.3°$ [18,19]. The polyphenol-titanium complexes formed during synthesis act as a phase-directing template: the bidentate coordination geometry of quercetin and EGCG to Ti^{4+} matches the octahedral titanium coordination environment in anatase more closely than in rutile [20]. In contrast, extracts containing fewer polyphenols and more simple sugars (e.g., certain fruit extracts) produce mixed anatase–

rutile phases at identical calcination temperatures, consistent with less effective phase templating [19].

Calcination temperature remains the dominant variable, but plant extract polyphenol content modulates the threshold at which phase transformation occurs. Govindappa et al. [21] demonstrated that TiO_2 nanoparticles synthesised using Calotropis gigantea latex showed a mixed phase at 500°C but retained predominantly anatase character to 550°C, in contrast to chemically synthesised controls that transitioned to rutile at 450°C, attributing the stabilisation effect to residual organic species from the latex acting as anatase-phase promoters during the sol–gel transition.

An underexplored dimension of phase selectivity is the role of extract preparation method. Aqueous extracts prepared by boiling (decoction) produce different polyphenol profiles and concentrations compared to cold-press, ethanol, or methanol extraction. Boiling-temperature aqueous extraction of green tea leaves yields higher EGCG concentrations than cold steeping, and this correlates with stronger anatase-directing effects in subsequent TiO_2 synthesis [18,20]. Standardisation of extract preparation conditions is therefore a prerequisite for reproducible phase-selective biogenic TiO_2 synthesis, and this standardisation gap represents a significant challenge for transitioning from academic proof-of-concept to pharmaceutical-grade manufacturing.

Table 1 summarises representative plant extracts, their active phytochemicals, the TiO_2 phases obtained, particle sizes, and primary bioactivities reported in the literature.

Plant Source	Active Phytochemicals	Phase Formed	Key Bioactivity
Azadirachta indica (Neem)	Quercetin, nimbin, azadirachtin	Anatase	Antibacterial, anticancer
Aloe vera	Aloin, acemannan, flavonoids	Anatase	Antifungal, anti-inflammatory
Calotropis gigantea	Calactin, calotropin, terpenoids	Anatase/Rutile mixed	Anticancer, antimicrobial
Psidium guajava (Guava)	Quercetin, lycopene, vitamin C	Anatase	Antioxidant, antifungal
Ocimum tenuiflorum (Tulsi)	Eugenol, rosmarinic acid, ursolic acid	Anatase	Antibacterial, anticancer
Camellia sinensis (Green tea)	EGCG, catechins, polyphenols	Anatase	PDT, antioxidant, anticancer
Moringa oleifera	Isothiocyanates, quercetin, kaempferol	Anatase	Antimicrobial, wound healing
Curcuma longa (Turmeric)	Curcumin, turmerones, demethoxycurcumin	Anatase	Anti-inflammatory, anticancer
Citrus sinensis (Orange peel)	Hesperidin, narirutin, limonene	Anatase/Rutile mixed	Antimicrobial, antioxidant
Hibiscus rosa-sinensis	Quercetin, cyanidin, hibiscin	Anatase	Antibacterial, antifungal

Table 1. Representative plant extracts used in biogenic synthesis of TiO_2 nanoparticles and their physicochemical outcomes.

3.3 Optimisation Parameters in Biogenic TiO_2 Synthesis

Beyond plant extract composition, several synthesis parameters critically influence nanoparticle quality, reproducibility, and bioactivity. pH is among the most influential: acidic conditions (pH 3–5) favour slower hydrolysis and smaller particle sizes, while alkaline conditions (pH 8–10) accelerate condensation and tend to produce larger, more polydisperse particles [16]. The optimal pH window for phase-pure anatase synthesis using polyphenol-rich extracts is generally pH 4–6, where Ti^{4+}–polyphenol complexes are most stable and hydrolysis proceeds at a controlled rate.

Reaction temperature during the initial mixing step influences both the kinetics of polyphenol–titanium complex formation and the nucleation density. Temperatures between 60–80°C have been found optimal for most plant extract systems, balancing sufficient thermal activation of nucleation against thermal degradation of heat-sensitive polyphenols such

as EGCG [17,18]. The titanium precursor-to-extract ratio (v/v or mg/mL equivalents) requires careful optimisation: insufficient extract concentration relative to titanium precursor yields poorly capped nanoparticles with broad size distributions, while excess extract introduces organic impurities that survive calcination and reduce photocatalytic efficiency by blocking surface active sites [6,16].

Calcination conditions represent the final and most consequential optimisation variable. A two-stage calcination protocol — initial low-temperature (200–250°C) treatment to remove volatile organics followed by higher-temperature (400–450°C) crystallisation — has been shown to produce superior anatase phase purity and smaller crystallite sizes compared to single-stage calcination, because the initial low-temperature stage prevents violent combustion of the organic matrix that would otherwise disrupt crystal nuclei organisation [7,17].

3.4 Characterisation Methods for Biogenic TiO_2

Comprehensive characterisation of biogenic TiO_2 requires a multi-technique approach that addresses crystal structure, particle morphology, surface chemistry, and photocatalytic activity independently. X-ray diffraction (XRD) with Rietveld refinement remains the gold standard for quantifying anatase–rutile phase ratios and calculating crystallite sizes via the Scherrer equation, but is insensitive to amorphous fractions that may contribute to particle size without contributing to photocatalytic activity [7,19]. Transmission electron microscopy (TEM) with selected area electron diffraction (SAED) provides complementary structural information at the single-particle level, resolving crystal lattice planes and confirming phase assignment for individual nanoparticles.

Surface area determination by BET nitrogen adsorption isotherms is essential for normalising photocatalytic activity measurements, since apparent differences in catalytic efficiency between samples of different size distributions reflect surface area differences rather than intrinsic catalytic properties [6]. Fourier-transform infrared spectroscopy (FTIR) identifies the phytochemical corona on biogenic TiO_2 surfaces, with characteristic Ti–O–C stretching vibrations at 1,080–1,120 cm^{-1} confirming covalent phytochemical binding versus physisorption [18]. Dynamic light scattering (DLS) and zeta potential measurements quantify hydrodynamic diameter and colloidal stability in physiologically relevant media, providing information directly relevant to in vivo behaviour.

4. PHOTOCATALYTIC THERAPEUTIC APPLICATIONS

4.1 Antimicrobial Mechanisms

The antimicrobial activity of biogenic TiO_2 nanoparticles under UV and visible light irradiation is mediated through multiple converging mechanisms that differ from conventional antibiotics, a distinction with significant implications for addressing multi-drug resistant (MDR) pathogens [22]. The primary mechanism is ROS-mediated cell wall and membrane disruption: hydroxyl radicals oxidise lipid bilayers through peroxidation of unsaturated fatty acids, disrupting membrane integrity and causing potassium ion leakage [23]. Secondary mechanisms include oxidative DNA strand breakage, inactivation of respiratory chain enzymes (particularly NADH dehydrogenase and succinate dehydrogenase), and inhibition of cell wall peptidoglycan synthesis [22,24].

Biogenic TiO_2 nanoparticles synthesised from Aloe vera, Moringa oleifera, and green tea extracts have demonstrated minimum inhibitory concentrations (MICs) of 32–128 µg/mL against Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, and Candida albicans under UV light activation [24,25]. Importantly, biofilm inhibition — a property poorly served by conventional antibiotics — has been reported at concentrations exceeding 60% reduction in biofilm biomass, attributed to the ability of hydroxyl radicals to degrade the polysaccharide matrix surrounding biofilms [25]. The combination of photocatalytic activity and the surface-capping phytochemicals retained from green synthesis adds a secondary layer of antimicrobial effect, as quercetin and catechins themselves possess documented antibacterial activity through membrane disruption mechanisms [18,25].

Resistance development is a central concern for any antimicrobial strategy. ROS-based mechanisms present a fundamentally lower resistance acquisition risk compared to antibiotic mechanisms because they target multiple essential cellular components simultaneously; the probability of simultaneous mutation across multiple targets is combinatorially small [22,24]. Serial passaging experiments of E. coli and S. aureus in sub-MIC concentrations of biogenic TiO_2 under UV irradiation have not demonstrated MIC shifts after 10

passages in reported studies, contrasting with well-documented rapid resistance development against ciprofloxacin and ampicillin under identical experimental conditions [24,25]. This resistance-sparing profile is a compelling advantage for clinical applications in MDR infection management, wound care, and surface decontamination.

4.2 Anticancer Mechanisms and Photodynamic Therapy

The application of biogenic TiO_2 in photodynamic therapy against cancer cells represents the most mechanistically sophisticated and clinically significant dimension of its therapeutic profile [11]. Upon UV or visible light activation, TiO_2 generates singlet oxygen ($^1O_2$) and hydroxyl radicals that initiate a sequential cellular death cascade: lipid peroxidation at the plasma and mitochondrial membranes elevates cytosolic calcium, depolarises the mitochondrial membrane potential ($\Delta\Psi m$), triggers cytochrome c release into the cytoplasm, and activates the intrinsic apoptotic pathway through caspase-9 and caspase-3 [11,26].

In vitro studies with biogenic TiO_2 against HeLa (cervical), MCF-7 (breast), and A549 (lung) cancer cell lines have reported IC_{50} values in the range of 20–80 µg/mL under UV irradiation, with apoptosis rates exceeding 70% confirmed by annexin V/PI flow cytometry [26,27]. Reactive oxygen species specificity is an important advantage over chemotherapy: ROS generation is spatially confined to TiO_2-localised cells, and the light-activation requirement means that tumour selectivity can be achieved through focal irradiation. Tumour cells are additionally more susceptible to oxidative stress than normal cells due to their elevated baseline ROS levels and impaired antioxidant defences, providing a secondary selectivity window [3,27].

Drug-loaded biogenic TiO_2 nanoparticles have shown synergistic anticancer activity. Chitosan-coated, doxorubicin-loaded TiO_2 nanoparticles synthesised using Ocimum tenuiflorum extract exhibited significantly enhanced tumour uptake and reduced cardiotoxicity compared to free doxorubicin in murine xenograft models, attributed to EPR-driven accumulation and light-triggered drug release [14,28]. The combination of chemotherapy drug delivery and concurrent photocatalytic PDT targets both proliferating cancer cells (via cytotoxic drug mechanism) and the tumour microenvironment (via ROS-mediated stromal disruption and immunogenic cell death induction), addressing the therapeutic resistance mechanisms that undermine single-modality treatment [11,14].

An emerging mechanistic dimension of TiO_2 anticancer PDT is immunogenic cell death (ICD). ROS-driven oxidative stress in cancer cells triggers the exposure of calreticulin on the cell surface, release of HMGB1 into the extracellular space, and ATP secretion — the three hallmarks of immunogenic cell death that activate dendritic cells and prime antigen-specific cytotoxic T lymphocyte responses [11]. This suggests that TiO_2 PDT may function not merely as a local cytotoxic treatment but as an in situ tumour vaccination strategy, with implications for abscopal effects on metastatic disease and synergy with immune checkpoint inhibitor therapies.

4.3 Anti-Inflammatory Properties

Beyond their photocatalytic ROS-generating capacity, biogenic TiO_2 nanoparticles demonstrate anti-inflammatory activity through a mechanism that operates independently of photocatalysis and relates instead to the phytochemical corona retained on the nanoparticle surface from green synthesis [29]. Quercetin, EGCG, and rosmarinic acid — which remain surface-associated on biogenic TiO_2 at concentrations insufficient to be removed by standard washing — suppress the nuclear factor kappa-B (NF-κB) signalling pathway, which governs the transcription of pro-inflammatory cytokines including TNF-α, interleukin-6 (IL-6), and interleukin-1β (IL-1β) [29,30].

In LPS-activated RAW 264.7 macrophage models, TiO_2 nanoparticles synthesised from Moringa oleifera and Psidium guajava extracts reduced TNF-α and IL-6 secretion by 40–65% at non-cytotoxic concentrations (25–50 µg/mL), with cyclooxygenase-2 (COX-2) protein expression suppressed by western blot analysis [30,31]. This dual function — photocatalytic antimicrobial/anticancer activity on demand with constitutive anti-inflammatory activity from the phytochemical corona — represents a unique therapeutic profile not replicated by chemically synthesised TiO_2.

The molecular mechanism of NF-κB suppression by polyphenol-coated TiO_2 involves inhibition of IκB kinase (IKK), preventing phosphorylation and degradation of the inhibitory IκBα subunit. Without IκBα degradation, NF-κB p65/p50 heterodimers cannot translocate to the nucleus and drive pro-inflammatory gene transcription [29,30]. Quercetin and EGCG additionally activate the Nrf2 pathway, upregulating

endogenous antioxidant enzyme expression (SOD, catalase, glutathione peroxidase) that further mitigates oxidative tissue damage in inflammatory conditions [18,30]. These converging molecular actions position biogenic TiO_2 as a mechanistically sophisticated anti-inflammatory agent with applications extending beyond infection and cancer to inflammatory diseases including arthritis, inflammatory bowel disease, and neuroinflammatory conditions.

4.4 Wound Healing Applications

Wound healing represents an emerging application for biogenic TiO_2 nanoparticles that integrates their antimicrobial, anti-inflammatory, and pro-regenerative properties [32]. The mechanism of wound healing facilitation is multi-phasic: in the inflammatory phase, the anti-inflammatory phytochemical corona suppresses excessive neutrophil-driven tissue damage; in the proliferative phase, low-level ROS generated under ambient light conditions acts as a signalling molecule that stimulates fibroblast migration and proliferation through the PI3K–AKT pathway; and angiogenesis is promoted through vascular endothelial growth factor (VEGF) upregulation [32,33].

In excision wound models in Wistar rats, TiO_2 nanoparticles synthesised from Aloe vera and Camellia sinensis extracts incorporated into carboxymethyl cellulose hydrogel wound dressings showed wound closure rates of 80–90% by day 14 compared to 60–70% in vehicle controls, with histological examination confirming enhanced collagen deposition, reduced neutrophil infiltration, and accelerated re-epithelialisation [33,34]. The antimicrobial photocatalytic activity additionally prevents wound colonisation by nosocomial pathogens including methicillin-resistant Staphylococcus aureus (MRSA) under UV lamp activation used in clinical wound management [34].

Advanced wound dressing formulations incorporating biogenic TiO_2 have explored electrospun nanofibre matrices (polycaprolactone/TiO_2), injectable hydrogels (hyaluronic acid/TiO_2), and foam dressings (polyurethane/TiO_2) as delivery vehicles. Electrospun nanofibre membranes incorporating TiO_2 nanoparticles synthesised from Moringa oleifera extract showed tensile strengths of 2.8–4.2 MPa with elongation at break of 45–80%, mechanical properties compatible with chronic wound bed management, while maintaining 85–95% bactericidal activity against S. aureus and P. aeruginosa under UV activation [32,34]. The physical structure of the nanofibre membrane additionally supports cell attachment and directional migration, contributing to wound bed organisation independent of chemical bioactivity.

Table 2 summarises the photocatalytic therapeutic applications, mechanisms, and key experimental outcomes for biogenic TiO_2 nanoparticles.

Therapeutic Area	Mechanism of Action	Key ROS Species	In vitro / In vivo Model	Outcome
Anticancer (PDT)	ROS-mediated oxidative stress, mitochondrial membrane disruption, caspase-3/9 activation, ICD induction	•OH, $^1O_2$, $O_2•^-$	HeLa, MCF-7, A549 cell lines; murine xenograft	IC_{50} 20–80 µg/mL; apoptosis >70%; ICD markers upregulated
Antimicrobial	Cell wall disruption, DNA strand breaks, respiratory enzyme inhibition; low resistance acquisition risk	•OH, H_2O_2	E. coli, S. aureus, C. albicans; MRSA	MIC 32–128 µg/mL; biofilm inhibition >60%; no MIC shift after 10 passages
Anti-inflammatory	NF-κB pathway suppression, TNF-α/IL-6 downregulation, COX-2 inhibition, Nrf2 activation	Indirect ROS modulation	LPS-activated macrophages (RAW 264.7)	Cytokine reduction 40–65%; COX-2 suppression confirmed
Wound Healing	Fibroblast proliferation, VEGF upregulation, angiogenesis promotion, collagen deposition	Low-level ROS signalling	Excision wound rat model; electrospun nanofibre dressings	Wound closure 80–90% by day 14; enhanced collagen deposition
Drug Delivery (PDT)	Surface functionalisation enables drug loading; light-triggered release; ICD priming for immunotherapy	•OH under UV/visible light	Doxorubicin-loaded TiO_2; cisplatin conjugates	Enhanced tumour uptake; reduced systemic toxicity; synergistic anticancer effect

Therapeutic Area	Mechanism of Action	Key ROS Species	In vitro / In vivo Model	Outcome
Theranostics	Photoluminescence and photocatalytic activity in single platform; MRI contrast via Fe-doped TiO_2	Controlled ROS	In vitro multimodal imaging + therapy	Simultaneous imaging and PDT; tumour-targeted delivery confirmed

Table 2. Photocatalytic therapeutic applications of biogenic TiO_2 nanoparticles: mechanisms and experimental evidence.

5. DOPING STRATEGIES AND VISIBLE-LIGHT-ACTIVE TiO_2

5.1 The UV Irradiation Limitation

A fundamental limitation of undoped TiO_2 for in vivo PDT applications is its band gap of 3.0–3.2 eV, which requires UV light for photoactivation ($\lambda < 390$ nm). UV light penetrates biological tissue to a depth of only 1–2 mm at therapeutic wavelengths, severely restricting the volume of treatable tissue accessible by surface irradiation [11,13]. Clinical PDT using haematoporphyrin derivatives and second-generation photosensitisers exploits visible and near-infrared (NIR) wavelengths (600–900 nm) where tissue optical transparency is maximised (optical window), with clinical light delivery via interstitial fibre optic probes for deeply seated tumours. Extending TiO_2 absorption into the visible and NIR regions is therefore a prerequisite for clinically practical TiO_2 PDT.

5.2 Non-Metal Doping (N, S, C, F)

Non-metal doping of TiO_2 with nitrogen (N-TiO_2), sulphur (S-TiO_2), carbon (C-TiO_2), and fluorine (F-TiO_2) extends visible light absorption by introducing intra-band gap states that allow sub-band gap photon absorption. Nitrogen doping is the most extensively studied: N substitution at oxygen lattice sites introduces N 2p states approximately 0.14 eV above the valence band, reducing the effective optical band gap to approximately 2.4–2.8 eV and enabling visible light absorption to approximately 520–520 nm [13,38]. N-doped biogenic TiO_2 can be achieved by incorporating nitrogen-rich plant extract components (alkaloids, amino acids) during synthesis or by post-synthesis treatment with urea or ammonia.

Carbon doping introduces C 2p states that hybridise with O 2p orbitals at the valence band, narrowing the effective band gap and enhancing visible light absorption through photosensitised electron injection mechanisms. C-TiO_2 derived from plant extract synthesis naturally incorporates carbon from decomposed organic phytochemicals during calcination, and deliberate optimisation of calcination atmosphere (limited oxygen) can enhance residual carbon incorporation and visible light response [15,38]. Sulphur doping, achieved using thiourea or DMSO as sulphur sources in combination with plant extract synthesis, produces S-TiO_2 with absorption extending to 550 nm and enhanced photocatalytic activity under fluorescent room lighting, relevant for hospital surface disinfection applications.

5.3 Metal Doping and Plasmonic Enhancement

Transition metal doping (Fe^{3+}, Cu^{2+}, Ag^{+}, Au^{3+}) modifies TiO_2 electronic structure through the introduction of d-orbital levels within the band gap that act as electron traps, extending charge carrier lifetime and reducing recombination [13,15]. Iron doping (Fe-TiO_2) is particularly well-studied: Fe^{3+} substitution at Ti_4^{+} sites introduces mid-gap energy levels that facilitate sub-band gap photon absorption and promote Fenton-like reactions ($Fe^{3+} + O_2^{\bullet-} \rightarrow Fe^{2+} + O_2$; $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH$) that amplify hydroxyl radical generation [15]. Fe-TiO_2 synthesised using Camellia sinensis extract showed visible light PDT activity against MCF-7 cells comparable to UV-activated undoped TiO_2, demonstrating the potential of metal doping to translate biogenic TiO_2 into visible-light-compatible clinical PDT agents.

Noble metal deposition (Au, Ag nanoparticles on TiO_2 surface) introduces localised surface plasmon resonance (LSPR) effects that dramatically amplify visible light absorption. The LSPR band of Au nanoparticles at approximately 520–580 nm transfers hot electrons to the TiO_2 conduction band via Schottky barrier injection, driving photocatalytic ROS generation under green light illumination. Au/TiO_2 nanocomposites synthesised using Aloe vera extract-capped gold seeds deposited on TiO_2 showed three-fold enhancement in photocatalytic dye degradation under visible light compared to undoped TiO_2, and demonstrated significantly enhanced PDT cytotoxicity against A549 lung cancer cells under green laser (532 nm) irradiation [13,14].

6. ENVIRONMENTAL REMEDIATION APPLICATIONS

6.1 Photocatalytic Degradation of Organic Pollutants

Beyond biomedical applications, biogenic TiO_2 nanoparticles demonstrate significant potential for environmental remediation through photocatalytic degradation of organic pollutants. Industrial effluents containing textile dyes (methylene blue, Congo red, rhodamine B), pharmaceutical compounds (antibiotics, hormones), and agricultural pesticides represent major environmental contamination challenges for which TiO_2 photocatalysis offers an attractive non-selective oxidative solution [39]. The same ROS cascade (•OH, $O_2•^-$, $^1O_2$) that mediates therapeutic cytotoxicity degrades aromatic pollutant structures through sequential hydroxylation, ring opening, and mineralisation to CO_2, H_2O, and inorganic ions.

Biogenic TiO_2 synthesised from Moringa oleifera seeds — already established as a natural water clarifier through flocculation — has demonstrated dual functionality as both a flocculant for particulate removal and a photocatalyst for dissolved organic pollutant degradation, with methylene blue degradation rates of 85–95% in 60 minutes under UV irradiation at catalyst concentrations of 100 mg/L [24,39]. Green tea-derived TiO_2 nanoparticles have demonstrated effective degradation of ciprofloxacin (>80% in 90 min, UV) and tetracycline (>75% in 120 min) under solar simulated irradiation, reducing antibiotic concentrations below ecotoxicological threshold values [39]. These environmental applications provide an additional commercial pathway for biogenic TiO_2 that could cross-subsidise the more expensive clinical development programme.

6.2 Photocatalytic Disinfection for Water Treatment

Photocatalytic disinfection of drinking water using TiO_2 is among the most technologically mature environmental applications. Solar-driven TiO_2 photocatalysis (SODIS) has been validated in pilot-scale studies for inactivation of E. coli, Cryptosporidium parvum oocysts, and Giardia lamblia cysts in water at turbidities below 2 NTU, achieving 4-log (99.99%) inactivation of E. coli in 2 hours of direct solar exposure [23,39]. Biogenic TiO_2 offers advantages over chemically synthesised TiO_2 for SODIS applications: the phytochemical capping agents act as dispersants in water, reducing particle aggregation and maintaining photocatalytic surface area; and the natural origin of the synthesis aligns with sustainability requirements for water treatment in resource-limited settings where chemical manufacturing infrastructure is unavailable.

7. TOXICITY PROFILE AND CLINICAL TRANSLATION BARRIERS

7.1 In Vitro and In Vivo Toxicological Data

Despite the impressive breadth of therapeutic activity demonstrated in vitro and in animal models, biogenic TiO_2 nanoparticles face substantial toxicological and regulatory challenges that presently preclude clinical translation [35]. The International Agency for Research on Cancer (IARC) classified TiO_2 as possibly carcinogenic to humans (Group 2B) in 2006, based on pulmonary inflammation and lung tumour formation in rats exposed to high concentrations of fine TiO_2 particles via inhalation [35]. This classification, though based on an inhalation exposure route irrelevant to intravenous or topical pharmaceutical administration, has cast a regulatory shadow over TiO_2 nanomedicine development.

In vitro cytotoxicity studies reveal a dose- and size-dependent toxicity profile. At concentrations below 50 µg/mL, biogenic TiO_2 nanoparticles are generally non-cytotoxic to normal cell lines (human dermal fibroblasts, HEK 293, Vero cells) in the absence of UV irradiation, suggesting an acceptable therapeutic window for photodynamic applications where ROS generation is light-controlled [36]. At concentrations exceeding 100 µg/mL, genotoxicity assessed by the comet assay and micronucleus test reveals DNA strand breaks in normal cells, attributed to intracellular ROS generation from photoactivation by ambient fluorescent lighting [36,37].

Nanoparticle size critically determines the toxicity-to-efficacy ratio. Particles below 20 nm demonstrate enhanced cellular internalisation via endocytosis and lysosomal accumulation, increasing intracellular ROS exposure; particles in the 50–100 nm range show preferential EPR-driven tumour accumulation with reduced non-specific uptake by normal tissues [1,3]. Biogenic synthesis using polyphenol-rich extracts (green tea, tulsi) consistently produces particles in the 8–35 nm range, which achieves high antimicrobial and anticancer efficacy but requires careful dose optimisation to avoid genotoxicity in clinical scenarios [18].

7.2 Surface Modification Strategies for Improved Biocompatibility

Surface modification represents the primary strategy for improving the clinical safety profile. PEGylation (polyethylene glycol coating) reduces macrophage-mediated clearance and extends circulation half-life; amino acid functionalisation with arginine-glycine-aspartate (RGD) peptides provides tumour-specific integrin targeting; and titanium doping with nitrogen, sulphur, or carbon extends visible light absorption to $\lambda > 400$ nm, reducing reliance on UV irradiation that itself poses tissue toxicity concerns [13,15]. The preservation of the phytochemical surface corona from biogenic synthesis appears to naturally enhance biocompatibility, as polyphenol-coated TiO_2 demonstrates significantly lower haemolysis rates and complement activation compared to uncoated chemically synthesised TiO_2 [18,37].

Protein corona formation upon nanoparticle entry into biological fluids is an underappreciated determinant of in vivo behaviour. Biogenic TiO_2 nanoparticles acquire a biomolecular corona of serum proteins (albumin, fibronectin, apolipoproteins) whose composition is shaped by the phytochemical surface chemistry. Polyphenol-coated surfaces preferentially adsorb albumin and apolipoproteins, which confer a 'stealth' character that reduces macrophage recognition, while uncoated TiO_2 surfaces adsorb fibronectin and immunoglobulins that trigger opsonisation and rapid clearance by the mononuclear phagocyte system [12,37]. Understanding and engineering the protein corona composition therefore represents a crucial but often neglected aspect of biogenic TiO_2 clinical development.

7.3 Regulatory Pathway Analysis

Clinical translation of biogenic TiO_2 nanoparticles must navigate a regulatory landscape shaped by the evolving frameworks for nanomedicines developed by the FDA (United States), EMA (European Medicines Agency), and CDSCO (India). The FDA considers nanoparticle-based drugs as drug–device combinations or new molecular entities depending on their mechanism of action, requiring a New Drug Application (NDA) or Biologics License Application (BLA) pathway with extensive preclinical pharmacokinetic, pharmacodynamic, and toxicological characterisation [35].

Critical regulatory requirements that biogenic TiO_2 formulations must address include: (i) demonstration of Good Manufacturing Practice (GMP)-compatible synthesis with validated batch-to-batch reproducibility for particle size distribution (target CV < 15%), phase composition (anatase fraction > 90%), surface chemistry (phytochemical loading within ±10% of specification), and photocatalytic activity (standardised ROS generation assay); (ii) comprehensive genotoxicity testing including Ames test, in vitro chromosomal aberration, and in vivo micronucleus assay according to ICH S2(R1) guidelines; (iii) 28-day and 90-day repeat-dose toxicity studies in two rodent species with full organ histopathology and recovery groups; and (iv) biodistribution studies using radiolabelled or ICP-MS-quantified TiO_2 to characterise organ accumulation patterns, elimination kinetics, and metabolic fate [35,37].

Two fundamental gaps currently impede regulatory progress: the absence of standardised synthesis protocols ensuring reproducible phase composition, size distribution, and phytochemical loading across batches; and the lack of systematic in vivo pharmacokinetic, biodistribution, and long-term toxicity data specifically for biogenic TiO_2 formulations. Both gaps reflect the field's relative immaturity compared to ZnO and silver nanoparticle biomedicine, and both are addressable through structured collaborative research programmes anchored to regulatory agency guidance.

8. FUTURE PERSPECTIVES AND EMERGING RESEARCH DIRECTIONS

8.1 Machine Learning-Guided Synthesis Optimisation

The multidimensional parameter space of biogenic TiO_2 synthesis — encompassing plant source, extraction conditions, precursor concentration, pH, temperature, reaction time, and calcination profile — creates an optimisation challenge ill-suited to conventional one-variable-at-a-time experimental design. Machine learning approaches, particularly Gaussian process regression (Bayesian optimisation) and random forest models, are emerging as powerful tools for navigating this parameter space with minimal experimental iterations [40]. Training datasets derived from published synthesis outcomes can identify non-obvious interactions between variables; for example, the interaction between extract polyphenol content and calcination ramp rate in determining anatase fraction may not be apparent from single-variable experiments but emerges clearly from multivariate analysis [17,40].

Active learning frameworks, where the machine learning model sequentially recommends the most informative next experiment based on current uncertainty in the parameter–outcome relationship, are particularly suited to biogenic nanoparticle synthesis because each experiment is resource-intensive and data collection speed is limited. Proof-of-concept applications of Bayesian optimisation to ZnO nanoparticle synthesis have demonstrated 60–80% reductions in the number of experiments required to identify optimal synthesis conditions compared to response surface methodology [40]. Application of equivalent approaches to TiO_2 biogenic synthesis represents a high-priority research direction with clear practical impact on synthesis reproducibility and GMP protocol development.

8.2 Theranostic TiO_2 Platforms

Theranostics — the integration of therapeutic and diagnostic functions in a single nanoplatform — represents a frontier application for biogenic TiO_2. TiO_2 nanoparticles exhibit intrinsic photoluminescence properties that enable fluorescence imaging, and their titanium content provides contrast in photoacoustic imaging through optical absorption at near-infrared wavelengths [13,41]. Iron-doped TiO_2 (Fe-TiO_2) introduces MRI T2 contrast through paramagnetic Fe^{3+} centres, enabling simultaneous MRI-guided PDT where tumour boundaries are delineated by MRI prior to focal light irradiation activation. Gold-decorated TiO_2 supports both LSPR-enhanced PDT under visible light and surface-enhanced Raman scattering (SERS) spectroscopic detection of cancer biomarkers at attomolar concentrations, creating a combined diagnostic-therapeutic platform.

Biogenic synthesis offers natural advantages for theranostic development because phytochemical capping agents serve simultaneously as biocompatibility enhancers, colloidal stabilisers, and pharmacologically active constituents. The phytochemical corona of green tea-derived TiO_2 has been shown to enhance cellular uptake in cancer cells relative to normal cells through interactions with cancer cell surface proteins, providing intrinsic tumour-targeting capability that complements antibody or ligand conjugation strategies [18,41].

8.3 Combination Therapies

The convergence of TiO_2 PDT with immune checkpoint inhibitor therapy (anti-PD-1, anti-CTLA-4) represents a particularly promising combination strategy. PDT-induced immunogenic cell death releases tumour antigens that prime tumour-specific T cell responses; checkpoint blockade simultaneously removes the immunosuppressive brake that tumours exploit to evade cytotoxic T lymphocyte killing [11]. The combination of TiO_2 PDT and anti-PD-1 therapy in syngeneic tumour models has shown complete tumour regression in 40–60% of treated animals and durable immunological memory against tumour rechallenge, suggesting abscopal effects on metastatic disease beyond the irradiated primary tumour volume. Clinical translation of this combination strategy would position biogenic TiO_2 PDT within the rapidly growing immuno-oncology therapeutic paradigm, potentially accessing the substantial existing clinical infrastructure for immune checkpoint inhibitor delivery.

Sonodynamic therapy (SDT) — the activation of sonosensitisers by ultrasound rather than light — extends TiO_2 therapeutic applications to deep-seated tumours inaccessible by optical irradiation. TiO_2 functions as both a photosensitiser and a sonosensitiser through related but mechanistically distinct pathways involving ultrasound-driven cavitation and piezoelectric effects [41]. Clinical-grade ultrasound equipment is universally available and offers real-time imaging guidance for therapeutic activation, making TiO_2 SDT a practically attractive complement to PDT for treating deep tumours where light penetration is limiting.

9. CONCLUSION AND FUTURE PERSPECTIVES

TiO_2 nanoparticles occupy a unique position in the landscape of photocatalytic nanomedicine: their chemical stability in biological environments, unmatched ROS generation under controlled light activation, and highly tunable surface chemistry collectively constitute a therapeutic platform that no alternative metal oxide has replicated. The biogenic synthesis of TiO_2 using plant extracts is more mechanistically complex than ZnO synthesis but is achievable through polyphenol-controlled hydrolysis and phase-directing templating, with anatase phase purity achievable using flavonoid-rich extracts from Camellia sinensis, Ocimum tenuiflorum, and Azadirachta indica.

The photocatalytic therapeutic profile — antimicrobial MICs of 32–128 µg/mL, anticancer IC_{50} values of 20–80 µg/mL with apoptosis induction, anti-inflammatory NF-κB suppression, and enhanced wound healing in animal models — provides a compelling foundation for translational development. The dual advantage of

constitutive anti-inflammatory activity from the retained phytochemical corona and on-demand photocatalytic cytotoxicity from light activation is a mechanistic combination unique to biogenic TiO_2. The emerging dimensions of immunogenic cell death induction, theranostic platform development, visible-light-active doped formulations, and machine learning-guided synthesis optimisation collectively define a research agenda that could accelerate clinical translation substantially.

Clinical translation requires resolution of four priorities: standardised GMP-compatible green synthesis protocols ensuring batch reproducibility; systematic in vivo pharmacokinetic and long-term toxicology studies specifically for biogenic TiO_2 formulations; visible-light-responsive doped formulations eliminating UV irradiation reliance; and formal regulatory engagement with FDA and EMA through pre-IND and scientific advice mechanisms to define the evidential requirements for first-in-human studies. The convergence of photodynamic therapy, drug delivery, anti-inflammatory activity, and immunogenic cell death priming in a single biogenically synthesised, plant-capped nanoparticle represents one of the most compelling and mechanistically integrated platforms in contemporary nanomedicine, meriting the structured translational investment these priorities require.

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