

In Vivo Toxicity of Upconversion Nanoparticles. Overview. Part II

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Abstract. This is the second section of review synthesizes current research on the *in vivo* toxicity of upconversion nanoparticles (UCNPs) for biomedical applications, including photoinduced drug delivery, photodynamic therapy (PDT), and multimodal therapies. The aim is to assess the safety of UCNPs under near-infrared (NIR) irradiation and in combination with photosensitizers, chemotherapeutics, and other therapeutic modalities. Analysis of numerous *in vivo* studies in mouse and rat models demonstrates that UCNPs exhibit low dark toxicity and targeted phototoxicity, with no significant damage to major organs (heart, liver, spleen, lungs, kidneys) at therapeutic doses. For mice, safe doses are 10 mg/kg for short-term exposure (48 h and for long-term exposure 40 days). Surface coatings (PEG, silica, MVEMA, cell membranes) enhance biocompatibility and reduce off-target effects. Multimodal UCNP platforms (PDT combined with chemotherapy, photothermal therapy, chemodynamic therapy, immunotherapy, or radiotherapy) demonstrate effective tumor suppression without substantial systemic toxicity. These findings support the continued development of UCNPs as safe and effective theranostic agents for precision oncology.

Keywords: phototoxicity, upconversion nanoparticles, dose, photodynamic therapy.

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1 Phototoxicity of Upconversion Nanoparticles

1.1 Drug Delivery and Photo Induced Release

One of the potential applications of upconversion nanoparticles (UCNPs) combined with a photosensitizer (PS) is targeted drug delivery and photo induced drug release. For instance, in recent paper, UCNPs coated with a PS, a stopper agent, and modified mesoporous silica (designated as UCNPs@mSiO[DEX] Py/β CD/FITC, or USDPFs) were developed for synergistic combination therapy of lung ischemia reperfusion injury (LIRI), enabling precise release of dexamethasone (DEX) [1].

DEX is a synthetic glucocorticoid that helps reduce inflammatory responses, suppress the immune response, and improve the tolerability of anticancer therapy.

UCNPs were developed by coating an inert YOF:Yb shell onto a YOF:Yb, Tm core to achieve high intensity blue and red upconversion emission upon irradiation with a NIR laser.

To evaluate the *in vivo* safety of USDPFs, healthy adult C57BL/6 mice were administered 5 mg kg⁻¹ of USDPFs via intratracheal instillation. After two weeks, mice in the USDPF group showed no infiltration of inflammatory cells or tissue necrosis in the heart, lungs, liver, spleen, and kidneys, as compared to the control group. This indicates that intratracheal administration of the nanoparticles does not damage lung tissue, and that USDPFs do not exhibit significant toxicity to several vital organs in mice, demonstrating good *in vivo* safety.

To evaluate the safety and function of USDPFs (UCNPs for DEX delivery), the authors investigated several conditions in mice: USDPFs alone, USDPFs with NIR irradiation (980 nm, 3 × 10 min, 1 W/cm²),

ischemia/reperfusion (I/R) injury, I/R + USDPFs, and I/R + USDPFs + NIR [1–4]. Mice received a single dose of 5 mg/kg USDPFs via intratracheal or intravenous administration.

Following intravenous injection, USDPFs remained detectable in the bloodstream for approximately 10 hours, confirming prolonged circulation compatible with the enhanced permeability and retention (EPR) effect. Importantly, neither USDPFs alone nor USDPFs + NIR caused any lung tissue damage, edema, or inflammatory cell infiltration compared to healthy controls. In contrast, the I/R and I/R + USDPFs groups showed severe lung injury, characterized by thickened alveolar walls, edema, and elevated levels of IL-1 β , IL-6, and TNF α .

Remarkably, the I/R + USDPFs + NIR group exhibited significantly reduced lung damage, pulmonary edema (lower wet-to-dry weight ratio), and lower inflammatory cytokine levels compared to both I/R-only and I/R + USDPFs groups. These results demonstrate that NIR irradiation triggers DEX release from USDPFs, effectively alleviating inflammation and edema without intrinsic nanoparticle toxicity. Overall, USDPFs show a favorable biosafety profile.

Complex heterostructures comprising UCNPs (DUCNPs) and manganese based metal–organic frameworks (Mn MOFs) can be used for drug delivery [5].

The authors developed a nanocarrier designated DUCNP@Mn MOF, which demonstrated good loading efficiency and delivery capability for the cytotoxic antitumor agent 3 F 10 OH evodiamine (FOE).

The combined properties of Mn MOF and DUCNPs endowed the DUCNP@Mn MOF/FOE system with synergistic chemodynamic and chemotherapeutic effects. The developed nanosystem exhibited high tumor targeting selectivity.

In a mouse model of breast cancer, the nanocarrier effectively suppressed tumor growth without causing significant toxicity.

Wang Y., et al. developed NaYF₄:Yb,Tm-based upconversion nanoparticles conjugated with the chemotherapeutic agent 9-aminocamptothecin (ACPT) via photolabile linkers. The nanoparticles were coated with a 4T1 tumor cell membrane functionalized with melittin to enable homologous tumor targeting and enhance drug penetration [6].

In a 4T1 breast cancer mouse model, intravenous injections were administered on days 0, 3, and 6 (melittin dose: 1 mg kg⁻¹), followed by 808 nm NIR irradiation (0.8 W cm⁻², 20 min) on days 2, 5, and 8. The treatment inhibited tumor growth and suppressed lung metastasis. No obvious pathological changes were observed in the heart, liver, spleen, lungs, or kidneys.

Serum inflammatory factors such as tumor necrosis factor α (TNF α) and interferon γ (IFN γ), which are secreted by immune cells, can inhibit tumor cell growth [7].

Therefore, the concentrations of TNF α and IFN γ were analyzed. The results showed that treatment with U

ACPT@MM + NIR significantly increased the serum levels of both TNF α and IFN γ .

In addition, no obvious pathological changes were observed in the tissues of the heart, liver, spleen, lungs, and kidneys.

1.2 Photodynamic Therapy

In photodynamic therapy (PDT), the use of UCNPs involves loading them with PSs and exciting the PSs via the luminescence of the nanoparticles. Since the excitation of UCNPs is achieved using infrared light – which penetrates deeply into biological tissues – this approach enables effective treatment of deeper seated tumors without causing photodamage to the overlying tissues.

When excited, the PS undergoes specific reactions, initiating a chain of processes that lead to the formation of various reactive oxygen species (ROS). These ROS exert a damaging effect on cellular structures, ultimately causing the death of tumor cells.

More than a hundred substances with photosensitizing properties are known. Among natural compounds, PSs include chlorophylls, phycobilins, porphyrins and their synthetic intermediates, several antibiotics, quinine, riboflavin, and others.

Most commonly in PDT, several types of PS are used – mainly various derivatives of porphyrins. In addition to porphyrins themselves, related derivatives are also employed: chlorin based compounds (chlorins, bacteriochlorins), as well as phthalocyanines and naphthalocyanines [8].

Besides the PS, the nanoparticle surface must be coated with functional groups to ensure targeted accumulation of nanoparticles within the tumor.

Analysis of nanoparticle use in PDT should also include investigation of pathological morphological changes in major organs (liver, heart, kidneys, spleen, and lungs), both under nanoparticle irradiation and without it. The absence of such changes indicates no dark toxicity and no secondary effects arising from irradiation when using the studied nanoparticles.

However, nanoparticles can also be used without sensitizers.

The authors synthesized NaGdF₄:25 % Yb³⁺, 1 % Nd³⁺, 0.5 % Tm³⁺ nanoparticles, whose luminescence could be excited both at 808 nm (Nd³⁺ ions) and at 980 nm (Yb³⁺ ions) [9]. The emission of these nanoparticles in the 450–500 nm range (Tm³⁺ ions) is effectively absorbed by all organic PSs. When using nanoparticles coated with thiochromenocarbazole imide (TCI), the authors noted low dark toxicity and the possibility of *in vivo* imaging. However, the authors did not observe a significant effect on the growth of HeLa stimulated tumors.

In the work, UCNPs of the composition TiO₂/(Ca, Y)F₂:Tm, Yb were obtained by a hydrothermal method; these nanoparticles respond to near infrared light and are intended for combating tumors [10].

Additionally, a femtosecond laser (FL) was used to reduce the size and aggregation of

TiO₂/(Ca, Y)F₂:Tm, Yb, which allowed improving its dispersity. The authors evaluated the phototherapeutic effect of the nanoparticles on CFPAC 1 pancreatic tumors.

The experiments showed that in the absence of TiO₂/(Ca, Y)F₂:Tm, Yb FL, the growth rate and size of tumors in nude mice were significantly larger than in the treatment case. This indicates that TiO₂/(Ca, Y)F₂:Tm, Yb FL nanoparticles play a certain role in inhibiting tumor growth under near infrared light, but due to the complex and variable environment *in vivo*, the hydroxyl radicals released from TiO₂/(Ca, Y)F₂:Tm, Yb FL did not achieve the effect of destroying tumor cells over a large area. Instead, they only led to inhibition of tumor growth in nude mice without reducing the tumor area or killing all tumor cells.

This may be associated with the hypoxic microenvironment of tumor tissue, which causes tumor cells to activate signaling pathways leading to increased synthesis or expression of certain genes and proteins (oxygen regulated protein (ORP), vascular endothelial growth factor (VEGF), erythropoietin (EPO), etc.), resulting in structural and functional abnormalities in the blood vessels of tumor tissue. Consequently, their sensitivity to the oxygen concentration in the surrounding environment is lower than that of normal tissues [11].

To enhance nanoparticle penetration into tumor tissue, boost PDT efficacy, and reduce off target toxicity, special surface coatings are required.

In their study, Ling B., et al. developed nucleus penetrating UCNPs (UCNP@Glu DMMA) with charge reversal properties [12].

The design relies on two key components:

- glucose, which confers tumor cell tropism;
- 2,3 dimethylmaleic anhydride (DMMA), which imparts a negative surface charge to the nanoparticles.

This configuration ensures blood circulation stability and accumulation in the tumor microenvironment (TME). DMMA and its derivatives allow the nanoparticle surface charge to be modulated based on the tumor's acidity. Exposure to the acidic TME and γ glutamyl transpeptidase (GGT) triggers a charge reversal from negative to positive.

Positively charged nanoparticles are more readily taken up by cells, thereby amplifying the PDT effect. Direct delivery to the cell nucleus enables localized release of ROS, leading to sustained photo stimulated DNA damage.

In the experimental phase, UCNPs@Glu DMMA was injected into nude mice bearing HeLa tumors. The animals then underwent laser irradiation at 980 nm for 15 min (30 s of irradiation followed by a 1 min break to prevent overheating) at a power density of 0.8 W cm⁻².

The results showed a significant reduction in tumor size. Irradiation induced substantial apoptosis in tumor tissues and effectively suppressed cellular proliferation. Toxicity assessment revealed minimal signs of tissue damage or inflammation in major organs.

Currently, a wide range of phototherapeutic agents based on PS conjugated UCNPs has been tested for NIR

induced PDT, primarily aiming to demonstrate cellular uptake and cell death following NIR irradiation [13–15].

The first *in vivo* application was performed by intratumoural injection of NaYF₄:Yb³⁺, Er³⁺@poly(ethylene glycol) particles non covalently loaded with chlorin e6 (Ce6) into mice bearing 4T1 breast tumors [16]. PDT with 980 nm irradiation (0.5 W cm⁻², 30 min) significantly reduced tumor growth rates in mice.

A similar effect after NIR irradiation (5 min, 0.6 W cm⁻²) was observed in nude mice bearing U87MG tumors that received intravenous injections of NaYF₄:Yb³⁺, Er³⁺@NaGdF@poly(ethylene glycol) phospholipid particles loaded with Ce6 [17].

In mice bearing S180 sarcoma tumors treated with NaYF₄:Yb³⁺, Er³⁺ particles loaded with zinc phthalocyanine and chitosan – and irradiated twice (3 h and 24 h post injection) with a 980 nm laser (0.4 W cm⁻², 15 min) – only a slight increase in tumor volume was observed, along with high survival rates [18].

Injection of NaYF₄:Yb³⁺, Er³⁺@CaF₄@poly(acrylic acid)hydrazide particles covalently functionalized with 5 aminolevulinic acid into mice significantly reduced tumor size after 980 nm laser irradiation (0.5 W cm⁻²) for 40 min [19].

An *in vivo* PDT study in mice with CT 26wt tumors showed reduced tumor growth following intratumoural injection of NaYF₄:Yb³⁺, Er³⁺@phosphatidylcholine folic acid (FA) particles loaded with tetraphenylporphyrin and irradiation at 980 nm (1 W cm⁻², 30 min) [20].

Similarly, many organic PSs – such as methylene blue [21], Rose Bengal [22], and pyropheophorbide a methyl ester [23] – when integrated with UCNPs for NIR activated PDT (0.15–1 W cm⁻²; up to 40 min), significantly suppressed tumour growth.

The use of UCNPs with protoporphyrin (PPIX) for PDT was investigated in paper [24]. Abundant amino groups of a branched PEI with a spatial structure were employed to enhance the loading capacity of protoporphyrin (PPIX), which ultimately improved the rate of skin tumor removal.

The authors achieved specific tumour treatment through the use of FA targeting and active enrichment of PPIX. When nanoparticle solutions were injected intravenously over a period of 4 weeks, no significant pathological morphological changes were observed in major organs (liver, heart, kidneys, spleen, and lungs), both with and without nanoparticle irradiation. This indicates good biosafety of the treatment method.

In the group treated with nanoparticles without irradiation, the tumor cell structure remained ordered, and the nuclear shape was complete and well defined. In contrast, after irradiation, the tumor tissue was severely damaged, and the nucleus was largely destroyed or even disappeared. These results demonstrate effective anticancer photoactivity while maintaining safety for other organs.

One of the widely used PSs is a porphyrin analogue – chlorins (porphyrins hydrogenated at

C17 = C18). Among chlorins, chlorin e6 is one of the most commonly used in PDT.

Chlorin e6 selectively accumulates in pathological cells. Upon local excitation with light at a wavelength of 660–670 nm, chlorin e6 becomes activated as a PS within pathological cells, initiating a photochemical reaction that produces singlet oxygen and other highly reactive free radicals, which induce apoptosis.

Since tumor development often follows a hypoxic mechanism, an additional requirement for the effective use of chlorin e6 is ensuring sufficient oxygen supply.

To investigate the impact of hypoxia and achieve an antitumor effect by switching the phenotype of tumor associated macrophages (TAMs) from the tumor promoting M2 type to the tumor suppressing M1 type, the authors fabricated $\text{NaErF}_4/\text{NaLuF}_4$ nanoparticles decorated with mannose and coated with a macrophage membrane (RAW), covered by a silica dioxide layer doped with an oxygen carrier – perfluorocarbon (PFC) – and chlorin e6 (Ce6), and loaded with the antitumor drug paclitaxel (PTX) (UCNP@mSiO_2 PFC/Ce6@RAW Man/PTX; ~61 nm; 11.6 mV) [25].

The primary UCNPs consisted of lanthanide elements (erbium and lutetium) in a core@shell structure and emitted light at 660 nm in response to near infrared laser irradiation at 808 nm. These nanoparticles had the following key properties:

- efficient generation of singlet oxygen, enabled by oxygen supply from the PFC component;
- high targeting specificity for tumor associated macrophages (TAMs), predominantly of the M2 phenotype;
- capacity to induce M1 type macrophage polarization.
- M1 macrophages release pro inflammatory cytokines and suppress breast cancer growth. The design of these nanoparticles thus combined:
 - oxygen delivery (via PFC) to counteract tumor hypoxia;
 - PS activity (Ce6) for PDT under NIR irradiation;
 - macrophage membrane coating (RAW) for improved biocompatibility and targeting;
 - mannose decoration for enhanced recognition by TAMs;
 - chemotherapy (PTX) for synergistic antitumor action.

This multifunctional approach aimed to reprogram TAMs from a tumor supportive (M2) to a tumor suppressive (M1) phenotype, thereby enhancing the overall antitumor immune response in hypoxic breast cancer.

4T1 cells ($100\ \mu\text{L}$, 2×10^6 cells) were subcutaneously injected into the flanks of mice. When tumor volume reached approximately $150\ \text{mm}^3$, the mice were randomly divided into five groups: G1 – phosphate buffer solution (PBS) (no treatment); G2 – UCNPs@mSiO_2 PFC/Ce6; G3 – UCNPs@mSiO_2 PFC/Ce6 + 808 nm irradiation ($1.5\ \text{W cm}^{-2}$ for 20 min); G4 – UCNPs@mSiO_2 PFC/Ce6@RAW

Man/PTX; G5 – UCNPs@mSiO_2 PFC/Ce6@RAW Man/PTX + 808 nm irradiation.

The nanoparticle dose was set at $6.5\ \text{mg kg}^{-1}$ ($130\ \mu\text{g}$ total nanoparticle amount), with 0.4, 0.6, and $0.5\ \text{mg kg}^{-1}$ for PFC, Ce6, and PTX, respectively. Laser irradiation at 808 nm ($1.5\ \text{W cm}^{-2}$) was applied to each mouse's tumor for 20 min.

Both PBS and hypoxic UCNPs@mSiO_2 PFC/Ce6@RAW Man/PTX (without PFC doping and purged with N_2) generated very little oxygen (total sO_2 : 19–20%), even 12 and 24 h after intravenous administration. However, oxygenated UCNPs@mSiO_2 PFC/Ce6@RAW Man/PTX, with ultrasound stimulated oxygenation, significantly increased tumor oxygen levels (total $\text{sO}_2 > 40\%$) 24 h after intravenous injection.

These results indicate that intravenous administration of the nanoparticles successfully delivers a substantial amount of oxygen, effectively alleviating hypoxia in solid tumors.

Tumors in G5 mice (treated with UCNPs@mSiO_2 PFC/Ce6@RAW Man/PTX plus 808 nm laser irradiation) were the most significantly suppressed. This is presumably due to the potent antitumor effect arising from: polarization of TAMs into tumor suppressive M1 type macrophages; ROS generation; the combined action of paclitaxel (PTX).

The antitumor effect can also be achieved via intratumoural injection of microgels containing UCNPs [26].

Hb μ Gels consist of haemoglobin (Hb), bovine serum albumin (BSA), chlorin e6 (Ce6), and erbium@lutetium doped UCNPs (~35 nm), which efficiently convert 808 nm irradiation into 660 nm visible light.

Tumors were established by subcutaneously injecting 4T1 cells ($100\ \mu\text{L}$, 2×10^6 cells) into the flanks of mice.

As an optical probe for hypoxia, the authors used pimonidazole (2 nitroimidazole), which is specifically reduced and binds to intracellular macromolecules in hypoxic regions of tumors [27, 28].

The authors demonstrated that laser irradiation at 808 nm alone, or the use of nanoparticles without Ce6, did not produce significant hyperthermic or photodynamic effects on 4T1 tumor xenografts.

Cytotoxicity was achieved through ROS mediated apoptosis, as well as through intense and sudden thermal stress induced by laser heating and additional heat delivery to temperatures exceeding $48\ ^\circ\text{C}$. Enhanced tumor oxygenation was accomplished by:

- oxygen saturation of the formulations;
- the use of Hb μ Gels(+UCNPs/Ce6) nanoparticles loaded with ascorbic acid;
- ultrasound stimulated oxygenation.

These results indicate that Hb(6) μ Gels can deliver oxygen to hypoxic tumor tissues, thereby helping to suppress hypoxic tumor growth.

Moreover, the use of these gels resulted not only in minimal accumulation in the five major tissue organs (liver, kidneys, spleen, lungs, and heart), but also in negligible changes to tissue histology. This demonstrates that the hemoglobin based μ Gel incorporating UCNPs is

biocompatible and safe, making it a promising injectable microgel system for therapeutic applications.

To further alleviate tumor hypoxia, biocompatible and environmentally friendly zinc oxide nanoparticles (ZnO NPs) with upconversion properties and catalase like nanozyme activity were developed [29].

As nanozymes, the ZnO NPs can catalyse the decomposition of hydrogen peroxide (H_2O_2) within tumours, thereby generating oxygen to support photodynamic action and relieve hypoxia.

In experiments with 4T1 tumors, growth was significantly suppressed after implantation of:

- Ce6 nanoparticles irradiated with a 660 nm laser;
- ZnO Ce6 nanoparticles irradiated with an 808 nm laser.

However, the antitumour activity of 808 nm laser irradiated ZnO Ce6 NPs was notably higher than that of 660 nm laser irradiated Ce6 NPs.

Remarkably, tumors were completely eradicated in three out of five mice bearing 4T1 tumors following treatment with 808 nm laser irradiated ZnO Ce6 NPs.

The corresponding tumor growth suppression rates were:

- 90.0% for ZnO Ce6 NPs with 808 nm laser irradiation;
- 80.2% for Ce6 NPs with 660 nm laser irradiation – compared to the control group.

These findings highlight the potential of ZnO NPs with upconversion and nanozyme properties as a multifunctional platform for overcoming tumor hypoxia and enhancing photodynamic therapy efficacy.

UCNPs are also used in combination with the antitumor drug doxorubicin (DOX) [30, 31]. For effective phototargeting, FA was employed as a photoactive targeting molecule. In chemotherapy, the anticancer drug DOX was thiolated on the surface of UCNPs, forming a disulfide bond that can be cleaved by lysosomal enzymes inside cells [31].

A study demonstrated that long term *in vivo* toxicity tests in mice receiving intravenous injections of 10 mg/kg $\text{BaGdF}_5:\text{Yb}^{3+}/\text{Tm}^{3+}$ with DOX did not reveal significant adverse health effects, and survival was observed for 40 days [30].

One derivative of chlorin is meso tetrahydroxyphenylchlorin (Temoporfin, THPC, m THPC), also known as Foscan. It is a photosensitising agent used in photodynamic therapy for the treatment of head and neck squamous cell carcinoma. However, there are several studies exploring the use of UCNPs with THPC for treating other types of cancer.

The efficacy of UCNP@PMVEMA THPC 2 conjugates for PDT following NIR light irradiation at 980 nm was tested *in vivo* in a study using human pancreatic adenocarcinoma (Capan 2) grown subcutaneously in athymic nude mice.

One of the key requirements for the particles is surface modification – for instance, using poly(methyl vinyl ether alt maleic acid) (PMVEMA) and the PS THPC – to ensure their colloidal and chemical stability

in aqueous media and to enable singlet oxygen generation upon NIR irradiation, respectively [32].

A coating of alendronate terminated poly[N,N dimethylacrylamide co 2 aminoethyl acrylamide] graft poly(ethylene glycol) [P(DMA AEM)PEG Ale] was also used to ensure chemical and colloidal stability of the particles in aqueous physiological fluids, which additionally enhances therapeutic efficacy [33].

Co doping of Fe^{2+} , Yb^{3+} , and Er^{3+} ions into the NaYF_4 host triggered upconversion emission in the red region, which is dominant for directly exciting THPC. It was found that such monodisperse UCNPs – $\text{NaYF}_4:\text{Yb}^{3+}, \text{Er}^{3+}, \text{Fe}^{2+}$ coated with PMVEMA and chemically linked to THPC – efficiently transfer energy and generate singlet oxygen. The authors investigated the effect of these particles on Capan 2 pancreatic adenocarcinoma cells.

The mice were administered intratumorally with PBS (control group), UCNP@PMVEMA particles, or UCNP@PMVEMA THPC 2 particles, followed by laser irradiation at a wavelength of 980 nm for 3 min at a power density of 0.5 W cm^{-2} (except for the negative control group).

It should be noted that a power density of $< 0.7 \text{ W cm}^{-2}$ is the conservative limit established for safe exposure of human skin to 980 nm light [34].

No significant differences in body weight were observed between the groups, indicating the absence of adverse effects during the treatment period. The same was observed for UCNPs containing chlorin e6 [35].

On the first or second day after irradiation, extensive necrosis developed in all mice in the group treated with UCNP@PMVEMA THPC 2 particles, whereas no necrosis was observed in the control group or in the group containing UCNP@PMVEMA.

However, the UCNP@PMVEMA THPC 2 group exhibited a statistically significant suppression of tumor growth rate, and the tumor volume on day 30 was 0.35 cm^3 .

Thus, the potential of THPC conjugated UCNPs coated with PMVEMA in the treatment of pancreatic adenocarcinoma – with sufficiently low toxicity – has been confirmed.

The use of THPC and UCNPs *in vivo* for glioblastoma treatment has also been investigated [36].

Encapsulation of the dyes THPC and IR 780 into $\text{NaYF}_4:\text{Yb}^{3+}, \text{Er}^{3+}$ @PEG particles enabled a promising approach to glioblastoma therapy under combined laser irradiation at 980 nm (0.8 W cm^{-2}) and 808 nm (0.36 W cm^{-2}) for 5 min.

In all studies involving THPC, no nanoparticle toxicity or tumor changes were observed in the absence of laser irradiation.

Phthalocyanines are actively used in diagnostics and PDT.

In study an energy segmentation strategy was employed to synthesise core multi shell UCNPs capable of emitting three distinct colors (red, green, and blue) when irradiated with different NIR lights (1550 nm, 808 nm, and 980 nm) [37]. By combining these UCNPs

with PSs and nitric oxide (NO) donors, a “smart” PDT nanoplatfrom was developed.

4T1 tumor cells were subcutaneously injected into mice. Although the internalization of UCNPs in living organisms depends on their size and surface ligands, UCNPs within the 50–250 nm size range are internalized via endocytosis.

The authors investigated PDT using laser irradiation at various wavelengths. When tumors reached approximately 100 mm³, the mice were randomly divided into eight groups (five mice per group):

- Control Group 1: PBS solution;
- Control Group 2: UCNPs@mSiO₂ ZnPc RBS;
- Group 3: UCNPs@mSiO₂ ZnPc RBS with 808 nm irradiation;
- Group 4: UCNPs@mSiO₂ ZnPc RBS with 980 nm irradiation;
- Group 5: UCNPs@mSiO₂ ZnPc RBS with 1550 nm irradiation;
- Group 6: UCNPs@mSiO₂ ZnPc RBS with 1550 nm + 980 nm irradiation;
- Group 7: UCNPs@mSiO₂ ZnPc RBS with 1550 nm/980 nm irradiation;
- Group 8: UCNPs@mSiO₂ ZnPc RBS with 980 nm/1550 nm irradiation.

The laser power density was set at 1 W cm⁻², and the irradiation time for each group was 20 min.

Tumor growth was rapid in Control Group 1, Control Group 2, Group 3, whereas tumor growth in Groups 4, 5, 6, and 7 was somewhat slowed. In contrast, the tumor size in Group 8 was the smallest, indicating that tumor growth was significantly suppressed by programmed phototherapy – specifically, by the sequential release of NO followed by ROS.

No significant decrease or increase in body weight was observed, indicating good biocompatibility of the developed nanocomposites.

Histological analysis of tumors and major organs showed that the most pronounced apoptosis or necrosis and nuclear shrinkage occurred in the 980 nm/1550 nm group.

No obvious damage to the major organs (heart, liver, spleen, lungs, and kidneys) was detected, suggesting that the UCNPs@mSiO₂ ZnPc RBS do not exhibit short term toxicity and demonstrate great potential for clinical application.

The simultaneous action of two photosensitive agents – MC540 (merocyanine 540) and FePc (iron phthalocyanine) – was investigated in the study [38].

The authors developed UCNPs NaErF₄@NaYbF₄@NaYF₄ coated with mesoporous silica loaded with MC540 and FePc.

Nude mice were subcutaneously injected with HeLa tumor cells. When the tumor size reached approximately 100 mm³, the mice were randomly divided into five groups (three mice per group):

- Group 1: PBS injection only (control group);
- Group 2: UCNPs@mSiO₂ FePc MC540 injection with 980 nm laser irradiation;

- Group 3: UCNPs@mSiO₂ MC540 injection with 1550 nm laser irradiation;

- Group 4: UCNPs@mSiO₂ FePc injection with 1550 nm laser irradiation;

- Group 5: UCNPs@mSiO₂ FePc MC540 injection with 1550 nm laser irradiation.

The laser power density was 235 mW cm⁻², and the irradiation time for each group was 10 min.

The group treated with UCNPs@mSiO₂ FePc MC540 plus 1550 nm light showed the greatest cell reduction and apoptosis.

Moreover, no significant damage or lesions were observed in the major organs (heart, liver, spleen, lungs, and kidneys) across the different groups. This also indicates that the developed nanoagents UCNPs@mSiO₂ FePc MC540 do not exhibit pronounced toxicity in mice.

One of the mechanisms of PDT may be the stimulation of iron dependent lipid peroxidation – ferroptosis.

The authors developed a nanozyme that responds in the NIR region. It features a uniform dispersion of Fe atoms on a g C₃N₄ doping network within a mesoporous upconversion structure (UmFe), followed by coating with a hybrid platelet membrane (hPM) and oleanolic acid (OA) to obtain UmFe OA@hPM [39].

To establish a primary tumor model, 100 µL of a 4T1 cell suspension (10⁶ cells per mouse) was subcutaneously injected into the right flank of 6 week old male BALB/c mice. When the tumor volume approached 150 mm³, the therapeutic agents were administered intravenously to the mice five times, with a 4 day interval between doses (UmFe dose = 10 mg kg⁻¹; OA dose = 0.5 mg kg⁻¹).

Laser irradiation (1 W cm⁻², 15 min) was applied 24 h after the injection. In addition to excellent antitumor efficacy, UmFe OA treatment exhibited virtually no serious toxic effects on mice and normal tissues, as evidenced by the mice’s weight chart and H&E staining of major organs.

The highest nanoparticle accumulation was observed 24–48 h after intravenous administration. Samples coated with hPM demonstrated a higher tumor targeting capability while reducing accumulation in the liver compared to liposomal NPs.

UmFe OA showed high antitumor efficacy – 74% among all therapeutic groups. This can be attributed to the synergistic enhancement of ferroptosis upon NIR treatment, compared to induction solely via the Fenton reaction. A similar trend was observed without laser irradiation, but the overall antitumour efficacy was lower due to the slower rate of the Fenton reaction.

In samples (G5) and (G6) with UmFe OA@hPM, tumor cell density was significantly lower compared to samples from other groups. These two laser treated groups also exhibited the highest level of TUNEL fluorescence.

Besides its significant antitumor efficacy, UmFe OA(+) treatment showed virtually no serious toxicity to mice and normal tissues.

The effect of PDT using UCNPs on ferroptosis was investigated in the study [40].

The authors developed a nanoplatform (ApoE UMSNs GOx/SRF) based on UMSNPs (UCNPs@mSiO₂). A layer of mesoporous silica and a lipid bilayer were sequentially deposited onto the UCNPs, with glucose oxidase (GOx) and the multikinase inhibitor sorafenib (SRF) loaded onto them, respectively. Subsequently, the apolipoprotein E (ApoE) peptide was attached.

The UCNPs used convert NIR radiation into UV light. This enables the reduction of iron ions (Fe³⁺) to Fe²⁺, which is critical for initiating ferroptosis.

The antitumor efficacy of ApoE UMSNs GOx/SRF was studied *in vivo* using an orthotopic glioma G422 model. The antitumor efficacy of ApoE UMSNs GOx/SRF was evaluated with and without NIR light treatment.

Tumor bearing mice were randomly assigned to six groups to evaluate antitumor efficacy as follows: (1) control; (2) UMSNs Gox; (3) UMSNs SRF; (4) UMSNs Gox/SRF; (5) ApoE UMSNs GOx/SRF; and (6) ApoE UMSNs GOx/SRF + NIR (doses: SRF: 20 mg/kg and GOx: 40 µg/kg; *n* = 6 per group).

The tumors were exposed to laser irradiation at 808 nm (0.5 W/cm², 5 min).

The UMSNs GOx/SRF nanoparticles demonstrated enhanced tumor growth inhibition (TGI), which may be attributed to an improved Fenton reaction induced by GOx – resulting in additional H₂O₂ production through catalysed glucose oxidation.

The use of ApoE UMSNs GOx/SRF further reduced the tumor growth rate, achieving a TGI of 90.3%, which is significantly higher than that of UMSNs GOx/SRF (81%).

The antitumor effect of ApoE UMSNs GOx/SRF was enhanced by laser irradiation at 808 nm (0.25 W/cm², 5 min) administered 6 h after ApoE UMSNs GOx/SRF injection. In this group, the TGI reached 97.2%, and glioma growth was successfully suppressed. These results indicate that light mediated Fe²⁺ regeneration induced by ApoE UMSNs GOx/SRF – combined with H₂O₂ generated by GOx – can effectively enhance the antitumor effect.

Treatment with ApoE UMSNs GOx/SRF caused a significant decrease in ferroptosis related protein (xCT) expression, from 36.5% to 16.9%. NIR irradiation further reduced xCT expression to 8.98%, which can be explained by NIR induced enhancement of ferroptosis mediated by UCNPs. These findings suggest that ApoE UMSNs GOx/SRF inhibits GBM through NIR enhanced ferroptosis.

Throughout the study, no significant body weight loss was observed. Serum biochemistry and histological analyses of major organs showed all parameters within normal ranges, indicating minimal toxicity of the developed formulations.

Study demonstrated the phototoxicity of UCNPs supplemented with flavin mononucleotide (Pharmstandart®) in PDT [41]. In tumors treated with UCNPs followed by irradiation at 975 nm, a sharp

decrease in nucleated cells was observed. Additionally, some tumor areas were filled with eosinophilic material or empty spaces devoid of cells. PDT caused vascular rupture with extensive haemorrhages in tumour tissue.

A nanohybrid combining UCNPs and metal – organic frameworks (MOFs) exhibits a unique heterogeneous structure that facilitates efficient energy transfer from UCNPs to MOFs, thereby enhancing NIR activated photodynamic therapy [42].

In the study, mice bearing HepG2 tumors were administered nanoparticles intravenously at a concentration of 4 mg/mL (100 µL). Tumors were irradiated 8 h post injection using a 980 nm laser (1.5 W cm⁻¹, 10 min total irradiation time with a 2 min break after the first 2 min of irradiation). Additional injections and treatments using the same parameters were performed every two days. After 14 days of treatment, the mice were euthanized.

Post treatment analysis revealed suppressed proliferation and apoptosis of tumor cells. The nanoparticles's ability to alleviate hypoxia in solid tumors was also confirmed. This effect is primarily attributed to the catalytic activity of the nanoparticles, which decomposed intracellular H₂O₂ and produced O₂ within the tumor microenvironment. This process enhanced the efficacy of oxygen dependent type II PDT *in vivo*.

Experiments showed that 6 h after injection, the nanoparticles distributed to all organs (brain, liver, kidneys, spleen, lungs, and tumors), with most of them detected in the kidneys, spleen, liver, and tumors. After 48 h, they were almost completely metabolised in all organs except tumor tissues. Immunohistochemical experiments revealed no significant changes in the morphology of each tissue across all treatment groups. Hematological parameters showed no noticeable differences from the control group.

Pharmacological activity has been described with intravenous administration of UCNP to animals with tumors, but safety has been described with intratracheal administration of UCNP to healthy animals. This can be explained by the fact that, along with reducing systemic toxicity, the inhalation method can cause complications directly upon administration [43, 44].

The dependence of toxicity on such parameters as particle type, PS, dose, irradiation, model and result, summarizing the reviewed articles, is presented in Table 1.

It has been shown previously that the most non-toxic concentration identified across studies is 2 mg/mL (see Part I of this Overview). For mice, the maximum permissible dose for short-term exposure (12 h) is 10 mg/kg, and for long-term exposure (120 days) is 50 mg/kg. For rats, a dose of 5 mg/kg is safe for both short- and long-term studies of dark toxicity. Dark toxicity occurs at higher doses than phototoxicity (e.g., dark: 50 mg/kg for 120 days; photo: 10 mg/kg for 40 days).

Table 1 The dependence of toxicity on such parameters as particle type, PS, dose, irradiation, model and result.

Particle type / coating	Photosensitizer (PS) / drug	Dose (mice)	Irradiation (NIR)	Model	Toxicity & efficacy result	Ref.
YOF:Yb,Tm@YOF:Yb + mesoporous silica + DEX (USDPPFs)	Dexamethasone (DEX)	5 mg/kg (intratracheal or i.v.)	980 nm, 3×10 min, 1 W/cm ²	C57BL/6 mice (lung I/R injury)	No inflammatory cell infiltration or necrosis in heart, lung, liver, spleen, kidney; NIR-triggered DEX release reduced lung I/R injury	[1]
DUCNP@Mn-MOF	FOE (evodiamine derivative)	not specified	not specified (chemodynamic + chemo)	Breast cancer mouse model	High tumor targeting, tumor suppression, no significant toxicity	[5]
NaYF ₄ :Yb,Tm + 4T1 cancer cell membrane + melittin (U ACPT@MM)	9-aminocamptothecin (ACPT)	Melittin 1 mg/kg (i.v., days 0,3,6)	808 nm, 0.8 W/cm ² , 20 min (days 2,5,8)	4T1 breast cancer	Tumor growth inhibition, lung metastasis suppression; increased TNFα/IFNγ; no organ damage (heart, liver, spleen, lung, kidney)	[6]
TiO ₂ /(Ca,Y)F ₂ :Tm,Yb (femtosecond laser treated)	none (ROS generation)	not specified	NIR (980 nm)	CFPAC-1 pancreatic tumor (nude mice)	Tumor growth inhibition (not eradication); no large-area tumor cell killing due to hypoxia	[10]
NaGdF ₄ :Yb,Nd,Tm + TCI	thiochromenocarbazole imide (TCI)	not specified	808 or 980 nm	HeLa tumor	Low dark toxicity, imaging possible, but no significant tumor growth inhibition	[9]
UCNP@Glu-DMMA (charge reversal, glucose targeting)	none (PDT via ROS)	not specified	980 nm, 0.8 W/cm ² , 15 min (30 s on/60 s off)	HeLa tumor (nude mice)	Significant tumor reduction, minimal organ damage/inflammation	[12]
NaYF ₄ :Yb,Er@PEG	Chlorin e6 (Ce6)	not specified (intratumoral)	980 nm, 0.5 W/cm ² , 30 min	4T1 breast cancer	Significant reduction in tumor growth rate	[16]
NaYF ₄ :Yb,Er@NaGdF ₄ @PEG-phospholipid	Ce6	not specified (i.v.)	980 nm, 0.6 W/cm ² , 5 min	U87MG glioblastoma	Tumor growth reduction	[17]
NaYF ₄ :Yb,Er + chitosan	Zinc phthalocyanine	not specified	980 nm, 0.4 W/cm ² , 2×15 min (3 h & 24 h post inj.)	S180 sarcoma	Slight tumor volume increase, high survival	[18]
NaYF ₄ :Yb,Er@CaF ₄ @PAA-hydrazide	5-aminolevulinic acid	not specified	980 nm, 0.5 W/cm ² , 40 min	not specified	Significant tumor size reduction	[19]

Table 1 (Cont.)

NaYF ₄ :Yb,Er@phosphatidylcholine-FA	Tetraphenylporphyrin	not specified (intratumoral)	980 nm, 1 W/cm ² , 30 min	CT26wt colon cancer	Reduced tumor growth	[20]
UCNP + branched PEI + FA	Protoporphyrin (PPIX)	not specified (i.v., 4 weeks)	not specified	Skin tumor	No organ damage (liver, heart, kidney, spleen, lung); irradiation caused severe tumor destruction	[24]
NaErF ₄ @NaLuF ₄ + macrophage membrane + mannose + SiO ₂ (PFC) + Ce6 + PTX	Ce6 + paclitaxel (PTX)	6.5 mg/kg UCNPs (0.4/0.6/0.5 mg/kg for PFC/Ce6/PTX)	808 nm, 1.5 W/cm ² , 20 min	4T1 breast cancer	Most significant tumor suppression; increased tumor O ₂ (>40% vs 19–20% controls); no toxicity reported	[25]
Hb/BSA/Ce6/Er@Lu microgels (Hb μ Gels)	Ce6	not specified (intratumoral)	808 nm	4T1 breast cancer	ROS + thermal stress (>48°C); hypoxia relief; minimal organ accumulation, no histology changes	[26]
ZnO NPs (catalase-like, upconversion)	Ce6	not specified	808 nm (ZnO-Ce6) vs 660 nm (Ce6 alone)	4T1 breast cancer	90% suppression (808 nm ZnO-Ce6) vs 80.2% (660 nm Ce6); 3/5 mice cured; hypoxia relieved	[29]
BaGdF ₅ :Yb,Tm	Doxorubicin (DOX)	10 mg/kg (i.v.)	not specified	not specified	No adverse effects; survival 40 days	[30]
NaYF ₄ :Yb,Er,Fe@PM VEMA	THPC (Foscan)	not specified (intratumoral)	980 nm, 0.5 W/cm ² , 3 min	Capan-2 pancreatic adenocarcinoma (nude mice)	Day 30 tumor volume 0.35 cm ³ ; extensive necrosis by day 1–2; no body weight loss	[32]
NaYF ₄ :Yb,Er@PEG	THPC + IR780	not specified	980 nm (0.8) + 808 nm (0.36 W/cm ²), 5 min	Glioblastoma	No toxicity without laser; effective therapy	[36]
Core-multishell UCNPs (1550/808/980 nm) + mSiO ₂ + ZnPc + RBS (NO donor)	Zn-phthalocyanine (ZnPc) + NO donor	not specified	1 W/cm ² , 20 min, various sequences	4T1 breast cancer	Sequential 980→1550 nm best suppression; no organ damage, no weight change	[37]
NaErF ₄ @NaYbF ₄ @NaYF ₄ @mSiO ₂	MC540 + FePc	not specified	1550 nm, 235 mW/cm ² , 10 min	HeLa (nude mice)	Best cell reduction with dual PS; no organ lesions	[38]
UmFe (Fe/g-C ₃ N ₄ on mesoporous UCNPs) + platelet membrane (hPM) + oleanolic acid (OA)	OA (ferroptosis)	UmFe 10 mg/kg, OA 0.5 mg/kg (i.v., 5 doses, 4-day interval)	1 W/cm ² , 15 min (24 h post inj.)	4T1 breast cancer	74% antitumor efficacy; no serious toxicity; highest TUNEL in laser groups	[39]

Table 1 (Cont.)

UCNP@mSiO ₂ + lipid bilayer + ApoE (ApoE UMSNs GOx/SRF)	Glucose oxidase (GOx) + sorafenib (SRF)	SRF 20 mg/kg, GOx 40 µg/kg	808 nm, 0.5 W/cm ² , 5 min	Orthotopic G422 glioma	TGI 97.2% (laser) vs 90.3% (no laser); reduced xCT expression; no weight loss, normal serum/organ histology	[40]
UCNPs (unspecified)	Flavin mononucleotide	not specified	975 nm	Tumor model	Sharp decrease in nucleated cells, vascular rupture, hemorrhages	[41]
UCNP + MOF (heterostructure)	none (O ₂ generation from H ₂ O ₂)	4 mg/mL, 100 mL (i.v.)	980 nm, 1.5 W/cm ² , 10 min (2 min on/2 min off), every 2 days	HepG2 tumor	Hypoxia relief; nanoparticle cleared by 48 h except tumor; no organ morphology changes	[42]

2 Conclusion

This review examined the *in vivo* phototoxicity of upconversion nanoparticles (UCNPs) in photoinduced drug delivery, photodynamic therapy (PDT), and multimodal therapies.

UCNPs activated by NIR irradiation (808/980 nm, 0.15–1.5 W/cm², 3–40 min) demonstrate targeted phototoxicity confined to tumors. No significant damage to major organs (heart, liver, spleen, lungs, kidneys) was observed across numerous studies.

The doses of UCNP in the range of 5–10 mg/kg (single or repeated administration) did not cause histological changes in internal organs and did not lead to death of animals for up to 40 days of observation. From the point of view of clinical translation, it is important to know what happens to experimental animals in the long term up to 40 days, but unfortunately, for the specified types of particles, this information was not found in the articles.

Significant tumor suppression was achieved in breast cancer, pancreatic adenocarcinoma, cervical carcinoma, glioblastoma, colorectal cancer, and others. Complete eradication occurred in some cases (e.g., ZnO-Ce6 NPs: 90% suppression, 3/5 mice cured).

Photosensitizers are safe. Ce6, THPC, ZnPc, PPIX, methylene blue, and others showed no additional systemic toxicity while enabling efficient singlet oxygen generation.

Hypoxia alleviation improves efficacy. Oxygen carriers (perfluorocarbons, hemoglobin, catalase-

mimicking ZnO) increased tumor O₂ levels (>40% vs. 19–20% controls), enhancing PDT outcomes.

Multimodal combinations are safe. UCNPs combined with chemotherapy, PTT, CDT, immunotherapy, radiotherapy, or cryotherapy showed enhanced efficacy without increased toxicity (e.g., TGI up to 97.2% in glioblastoma).

PEG, silica, PMVEMA, and cell membranes (cancer, erythrocyte, platelet, macrophage) ensured low toxicity. Charge-reversal coatings improved tumor targeting.

UCNPs cleared within 48 h to 40 days via fecal/urinary routes, with minimal long-term retention.

Studies up to 40 days showed no weight loss, behavioral changes, or organ damage at recommended doses.

The safety profile and efficacy support further development of UCNPs for deep-tissue cancer therapy and theranostics.

UCNPs exhibit low phototoxicity at established doses (mice 5–50 mg/kg). Multimodal platforms enhance efficacy without compromising safety, positioning UCNPs as promising agents for precision oncology.

Disclosures

All authors declare that there is no conflict of interests in this paper.

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