REVIEW ARTICLE

Design of Multi-Stimuli Responsive Nanocarriers for Co-delivery of Phytochemicals and Immune Modulators: A Synergistic Approach to Overcoming Tumor Resistance

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Abstract

Overcoming therapeutic resistance continues to be a major obstacle in cancer treatment, driven by intrinsic survival pathways within tumor cells and the immunosuppressive pressures exerted by the tumor microenvironment (TME). Recent advances in nanotechnology have enabled the design of multi stimuli responsive delivery system capable of releasing a therapeutic agent in a controlled and site-specific manner by exploiting characteristic tumor cues such as acidic pH, elevated reactive oxygen species, high intracellular glutathione, and dysregulated enzymatic activity. This review examines the rationale for co-delivering phytochemicals and immune-modulating agents, two classes of therapeutics that act through complementary mechanism although not always synchronized. Although phytochemicals such as curcumin, quercetin, and resveratrol possess antioxidant, anti-inflammatory, and pro-apoptotic properties, their clinical translation is limited by poor solubility, rapid metabolism, and inconsistent bioavailability, conversely immune modulators, including checkpoint inhibitors and cytokine-based therapeutics, can restore antitumor immunity but often show limited benefit in tumor with weak immunogenicity or exhausted immune cell phenotypes. Incorporating these agents into intelligent nanocarriers constructed from biodegradable polymer, for example, poly(lactic-co-glycolic acid)-poly(ethylene glycol) chitosan, inorganic matrices, for example, mesoporous silica gold nanoparticles or hybrid lipid polymer platforms provide a means of achieving synergistic therapeutic activity, although formulation complexity remains a challenge. Advanced encapsulation strategies, including co-loading within single nanoparticles layer-by-layer architectures and core-shell nanogels allows for precise coordination of drug release, enabling immune activation followed by cytotoxic or regulatory effects, but sometimes overlapping release profiles occur. Preclinical investigations of combinations such as curcumin with anti-programmed death ligand 1, resveratrol with interleukin 2 (IL-2), and quercetin with small interfering RNAs, as well as emerging approaches involving epigallocatechin gallate/IL-12 or berberine/anti-cytotoxic T lymphocyte associated antigen-4

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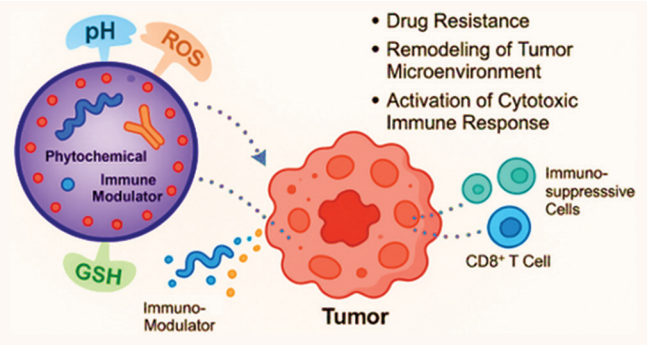
demonstrates enhanced immune cell recruitment, suppression of resistance pathway, and remodeling of the TME toward a more immunoreactive state. However, results vary between models. Collectively, these finding highlights the potential of multi-stimuli responsive nanoplatforms as a strategy to integrate phytochemical activity with immune modulation for improved antitumor efficacy, although clinical translation remains to be fully realized.

Key words: Cancer nanomedicine, co-delivery systems, immune checkpoint blockade, phytochemicals, public health, tumor microenvironment

GRAPHICAL ABSTRACT



INTRODUCTION

Cancer remains one of the most pressing public health challenges of this century. According to the latest estimates from the International Agency for Research on Cancer, approximately 20 million new cancer cases and 9.7 million deaths occurred in 2022, with lung, breast, and colorectal cancers accounting for nearly one third of the global burden. On a population scale, this translates to one in five individuals developing cancer during their lifetime, while one in nine men and one in twelve women ultimately die from the disease.[1] In addition to its human cost, the economic toll now surpasses US $ 1 trillion annually, disproportionately impacting low and middle-income nations where nearly 70% of cancer-related mortality is concentrated. Despite significant advances in surgery, radiotherapy, targeted therapeutics, and immuno-oncology, many solid tumors remain refractory to long term control, highlighting the need for alternative treatment modality and integrated therapeutic strategies.[2]

One of the primary reasons for inadequate therapeutic response is the emergence of multidrug resistance (MDR), a complex phenotype shaped by multiple molecular and cellular adaptations. These include the overexpression of ATP-binding cassette efflux transporter, activation of epithelial-mesenchymal transition programs, epigenetic alteration, acquisition of cancer stem cell traits, dysregulated DNA repair pathways, and defects in apoptotic signaling.[3] The challenge is further compounded by the tumor microenvironment (TME), a heterogeneous and immunosuppressive milieu. Hallmark features of the TME include hypoxic gradient, acidic extracellular pH, elevated reactive oxygen species (ROS) and glutathione (GSH) turnover, dense extracellular matrix architecture, and infiltration by regulatory T-cells (Tregs) myeloid-derived suppressor cells (MDSCs), and M2 polarized tumor-associated macrophages (TAMs). Together MDR mechanism and TME driven barrier impede drug penetration neutralize cytotoxic agents, and suppress effector immune response, ultimately enabling tumor persistence and relapse.[4]

Growing evidence suggests that rational drug combination is more effective than single agent approach in dismantling these layers of resistance. Of particular interest is the pairing of plant-derived phytochemicals such as curcumin, resveratrol, quercetin, or epigallocatechin gallate (EGCG) with immune modulating agent, including checkpoint inhibitors, cytokines T-cell agonist or small interfering RNAs (siRNA) that silence immunosuppressive pathway.[5] Phytochemicals exert multifaceted anticancer action, such as dampening nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription-3 signaling, restoring pro-apoptotic protein balance, and sensitizing MDR population to cytotoxic therapies. Immune modulators, in turn, restore cytotoxic T-cell function and reprogram myeloid cells within the TME; however, both therapeutic classes face major translational limitations when administered freely, including low water solubility, rapid systemic degradation off-target immune activation, and mismatched pharmacokinetic that hinder cooperative activity.[6]

To address these limitation researchers have developed multi stimuli responsive nanocarrier capable of achieving spatially and temporally controlled co-delivery of phytochemicals and immune modulators. These smart systems, constructed using biocompatible polymers (e.g., poly(lactic-co-glycolic acid)-poly(ethylene glycol) [PLGA PEGylated] polyesters), liposomes, dendrimers, or mesoporous silica, are engineered with a molecular linker or structural component that responds to tumor associated cue, such as acidic pH, heightened ROS production, elevated intracellular GSH, overexpressed matrix metalloproteinases (MMP), or externally applied mild hyperthermia.[7] Such a design establishes a highly selective Trojan horse effect; the nanocarrier remains stable in circulation, avoids premature clearance preferentially accumulates at tumor site through the enhanced permeability and retention effect or ligand-mediated targeting and subsequently release its combined payload precisely where MDR activity and immunosuppressive mechanism are most pronounced. By synchronizing the pharmacodynamics of

both agents at the tumor site, these nanoplatform enhance therapeutic synergy, minimise systemic toxicity, and have demonstrated superior tumor regression, reversal of drug resistance, and durable immune memory in preclinical model when compare with single stimulus systems or monotherapies.[8]

Against this background, the present review survey the emerging landscape of multi-stimuli responsive nanocarrier technology designed for the co-delivery of phytochemicals and immune-modulating agents. We discuss material engineering, principal linker and trigger chemistries, encapsulation strategies, and mechanistic insight into how these constructs remodel the TME, overcome MDR, and augment anti-tumor immunity. Key translational challenge including scaling up manufacturing, ensuring batch reproducibility, managing pharmacokinetic complexity, and navigating regulatory pathway are also examined. Finally, we outline future research direction such as artificial intelligence-supported formulation design, that may accelerate the development of safer, more effective, and ultimately personalized nanomedicine-based cancer therapies.

RATIONALE FOR COMBINATION THERAPY

Phytochemicals as anti-cancer agents

Naturally derived polyphenols, including curcumin resveratrol, EGCG, and quercetin have been widely studied for their broad-spectrum anticancer potential. These compounds influence multiple cellular processes, such as promoting apoptotic signaling, inhibiting angiogenesis, and modulating key regulatory pathway including NF-κB and PI3K/Akt. Their capacity to counteract oxidative stress further contributes to their anticancer activity, as they can neutralize reactive species and regulate redox-sensitive signaling network.

Despite these favorable pharmacological attributes, the clinical translation of these polyphenols remains limited and inconsistent. Their therapeutic effectiveness is hindered by several biopharmaceutical challenges, notably poor water solubility, low and variable systemic bioavailability, chemical instability under physiological condition and rapid metabolic conversion, all of which significantly restrict their efficacy *in vivo*.[9-11]

Immune modulators in cancer therapy

Immune modulation has reshaped modern cancer therapy by enabling the host immune system to more effectively recognize and eliminate malignant cell. A major breakthrough in this field has been the development of immune checkpoint inhibitor (ICIs), which target key inhibitory receptor such as programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). These checkpoints are frequently exploited by tumor or cells within the TME to dampen immune activity and promote immune escape. Blocking these pathways with ICIs helps to restore T-cell effector function reestablish cytotoxic response, and support durable antitumor immunity.[12,13]

Beyond checkpoint inhibition, cytokine-based therapies represent another cornerstone of immune modulation. Agents such as interleukin 2 (IL-2) and interferon gamma (IFN-γ) have been used clinically to stimulate the activation, proliferation, and survival of various immune cell population. IL-2 promotes the expansion of cytotoxic T lymphocytes and natural killer (NK) cells while IFN-γ enhances antigen presentation modulate the tumor microenvironment (TME), and exert direct antiproliferative effect on tumor cell. Despite their therapeutic value, the efficacy of cytokine therapies is often constrained by systemic toxicity and the complex regulatory network that govern immune activation.

A persistent challenge for both ICIs and cytokine therapies is the immunosuppressive TME, which can significantly limit treatment response. The TME frequently contain elevated number of Tregs TAMs, and MDSCs, all of which suppress effective antitumor immune surveillance. Tumor with a low mutational burden or lacking major histocompatibility complex expression further complicates immune recognition by reducing the visibility of tumor antigen. These features contribute to primary or acquired resistance and underline the need for combination strategies that can both modulate immunity and remodel the TME.[13,14]

Synergistic potential of co-delivery

The combined delivery of phytochemicals and immune-modulating agents through nanocarrier platform offers a strategic therapeutic advantage by addressing both the cellular and immunological barriers that limit anticancer efficacy. Beyond their well-recognized antioxidant and cytotoxic properties many phytochemicals exert important immunomodulatory effect within the TME. These compounds have been shown to enhance tumor antigen expression influence immune checkpoint regulation and diminish the prevalence of immunosuppressive populations such as Tregs and MDSCs. By reshaping the TME toward a more immune-responsive milieu, phytochemicals can help establish the condition needed for immune-based therapies to be more effective.

Immune modulators including cytokines and checkpoint inhibitor often require a supportive immune environment to function optimally; however, their therapeutic benefit is frequently limited by poor vascularization dense stromal barrier and the diverse immune escape mechanism characteristic of many tumor.[15,16] Phytochemicals can help

counter these obstacles by enhancing antigen presentation and reversing local immune tolerance, thereby priming the tumor for immunotherapy. Encapsulating both classes of agents within a single nanocarrier system, particularly one engineered to respond to tumor-associated stimuli such as acidic pH, elevated reductive potential, or aberrant enzyme activity, allows for coordinated and controlled drug release at the tumor site.

Such nanocarriers enable simultaneous or sequential release of the encapsulated agent, depending on the desired therapeutic design, thereby improving pharmacokinetic performance and reducing systemic toxicity. Importantly, incorporation into a nanocarrier enhances the stability and bioavailability of phytochemicals, many of which otherwise exhibit poor solubility and rapid metabolic degradation. The dual action therapeutic effect achieved through this co-delivery direct tumor cell targeting by phytochemicals combined with immune activation mediated by modulators addresses both the intrinsic resistance mechanism of cancer cell and the extrinsic immunosuppressive feature of the TME. This integrated approach provides a multifaceted strategy for improving treatment outcome and overcoming therapeutic resistance in solid tumor.[16]

TME: A STRATEGIC TARGET FOR STIMULI-RESPONSIVE DRUG DELIVERY

TME is characterized by a set of abnormal physicochemical condition that differ markedly from those of normal tissue making it an attractive target for stimuli responsive therapeutic system. One of the most prominent features of the TME is its mildly acidic extracellular pH, typically around 6. 5 which results from heightened glycolytic activity and insufficient vascular perfusion. This acidification not only facilitate local invasion and metastatic spread but also provide a dependable trigger for pH sensitive linker incorporated into smart nanocarriers.

Another defining characteristic of the TME is its elevated concentration of ROS driven by mitochondrial dysfunction oncogenic signaling and chronic inflammation. These ROS rich environment can activate oxidation responsive chemical motif such as thioketal or boronic ester linker allowing for selective drug release within tumor tissue. In parallel tumor cells maintain substantially higher intracellular GSH level then their healthy counterpart typically in the millimolar range. This reductive environment can be exploited by incorporating disulfide or diselenide bond into nanocarriers enabling rapid cleavage and payload release once internalized by cancer cell.

In addition to pH and redox gradient the TME feature abundant proteolytic enzyme including MMPs and cathepsins that participate in extracellular matrix remodeling. Embedding MMP or cathepsin cleavable peptide sequence within the structural component of delivery platform allow enzyme triggered activation and enhance tissue penetration.[17,18]

Beyond these physicochemical cues the TME also contain immunosuppressive cellular population notably Tregs and TAMs, which suppress cytotoxic immune response and contribute to tumor maintenance. Modern multi stimuli responsive nanoplatform are therefore being engineered not only to trigger drug release in response to the TME s unique biochemical feature but also to modulate or deplete these immunoregulatory cell population. By simultaneously disrupting tumor promoting stroma and enhancing antitumor immunity these systems aim to dismantle several layer of tumor defense and improve therapeutic effectiveness.[19,20]

MULTI-STIMULI RESPONSIVE NANOCARRIERS: DESIGN PRINCIPLES

The development of multi stimuli responsive nanocarriers is grounded in the ability to exploit defining physicochemical feature of TME. These platforms are engineered to react selectively to internal cue such as acidic pH heightened ROS elevated intracellular GSH and tumor associated enzymatic activity thereby enabling controlled and localized release of therapeutic agent. Among these trigger pH alterations are one of the most widely used. Tumor tissue and intracellular compartment such as endosomes and lysosomes typically exhibit mildly acidic condition (pH ~ 6.5) which can be leveraged through acid labile linker (e.g., hydrazone bond) or pH responsive polymer like poly (histidine). An illustrative example is the incorporation of pH cleavable linker into PLGA PEG conjugate (PLGA pH PEG) allowing stable circulation at physiological pH while facilitating rapid drug release in acidic tumor site.[7,21]

Nanocarriers designed to respond to oxidative stress capitalize on the elevated ROS concentration characteristic of many cancers cell. These systems often incorporate a thioketal bond or other peroxide-sensitive motif that undergoes cleavage in the presence of ROS, enabling targeted and timely release of the payload. For instance, PLGA particles containing a thioketal-based ROS-sensitive core have been employed to enhance intracellular delivery of curcumin, leading to improved anticancer activity in ROS rich setting. Redox-responsive nanocarriers further exploit the substantial difference in GSH concentration between tumor cells and healthy tissue. Disulfide linkage is commonly used in these constructs as they are readily cleaved by intracellular GSH, offering a reliable mechanism for site-specific release. Lipid PEG architecture incorporating GSH labile disulfide bond exemplify this redox-triggered delivery strategy.

Enzyme-responsive nanocarriers provide an additional layer of specificity by incorporating peptide linker that are selectively degraded by tumor overexpressed enzyme. MMPs, which are abundant in the invasive margin of many

solid tumors, are frequently targeted for this purpose. Nanocarrier system integrating MMP-sensitive peptide spacer, such as MMP PEG PLGA construct remain stable during systemic circulation but release their therapeutic cargo upon encountering the enzymatically active TME. These platforms, summarized in [Table 1], highlight how biomimetic and stimulus-reactive design principles can be integrated to achieve precise spatiotemporal drug release.[22,23]

Materials employed in stimuli-responsive nanocarrier construction

The development of stimuli-responsive nanocarriers relies on a broad range of organic, inorganic, and hybrid material each selected for its ability to react to specific physiological or pathological trigger within the TME. Among organic material, biodegradable polymers such as PLGA, polylactic acid, and polycaprolactone are widely utilized due to their predictable degradation profile and compatibility with both hydrophilic and hydrophobic therapeutic. PEG is frequently introduced into this system to enhance aqueous solubility, prolong circulation time, and reduce immune recognition through its stealth-like behaviour. Natural polymers, including chitosan, alginate, dextran, and gelatin, further contribute to responsive nanocarrier design by offering intrinsic pH sensitivity, mucoadhesive property, and excellent biocompatibility, making them particularly suitable for drug release in the acidic tumor milieu.[24,25]

Inorganic material provides additional structural and functional benefits for nanocarrier construction. Mesoporous silica nanoparticle, gold nanoparticles, superparamagnetic iron oxide nanoparticles, and zinc oxide nanostructures offer tunable surface chemistry, mechanical robustness, and the capacity to respond to external stimulus such as light heat or magnetic field. Many of these inorganic platforms can also generate ROS enabling a therapeutic strategy that leverages oxidative stress. Dendrimers highly branched macromolecule with controllable architecture permits multivalent functionalization, precise drug conjugation, and the incorporation of targeting moiety. Lipid-based material, including liposomes and solid lipid nanoparticles remain versatile carrier due to their biocompatibility and ability to encapsulate a wide spectrum of bioactive compound.

To improve specificity and enhance uptake, malignant cell nanocarriers are often engineered with surface ligands such as folate, transferrin, RGD peptide aptamers, or a monoclonal antibody that binds preferentially to receptors overexpressed in tumor. The integration of this material into intelligently designed stimuli responsive system allows for controlled trigger-dependent drug release, improved intratumoral accumulation, and reduced systemic toxicity. Collectively, these material platforms create an opportunity for more precise and personalized therapeutic intervention in oncology.[26,27]

DUAL-AGENT ENCAPSULATION AND CONTROLLED SEQUENTIAL RELEASE

The development of a nanocarrier capable of co-delivering phytochemicals alongside immune modulating agent has become an important direction in modern cancer nanomedicine. Achieving this require carrier architecture that protects each therapeutic component while enabling precise sequential release at the tumor site. One widely used strategy is the single particle co-loading approach in which amphiphilic block copolymers self-assemble into a nanoparticle with a hydrophobic core and hydrophilic outer layer. Lipophilic phytochemicals such as curcumin or quercetin tend to localize within the hydrophobic interior, whereas hydrophilic macromolecule including cytokines, nucleic acid or checkpoint inhibitor may be incorporated through electrostatic interaction or conjugated to the nanoparticle surface. This structural organization improves solubility enhance colloidal stability, and reduces premature clearance by the mononuclear phagocyte system, prolonging systemic circulation and improving tumor accumulation.[28,29]

To achieve ordered stimuli-responsive release, researchers increasingly employ layer-by-layer assembly, which enables the construction of a nanoscale multilayer through sequential deposition of oppositely charged polymer, protein, or inorganic sheet. Each layer can be engineered with cleavable linkage such as pH-sensitive hydrazone, ROS-responsive

Table 1: Summary of stimuli-responsive nanocarrier systems for targeted drug delivery

Stimulus	Responsive moiety	Mechanism of action	Representative example
pH	Poly (histidine), hydrazone linkage	Acidic pH-triggered bond cleavage	PLGA-pH-PEG system
ROS	Thioketal-containing linkers	Oxidative cleavage in ROS-rich environment	ROS-sensitive PLGA–curcumin nanocarrier
GSH	Disulfide bonds	Reductive cleavage in glutathione-rich cytosol	Lipid-PEG conjugates with GSH-labile linkers
Enzyme	Matrix metalloproteinase-cleavable peptides	Enzymatic degradation at tumor site	MMP-sensitive PEG–PLGA platform

ROS: Reactive oxygen species, GSH: Glutathione, PLGA PEG: poly (lactic-co-glycolic acid)-poly (ethylene glycol), MMP: Matrix metalloproteinases

thioketal group, or MMP cleavable peptide. These features ensure that the outer layer disassembles first in the TME, allowing early liberation of immune modulator that activate or reshape the immune milieu. Subsequent breakdown of the deeper layer then releases the phytochemical agent, enabling a therapeutic sequence in which immune activation precedes cytotoxic or antioxidant action.

Additional versatility is offered by core-shell nanogels and lipid polymer hybrid nanoparticle which integrate the high drug loading capacity and mechanical stability of polymeric matrices with the biomimetic property of lipid coating. In this system, the polymeric core can be tailored to swell or degrade in response to redox change or enzymatic activity within the tumor, whereas the lipid shell enhances cellular uptake facilitate membrane fusion, and can improve endosomal escape. This dual structure design provides orthogonal control over release kinetics and enhances the likelihood of both payloads reaching their intended intracellular target.[30]

Together, these advanced encapsulation platforms provide a flexible toolkit for engineering co-delivery system that synchronizes immune priming with subsequent phytochemical-mediated cytotoxic or regulatory effect. Such coordinated release profile enhances therapeutic synergy reduce systemic toxicity, and supports the development of more precise and effective combination therapies in oncology [Figure 1 and Table 2].

THERAPEUTIC OUTCOMES: EVIDENCE FROM PRECLINICAL INVESTIGATIONS

Preclinical studies have increasingly demonstrated that co-delivering phytochemicals and immune modulators through multi-stimuli responsive nanocarriers can produce notable therapeutic benefit in cancer models. By harnessing tumor-specific physiological cue these engineered systems achieve localized and controlled release of its cargo, thereby enhance antitumor activity while limiting the systemic exposure. Such a nanocarrier not only improves drug accumulation within the tumor but also help reversing MDR and alleviate the immunosuppressive feature of the TME, both of which commonly hinder therapeutic efficacies. Evidence from a recent experimental study illustrates how these integrate delivery platform can potentiate immune activation, amplify the cytotoxic response, and promote more durable tumor regression.[31,32]

Curcumin and anti-PD-L1 antibody in dual pH/ROS-responsive nanocarriers

Dual-responsive nanocarriers, engineered to react to both acidic pH and elevated ROS levels, have shown considerable promise for co-delivery of curcumin and anti-PD-L1 antibodies in preclinical tumor models. In murine studies, the encapsulated formulation enables controlled release of both agents specifically within the chemically distinct TME, where acidity and oxidative stress are markedly elevated. This targeted delivery enhanced the accumulation of cytotoxic $CD8^+$ T-cells within tumor tissue, mitigated PD-L1–mediated immune suppression, and produces a pronounced reduction in tumor burden. The coordinated modulation of oxidative stress by curcumin and the immune restorative effects of PD-L1 blockade contribute to the synergistic therapeutic outcomes observed in these models.[33,34]

Resveratrol and IL-2 co-delivery for immune activation

The combined delivery of resveratrol a polyphenolic molecule known for its immunoregulatory and anti-inflammatory properties, with the cytokine IL-2 has shown notable potential in enhancing antitumor immunity. When encapsulated within biodegradable, nanocarriers, this dual agent strategy has demonstrated the ability to reshape the TME and restore functional activity in exhausted T-cell populations. Preclinical studies report significant reductions in tumor burden following co-administration, attributable to the synergistic enhancement of both innate and adaptive immune response. Through coordinated modulation of immune cell activation and cytokine signaling, resveratrol and IL-2 co-delivery represent a promising therapeutic approach for strengthening antitumor immune surveillance and improving treatment outcomes in resistant malignancies.[35]

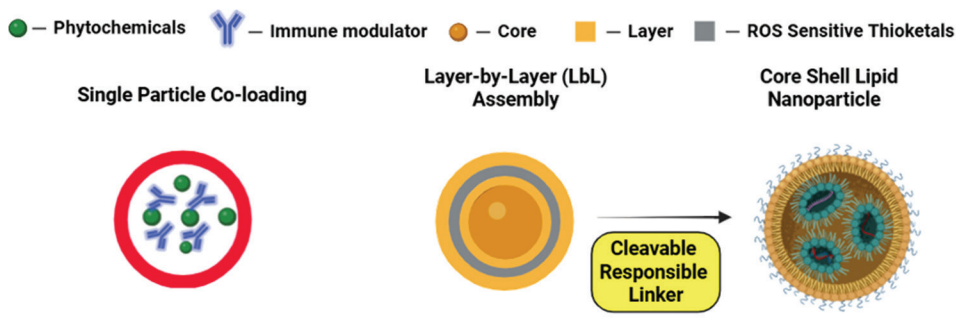


Figure 1: The advanced strategies for dual-agent encapsulation and controlled sequential release in cancer nanomedicine

Table 2: Comparative overview of encapsulation architectures for co-delivery of phytochemicals and immune modulators

Encapsulation architecture	Structural features	Typical payload distribution	Stimuli/release profile	Representative materials	Principal advantages
Single–particle–coloading	Core–shell nanoparticle (hydrophobic core, hydrophilic corona)	Hydrophobic core → phytochemicals; hydrophilic shell/surface → immune modulators	Simultaneous or mildly staggered; pH– or redox–triggered	PLGA–PEG, lipid–polymer hybrids, amphiphilic block copolymers	High drug loading; simple design; prolonged circulation
Layer–by–layer assembly	Multilayer film of oppositely charged materials or biomolecules	Outer layers → immune agents; inner layers → phytochemicals	Sequential, stimuli-sensitive (e.g., pH, ROS, enzymes)	Chitosan–alginate, PEI–PSS, polypeptides, mesoporous silica core	Programmable release; high structural tunability
Core–shell nanogels/lipid–polymer hybrids	Polymeric or hydrogel core with lipid or amphiphilic outer layer	Core → phytochemicals; shell or surface → immune modulators	Dual-release profiles (enzyme, GSH, temperature)	PEGylated nanogels, cholesterol–PLGA, dendrimer–liposome hybrids	Tunable degradation; improved membrane fusion and endosomal escape
Polyelectrolyte complex nanoparticles	Electrostatic complexes formed between cationic and anionic components	Co-loaded or separated within electrostatic domains	pH-sensitive or ionic strength-triggered disassembly	Chitosan–dextran sulfate, alginate–gelatin systems	Mild fabrication; good for sensitive biomolecules like siRNA/cytokines
Micelle-in-microparticle systems	Nanoscale micelles encapsulated within a microparticle matrix	Inner micelles → hydrophobic drugs; matrix → hydrophilic/immunological agents	Dual-release based on inner/outer matrix degradation	PEG–PLA micelles inside PLGA microparticles	Long-term release; depot effect; enhanced stability of fragile drugs

PLGA-PEG: Poly (lactic-co-glycolic acid)-poly (ethylene glycol), PEI: Polyethylenimine, PSS: Poly (sodium-4-styrenesulfonate, ROS: Reactive oxygen species, GSH: Glutathione

Quercetin and siRNA encapsulation in GSH-responsive nanogels

Nanogel platforms, engineered to co-deliver quercetin alongside siRNA directed against drug resistance-associated genes, have demonstrated considerable promise in addressing MDR in cancer therapy. These systems are typically constructed using polymeric networks stabilized by disulfide bonds, which remain intact under extracellular conditions but undergo rapid cleavage within the reductive intracellular milieu characterized by elevated GSH concentration. This redox-sensitive design enables selective nanogel disassembly following cellular internalization, ensuring efficient cytosolic release of both quercetin and siRNA.

Functionally, the coordinated delivery of quercetin and gene silencing agents results in simultaneous modulation of multiple resistance mechanisms. Quercetin contributes to oxidative stress induction and apoptotic signaling, while siRNA-mediated knockdown of MDR-related targets suppresses efflux transporter expression and survival pathways. In preclinical tumor models, including xenograft systems such as GSH-responsive nanogels, have been shown to significantly enhance apoptotic cell death, reduce expression of resistance-associated genes, and suppress tumor growth when compared with single-agent formulations.[36,37]

Additional synergistic formulations: Recent advances

Recent progress in nanotechnology has expanded the range of synergistic phytochemical – immune modulator combinations, designed for precision cancer therapy. These formulations are engineered to respond selectively to tumor-associated stimuli, including pH gradients, elevated ROS redox imbalances, and aberrant enzyme activity, thereby enabling spatially and temporally controlled drug release within the TME. By aligning therapeutic activation with tumor-specific physicochemical cues, these systems enhance antitumor efficacy while limiting off-target toxicity.

Among emerging strategies, the co-delivery of EGCG with IL-12 using enzyme-degradable lipid-based carriers has demonstrated robust immune activation in preclinical melanoma models. This approach markedly increased NK cell recruitment and activity, leading to significant tumor regression. In a complementary example, berberine, an alkaloid with established anti-inflammatory and anticancer properties, has been incorporated alongside anti-CTLA-4 antibodies within pH-responsive hydrogel platforms. This formulation enabled sustained immune checkpoint inhibition and effectively reduced metastatic spread in lung cancer models.[38,39]

Table 3: Preclinical evaluation of multi-stimuli responsive nanocarriers co-delivering phytochemicals and immune modulators: formulation strategies and therapeutic outcomes

Formulation	Stimuli–responsive platform	Principal immunologic/antitumor outcomes
EGCG+IL–12	Enzyme–cleavable lipid nanoparticles	Enhanced NK–cell activation and tumor regression in melanoma
Berberine+Anti–CTLA–4	pH–sensitive hydrogel depot	Sustained checkpoint blockade; reduced metastatic burden in lung–cancer models
Myricetin+mRNA Vaccine	Redox–responsive dendrimers	Potent –Tcell priming and durable immune memory in hepatocellular carcinoma
Silibinin+Anti–PD–1	Dual pH/ROS–labile lipid–polysaccharide vesicles	Heightened $CD8^+$ infiltration and complete tumor remission in colorectal carcinoma
Luteolin+OX40 Agonist	MMP–degradable polymeric micelles	Increased effector/memory T–cell ratios and prolonged survival in orthotopic breast tumors
Baicalein+TLR7/8 Agonist (R848)	GSH–responsive PEG–PLA micelles	M1–polarized macrophage shift, amplified IFN–γ production, and tumor growth delay in pancreatic cancer
Pterostilbene+IL–15 Superagonist (ALT–803)	Redox–sensitive lipid–polymer hybrid NPs	Robust NK–cell expansion and significant metastatic suppression in osteosarcoma

EGCG: Epigallocatechin gallate, IL-2: Interleukin 2, CTLA-4: Cytotoxic T lymphocyte associated antigen 4, PD-1: Programmed death-1, ROS: Reactive oxygen species, MMP: Matrix metalloproteinases, GSH: Glutathione, PEG: Poly (ethylene glycol), IFN-γ: Interferon gamma, NK: Natural killer, NPs: Nanoparticles

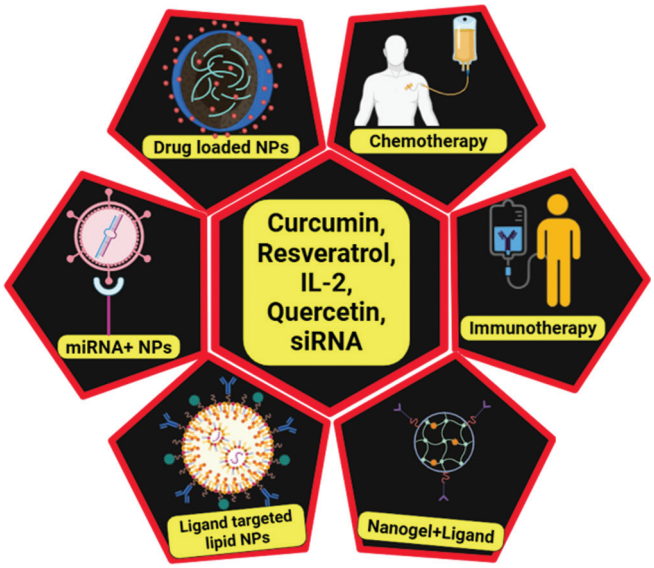


Figure 2: Strategic integration of phytochemicals and immunomodulators in multifunctional nanocarrier platforms for advanced cancer therapy

More advanced platforms have also been shown to induce durable antitumor immunity. A notable example involves the co-delivery of myricetin with mRNA-based vaccines using redox-responsive dendrimeric nanocarriers. This system enhanced cytotoxic T lymphocyte activation and conferred long-term protection against tumor rechallenge in hepatocellular carcinoma models. Additional combinations, including silibinin with anti-PD-1 antibodies, luteolin paired with an OX40 agonist, and baicalein co-delivered with the TLR7/8 agonist R848, highlight the versatility of dual delivery platforms in modulating both innate and adaptive immune responses. These formulations operate through diverse mechanisms such as repolarization of tumor-associated macrophages, amplification of effector T-cell expansion, and restoration of immune memory balance.

Collectively, these studies illustrate how stimulus-responsive nanocarriers can be tailored to the biological context of specific tumor types, enabling precise immune modulation and enhanced therapeutic synergy. Such strategies represent an important step toward the rational design of combination nanomedicines capable of overcoming immune suppression and improving long-term treatment outcomes in cancer[40,41] [Figure 2 and Table 3].

CONCLUSION

The coordinated delivery of phytochemicals and immune-modulating agents using multi-stimuli responsive nanocarriers represents an emerging and versatile strategy for addressing therapeutic resistance in cancer. By exploiting distinct features of the TME, such as altered redox balance, pH gradients, and enzymatic activity, these advanced nanoplatforms enable controlled and site-specific drug release, allowing immune activation to precede or coincide with tumor-directed cytotoxic effects. The incorporation of biodegradable polymers and hybrid nanostructures has consistently improved drug stability bioavailability, and intratumoral accumulation while also enhancing immune cell recruitment and functional activation in preclinical cancer models.

Beyond improving the performance of individual agents, this combinatorial approach offers a framework for integrating immune modulation with natural bioactive compounds in a manner that aligns with tumor heterogeneity and patient-specific biology. The ability to fine-tune release kinetics and therapeutic sequencing provides a level of control

that is difficult to achieve with conventional formulations. While further optimization and clinical validation are required, the accumulating evidence suggests that multi–stimuli–responsive nanocarriers may play a pivotal role in the future of precision oncology, particularly for tumors that show limited responsiveness to single-agent therapies.

DATA AVAILABILITY

Data will be made available on request.

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