

# EGCG-Building Nanocarriers for Multitasking Drug Delivery: Design Principles, Therapeutic Opportunities, and Translational Challenges

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**Abstract:** Recent advances in nanotechnology for drug delivery have enabled improved pharmacokinetics, controlled drug release, and enhanced tissue targeting. However, the clinical impact of many nanocarrier systems remains limited because most carriers exhibit typically low drug loading, resulting in modest therapeutic benefit and concerns related to excipient burden. Conventional nanocarriers are often composed predominantly of pharmacologically inert materials, requiring large carrier doses that may contribute to immune-related effects, undesired tissue accumulation, and manufacturing complexity. Moreover, the traditional drug loading–stability trade-off has long constrained nanocarrier design. These limitations have stimulated increasing interest in therapeutically active carriers, in which the carrier itself contributes to therapeutic efficacy. (–)-Epigallocatechin-3-gallate (EGCG), the major catechin found in green tea, has emerged as a promising molecular building block for such systems. EGCG possesses intrinsic biological activities such as antioxidant, anti-inflammatory, anticancer, and drug resistance-modulating effects. In addition, the polyphenolic structure of EGCG enables diverse molecular interactions, including hydrophobic interaction,  $\pi$ – $\pi$  stacking, hydrogen bonding, metal coordination, and dynamic boronate–catechol bonding, allowing EGCG to associate with a wide range of therapeutic agents and promote nanoscale assembly in aqueous environments. Through these combined physicochemical and pharmacological properties, EGCG-building nanocarriers integrate structural and therapeutic functions within a single platform. Such systems can achieve relatively high drug loading, reduce reliance on inert excipients, and promote combinational therapeutic effects between carrier and payload, including the modulation of drug resistance pathways. EGCG-building nanocarriers can be constructed either through direct assembly with therapeutic agents or through chemical modification that programs EGCG into hierarchically organized nanostructures. This review provides an up-to-date overview of EGCG-building nanocarriers, highlighting their design principles, nanocarrier architectures, functional advantages, predominantly preclinical and cancer-focused applications, and key challenges for clinical translation.

**Keywords:** EGCG, nanocarriers, drug delivery, pharmacoactive nanocarriers, polyphenols, synergistic therapy

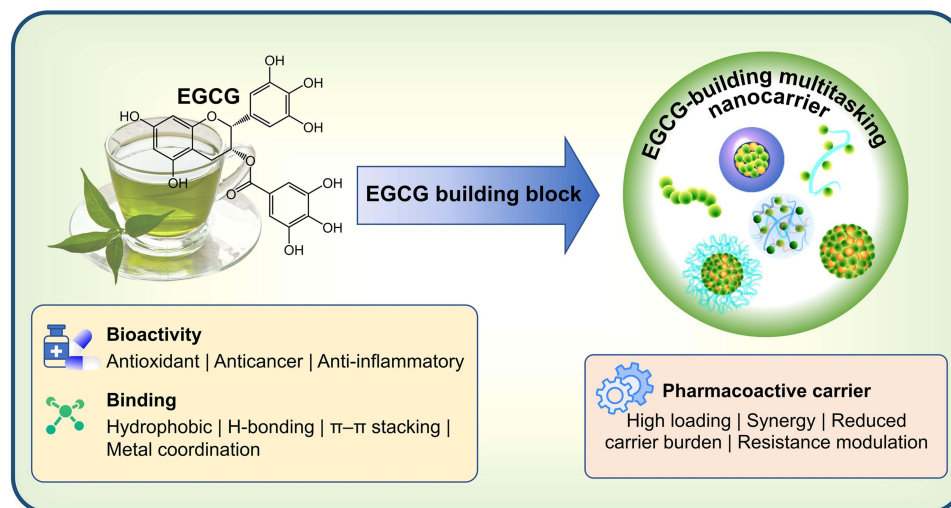
## Introduction

Nanocarrier-based drug delivery systems (DDS) have become a central strategy in modern pharmaceutical development, offering opportunities to improve pharmacokinetics, tissue targeting, and therapeutic indices for a wide range of therapeutic modalities. Liposomes, polymeric micelles, polymeric nanoparticles (NPs), inorganic nanomaterials, and hybrid systems have been extensively investigated and, in several cases, successfully translated into clinical products.<sup>1–3</sup> These platforms can enhance drug solubility, prolong systemic circulation, modulate release kinetics, and reduce off-target toxicity. Nevertheless, despite decades of progress in nanotechnology and materials engineering, the clinical advantages of many nanoformulations over free drugs remain modest and often insufficient to produce transformative therapeutic outcomes.<sup>4,5</sup>

One of the most persistent formulation challenges in DDS is the drug loading dilemma. In many conventional nanocarrier systems, the drug loading is typically around 10% (w/w), meaning that a substantial proportion of the administered dose consists of pharmacologically inactive carrier materials.<sup>6</sup> These materials may induce immune-related



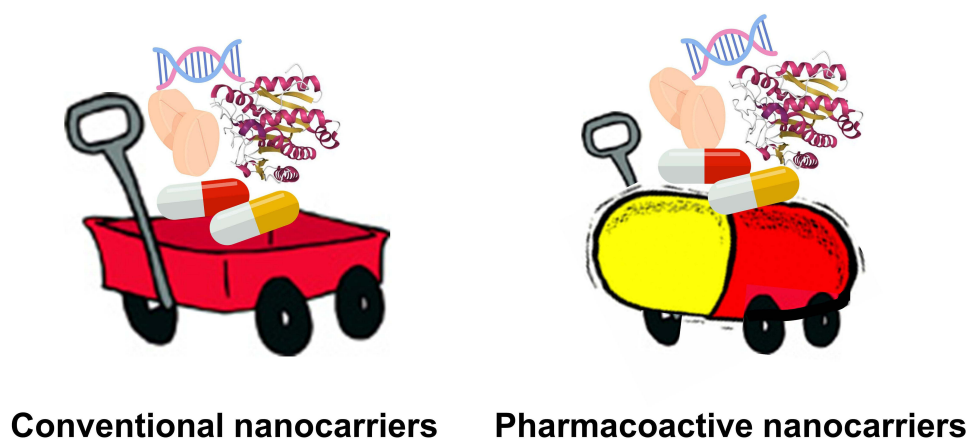
## Graphical Abstract



effects, including complement activation and accelerated blood clearance (ABC phenomenon), as well as accumulation in reticuloendothelial organs such as the liver and spleen under repeated administration.<sup>7,8</sup> In addition, a high excipient burden complicates manufacturing scalability and regulatory evaluation. Despite extensive efforts, achieving high drug loading while maintaining robust colloidal stability and controlled release remains a major design challenge because of the traditional drug loading–stability trade-off that limits nanocarrier development. Accordingly, there is growing interest in streamlined carrier systems that minimize inert carrier components while preserving structural stability and therapeutic efficacy.<sup>9</sup>

In this context, pharmacoactive carrier systems have attracted increasing attention. In these systems, structural components of the nanocarrier contribute pharmacological activity rather than serving solely as pharmacologically inert excipients, thereby integrating structural and pharmacological functions within a single platform.<sup>9</sup> This design strategy can reduce excipient burden and may also promote synergistic effects between the carrier and the payload. Importantly, because the carrier itself contributes pharmacological activity, efficacy does not rely solely on maximizing drug loading, in contrast to conventional nanomedicines that primarily depend on high drug content. As a result, pharmacoactive carrier systems offer the possibility of simultaneously achieving structural stability, reduced inert carrier burden, and improved therapeutic outcomes (Figure 1).

Bioactive molecules capable of forming multiple noncovalent interactions with therapeutic agents, such as polyphenols (eg, tannic acid (TA) and curcumin) and other aromatic bioactive compounds, have attracted attention as promising building blocks for pharmacoactive nanocarriers. Among them, (–)-epigallocatechin-3-gallate (EGCG), the predominant catechin in green tea, has emerged as a particularly attractive candidate. EGCG possesses a polyphenolic structure containing multiple catechol and galloyl moieties that confer versatile intermolecular interaction capabilities, including hydrogen bonding,  $\pi$ - $\pi$  stacking, hydrophobic interactions, metal coordination, and dynamic boronate–catechol bonding.<sup>10</sup> These interactions enable EGCG to bind diverse therapeutic agents, including hydrophobic small molecule drugs, proteins, peptides, and nucleic acids and promote spontaneous nanoscale assembly in aqueous environments.<sup>11,12</sup> From a formulation perspective, several reported EGCG-based assemblies exhibit relatively high drug loading, often exceeding 30% (w/w) and in some cases reaching markedly higher levels depending on the strength of interactions between EGCG and the drug, as well as the assembly strategy. These values are generally higher than those typically reported for conventional liposomal or polymeric nanocarriers.



**Figure 1** Conventional nanocarriers and pharmacoactive nanocarriers. Conventional nanocarriers are generally composed of pharmacologically inert carrier components and may be limited by low drug loading, high excipient burden, carrier-associated toxicity or immunogenicity, and a drug loading–stability trade-off. In contrast, pharmacoactive nanocarriers contain carrier components with intrinsic therapeutic activity, which can contribute to enhanced efficacy through drug–carrier synergy, reduced inert excipient burden, and less dependence on high drug loading or strict drug-to-carrier ratio optimization.

TA, curcumin, and other aromatic polyphenols can participate in supramolecular assembly through hydrogen bonding, hydrophobic interactions,  $\pi$ – $\pi$  stacking, and metal coordination, and some carrier-free or drug-rich systems can achieve high drug loading by minimizing inactive carrier components.<sup>13</sup> However, these platforms differ substantially in their molecular properties and formulation behavior. Curcumin-based systems benefit from intrinsic anticancer and anti-inflammatory activity but are often limited by poor aqueous solubility, crystallization tendency, and formulation-dependent dose-related toxicity concerns.<sup>14</sup> TA provides strong multivalent binding and metal–phenolic network formation, but its high molecular weight and broad binding capacity can lead to nonspecific interactions.<sup>15</sup> EGCG is distinguished by its relatively small molecular size, water compatibility, catechol/galloyl-rich structure, and ability to combine drug binding with antioxidant, anti-inflammatory, anticancer, and resistance-modulating activities. These features provide a rationale for considering EGCG as a versatile pharmacoactive building block for nanocarrier construction.

Beyond its formulation utility, EGCG has been extensively investigated as a bioactive molecule for diverse pathological conditions, including cancer, inflammatory diseases, metabolic disorders, cardiovascular injury, neurodegenerative diseases, and tissue damage associated with oxidative stress.<sup>16–19</sup> Its therapeutic activities are associated with modulation of oxidative stress, inflammatory signaling, apoptosis, angiogenesis, and epithelial–mesenchymal transition (EMT) through scavenging of reactive oxygen species (ROS) and binding to biological molecules. EGCG has also been reported to modulate drug resistance mechanisms, increase intracellular drug accumulation in resistant cells, and mitigate drug-induced toxicity through bioactive pathways of EGCG when co-administered with drugs.<sup>20</sup> These pleiotropic biological effects make EGCG attractive as a therapeutic agent.

However, the direct therapeutic application of free EGCG remains limited by poor chemical stability, rapid oxidation, extensive metabolism, limited systemic bioavailability, and possible dose-dependent toxicity at high systemic exposure.<sup>21,22</sup> In addition, nonspecific interactions of EGCG with proteins, nucleic acids, transporters, and drug molecules may alter pharmacokinetics or reduce therapeutic activity when EGCG is simply co-administered with drugs. These limitations provide a strong rationale for engineering EGCG into nanocarrier architectures, where its interaction capacity can be directed toward drug binding, structural stabilization, and controlled release. Moreover, when incorporated as a pharmacoactive carrier component, EGCG can cooperate with encapsulated therapeutic agents through its inherent biological activities, promoting therapeutic synergy, thereby enabling it to serve dual roles as both a structural binder and a pharmacologically active component. Collectively, these properties distinguish EGCG-building nanocarriers from conventional inert-carrier systems and highlight their potential as pharmacoactive nanocarrier platforms.

A growing number of studies have incorporated EGCG into drug delivery platforms; however, the functional roles of EGCG in these systems are often heterogeneous and conceptually underdefined. In some formulations, EGCG acts

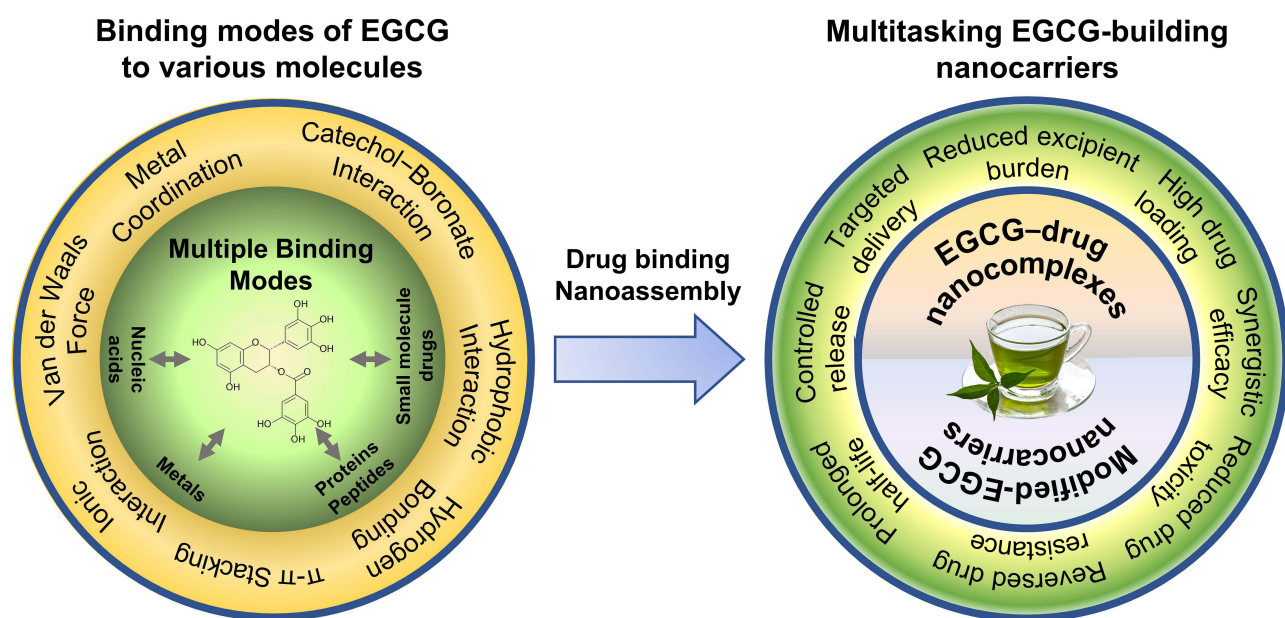
merely as a co-delivered therapeutic molecule, whereas in others it functions as a structural component that directly drives NP formation through multivalent intermolecular interactions. Distinguishing these roles is important from a formulation science perspective because the interaction chemistry of EGCG can strongly influence drug loading capacity, assembly stability, and release behavior.<sup>23–25</sup>

Based on these physicochemical interaction mechanisms and functional characteristics, EGCG-building nanocarriers can generally be classified into two principal design strategies. The first involves carrier-free or metal-bridged EGCG–drug nanocomplexes, in which unmodified EGCG interacts with drugs through noncovalent interactions or metal coordination to form nanoscale assemblies. In such systems, EGCG acts primarily as a molecular binder and structural crosslinker. The second strategy comprises chemically modified EGCG architectures, where EGCG is conjugated to polymers, targeting ligands, or other functional groups to construct hierarchically organized nanostructures with improved stability and tunable pharmacokinetic behavior. Representative interaction modes and nanocarrier architectures enabled by EGCG chemistry are illustrated in Figure 2.

Nevertheless, the chemical fragility of EGCG may still influence the reproducibility and scalability of EGCG-building nanocarriers during manufacturing. In addition, the physicochemical complexity of interaction-driven assemblies introduces further challenges related to large-scale production, batch-to-batch consistency, and regulatory classification. A systematic and formulation-oriented understanding of their design strategies, interaction mechanisms, and formulation characteristics is therefore timely and important for guiding further advancement as next-generation drug delivery platforms.

At the current stage, EGCG-building nanocarrier research is rapidly expanding yet remains largely preclinical, with no formulation having yet progressed to clinical trials. Accordingly, this review focuses on formulation design principles, preclinical therapeutic performance, and key physicochemical and translational challenges that must be addressed to support future clinical development.

This review provides a formulation-focused overview of EGCG-building nanocarriers within the framework of drug delivery science and technology. The literature considered in this review is drawn from peer-reviewed studies describing nanocarrier systems in which EGCG functions as an integral structural component. Systems that merely deliver EGCG itself or involve simple EGCG–drug co-delivery without structural integration are outside the scope of this article. Unlike previous reviews that primarily emphasize the pharmacological activities of EGCG or its co-administration with therapeutic agents, this review specifically examines EGCG as a molecular building block for nanocarrier construction.



**Figure 2** Conceptual framework of (–)-epigallocatechin-3-gallate (EGCG)-building nanocarriers as multitasking pharmacoactive nanocarriers.

Particular attention is given to the intermolecular interaction chemistry of EGCG and how these interactions facilitate the formation of carrier-efficient DDS architectures characterized by high drug loading, reduced reliance on inert excipients, and integrated therapeutic functionality. Representative EGCG-building nanocarrier formulations developed for diverse classes of therapeutic agents are discussed, with emphasis on their formulation design principles and key physicochemical and functional characteristics, including drug loading capacity, assembly stability, and therapeutic performance. Through this perspective, the review aims to clarify the potential advantages and remaining challenges associated with EGCG-building nanocarriers. Emerging formulation strategies and design considerations derived from these systems are also highlighted to support the continued development of pharmacoactive nanocarrier platforms for advanced drug delivery applications. Relevant literature was identified through searches of PubMed, Web of Science, Scopus, and Google Scholar. Search terms included “epigallocatechin gallate nanoparticle”, “EGCG nanocarrier”, “EGCG drug delivery”, “EGCG drug interaction”, “EGCG drug binding”, “polyphenol nanocarrier”, “polyphenol-mediated assembly”, “metal–polyphenol network”, “boronate catechol drug delivery”, and “pharmacoactive nanocarrier.” Additional relevant studies were identified by screening the reference lists of selected articles. The final selection of studies was guided by the scope and conceptual framework of this review, as outlined above.

## EGCG–Drug Interactions in Combination Relevant to Nanocarrier Design

Because EGCG exhibits diverse biological and pharmacological activities, it has attracted increasing attention as a synergistic agent in combination therapies. Numerous studies have reported that EGCG can enhance therapeutic efficacy, reduce drug-associated toxicity, and modulate resistance mechanisms when administered together with various therapeutic agents, particularly in oncology. Collectively, these studies suggest that the pharmacological outcomes of EGCG combinations with drugs are strongly influenced by the interactions between EGCG and co-administered drugs.<sup>20,26–29</sup> Understanding these interactions is therefore important not only for interpreting the therapeutic behavior of EGCG-containing combination therapies but also for informing the rational design of EGCG-building drug delivery systems.

In the following sections, representative examples of combination therapies of EGCG and drug are summarized according to their effects on therapeutic outcomes, toxicity reduction, drug resistance-modulation, and pharmacokinetic behavior, providing insights relevant to the design of EGCG-building nanocarriers.

### Enhanced Efficacy

A substantial body of evidence demonstrates that EGCG can enhance the therapeutic efficacy of anticancer drugs when used in combination, functioning as a chemosensitizer or adjuvant. These enhanced effects have been observed across multiple cancer types and drug classes, including anthracyclines, platinum agents, kinase inhibitors, and antimetabolites, in both *in vitro* and *in vivo* studies, indicating that combinations of EGCG and anticancer drugs can achieve stronger antitumor activity than monotherapy.<sup>20</sup>

One well-characterized example is the combination of EGCG and doxorubicin (DOX). In bladder cancer models, EGCG markedly potentiated DOX-induced apoptosis and tumor suppression both *in vitro* and in xenografted mice by suppressing NF- $\kappa$ B and MDM2 signaling while restoring p53 activity, resulting in significantly greater tumor growth inhibition compared with DOX alone.<sup>26</sup> Platinum-based chemotherapy has likewise been widely investigated in combination with EGCG. In ovarian cancer models, EGCG enhanced cisplatin sensitivity by upregulating the copper transporter CTR1, increasing intracellular cisplatin accumulation and DNA–platinum adduct formation, and inhibiting nucleic acid repair enzymes such as ERCC1/XPF, thereby improving tumor suppression *in vivo* relative to cisplatin monotherapy.<sup>27</sup>

Enhanced efficacy has also been observed with targeted therapies. EGCG combined with the epidermal growth factor receptor (EGFR) inhibitor, erlotinib significantly increased apoptosis in head and neck squamous cell carcinoma through post-transcriptional regulation of Bim and Bcl-2.<sup>30</sup> In addition, EGCG has been shown to augment the antitumor activity of kinase inhibitors such as apatinib and sorafenib by suppressing vascular endothelial growth factor (VEGF)-regulated metabolic pathways and promoting apoptotic signaling.<sup>31,32</sup> Similar cooperative effects have been reported with antimetabolite drugs. EGCG increased the chemosensitivity of colorectal cancer cells to 5-fluorouracil (5-FU), including

in chemoresistant and cancer stem-like cell populations, through enhanced apoptosis, cell-cycle arrest, and suppression of stemness-related signaling pathways.<sup>33</sup> In pancreatic cancer models, EGCG combined with gemcitabine significantly reduced tumor proliferation, migration, and invasion and suppressed tumor growth in xenograft models by modulating glycolytic metabolism and EMT signaling.<sup>34</sup>

## Reduced Drug Toxicity

Non-specific toxicity of anticancer drugs represents one of the major limitations of chemotherapy and frequently leads to dose reduction or discontinuation of treatment. Combination strategies incorporating EGCG have been proposed to mitigate such toxicity through two complementary mechanisms: (i) enabling dose reduction of cytotoxic drugs via synergistically enhanced therapeutic efficacy, and (ii) directly counteracting drug-induced toxic mechanisms, including oxidative stress and inflammation.

One of the most extensively studied examples is cisplatin-induced nephrotoxicity, a clinically significant complication that limits cumulative dosing and long-term treatment. Cisplatin-associated renal injury is closely linked to oxidative stress, mitochondrial dysfunction, inflammation, and tubular cell apoptosis. Experimental studies have shown that EGCG protects against cisplatin-induced nephrotoxicity through antioxidant and anti-apoptotic mechanisms, reducing tubular apoptosis and inflammatory responses while preserving renal histological integrity.<sup>35</sup> EGCG has also been reported to attenuate mitochondrial ROS production and apoptotic cell death in cisplatin-treated human renal tubular cells, accompanied by increased activities of antioxidant enzymes such as manganese superoxide dismutase and glutathione peroxidase.<sup>36</sup> Furthermore, EGCG exhibited neuroprotective effects against cisplatin-induced neurotoxicity also by activating the Nrf2/HO-1 antioxidant pathway while inhibiting NF- $\kappa$ B-mediated inflammation.<sup>37</sup> EGCG has also been reported to mitigate other cisplatin-associated toxicities, including ototoxicity and salivary gland damage, through suppression of oxidative and inflammatory injury pathways.<sup>38</sup>

Cardiotoxicity associated with anthracycline chemotherapy, particularly DOX, represents another major dose-limiting adverse effect. DOX-induced cardiac injury is largely driven by excessive ROS generation, mitochondrial dysfunction, and activation of apoptotic signaling pathways in cardiomyocytes. Several studies have shown that EGCG can attenuate these pathological processes without compromising the anticancer activity of DOX. For instance, EGCG reduced DOX-induced cardiotoxicity in tumor-bearing mice by decreasing oxidative stress, stabilizing mitochondrial function, and suppressing apoptosis in cardiac tissue.<sup>39</sup> Additional studies demonstrated that EGCG pretreatment ameliorated DOX-induced oxidative stress and inflammatory responses in the heart while improving antioxidant defense systems.<sup>40</sup> Mechanistic investigations further revealed that EGCG can protect against DOX-induced cardiotoxicity by activating AMPK-dependent autophagy and suppressing ferroptotic cell death, thereby preserving mitochondrial integrity and reducing lipid peroxidation.<sup>41</sup> A synthetic EGCG derivative, Y6 showed strong cardioprotective and antitumor effects of daunorubicin by suppressing CBR1 expression through PI3K/AKT and MEK/ERK signaling pathways.<sup>42</sup>

EGCG has also demonstrated protective effects against toxicities associated with other anticancer agents. In experimental models of bleomycin-induced pulmonary fibrosis, EGCG administration restored antioxidant capacity, reduced extracellular matrix accumulation, and suppressed inflammatory cytokine production, thereby attenuating lung injury.<sup>43</sup>

## Reversal of Drug Resistance

Drug resistance represents a major obstacle to successful chemotherapy and is a key factor contributing to treatment failure and poor clinical outcomes. Increasing evidence suggests that EGCG can restore the sensitivity of resistant cancer cells to various anticancer agents by modulating multiple resistance-associated mechanisms. One of the most widely reported mechanisms involves inhibition of drug efflux transporters. EGCG has been shown to suppress the activity of P-glycoprotein (P-gp), an ATP-binding cassette transporter responsible for the efflux of numerous chemotherapeutic drugs. Inhibition of P-gp by EGCG enhances intracellular drug accumulation, thereby restoring chemosensitivity in multidrug-resistant tumor cells.<sup>20</sup>

For example, in colorectal cancer cells, EGCG significantly enhanced the cytotoxicity of 5-FU by suppressing the GRP78/NF- $\kappa$ B/miR-155-5p signaling pathway, leading to downregulation of the MDR-1/P-gp efflux transporter, increased intracellular drug retention, and enhanced apoptotic cell death.<sup>44</sup> Similar chemosensitizing effects have been reported in gastric cancer, where EGCG restored sensitivity to 5-FU through suppression of the TFAP2A/VEGF

signaling axis and reduced expression of MDR-1 and P-gp.<sup>45</sup> EGCG has also been shown to enhance the efficacy of anthracyclines. In DOX-treated cancer cells, EGCG increased intracellular drug accumulation, promoted apoptotic signaling through activation of the p53 pathway, and significantly improved antitumor activity both *in vitro* and *in vivo*.<sup>26,39</sup>

Beyond modulation of drug efflux, EGCG can influence resistance through epigenetic and signaling pathway regulation. In estrogen receptor-negative breast cancer cells, EGCG sensitized tumors to tamoxifen by epigenetically reactivating ER $\alpha$  expression via histone modification and DNA methylation changes, thereby restoring estrogen-responsive growth inhibition.<sup>46</sup> EGCG has also been reported to suppress proliferation and survival signaling in trastuzumab-resistant breast cancer cells by inhibiting AKT activity and promoting nuclear accumulation of FOXO3a and p27Kip1.<sup>47</sup> Furthermore, EGCG resensitized non-small cell lung cancer cells to cisplatin through demethylation of genes associated with cell death pathways,<sup>48</sup> and exhibited antitumor activity in platinum-resistant ovarian cancer by downregulating S100A4 and NF- $\kappa$ B while restoring p53 signaling.<sup>49</sup>

## Molecular Binding and Pharmacokinetic Interactions

Although numerous studies have reported beneficial pharmacological effects of EGCG and drugs in combinations, unfavorable interactions can also occur depending on the physicochemical and pharmacokinetic characteristics of the co-administered agents. EGCG has been shown to influence the pharmacokinetics and pharmacodynamics of various therapeutic drugs by altering their absorption, metabolism, transport, or chemical stability.<sup>28,29,50–52</sup> Consequently, co-administration of EGCG does not always lead to improved therapeutic outcomes and may, in certain cases, reduce drug efficacy or alter systemic exposure.

Several studies have reported antagonistic interactions between EGCG and anticancer agents. For example, Golden et al demonstrated that EGCG markedly abolished the antitumor activity of bortezomib (BTZ), a boronate-based proteasome inhibitor widely used for the treatment of multiple myeloma and mantle cell lymphoma.<sup>28</sup> This antagonism results from the formation of a cyclic boronate complex between EGCG and BTZ, which chemically inactivates the drug. Another representative example involves the multikinase inhibitor sunitinib (SU). While delayed administration of EGCG after SU treatment enhanced antitumor efficacy in some studies,<sup>53</sup> other investigations reported that the simultaneous administration of EGCG significantly reduced plasma concentrations of SU by forming poorly soluble complexes in the gastrointestinal tract, thereby impairing drug absorption.<sup>29</sup>

EGCG can also influence drug disposition by modulating membrane transporters and metabolic enzymes. Inhibition of P-gp by EGCG may enhance intracellular drug accumulation and reverse multidrug resistance, but it can also alter the pharmacokinetics of P-gp substrate drugs such as verapamil, diltiazem, digoxin, tamoxifen, and doxorubicin.<sup>51,54–57</sup> Because P-gp contributes to biliary drug elimination,<sup>51</sup> its inhibition may increase systemic drug exposure and potentially elevate toxicity risk. For instance, EGCG administration significantly increased plasma concentrations and half-life of irinotecan and its active metabolite SN-38.<sup>52,58</sup> EGCG has also been shown to enhance the bioavailability of 5-FU by inhibiting dihydropyrimidine dehydrogenase, the key enzyme responsible for 5-FU metabolism.<sup>59</sup> In contrast, co-administration of green tea catechins has been reported to decrease systemic exposure of certain drugs, including digoxin, highlighting the complexity of EGCG–drug pharmacokinetic interactions.<sup>51</sup> In addition to transporter-mediated effects, EGCG may influence drug disposition through inhibition of organic anion transporting polypeptides (OATP)<sup>60</sup> and interference with CYP3A4-dependent metabolic pathways.<sup>61</sup> Clinical studies have also shown that green tea consumption can reduce the oral bioavailability of several drugs, including folic acid and warfarin.<sup>62</sup> These observations emphasize the need for caution when EGCG is co-administered with drugs that possess narrow therapeutic indices or limited solubility.<sup>63</sup>

## Implications of EGCG–Drug Interactions for Nanocarrier Design

EGCG–drug interactions exert multifaceted effects on therapeutic efficacy, toxicity, resistance, and drug disposition, providing a mechanistic foundation for EGCG-building nanocarrier design. The same interactions that enhance apoptosis, suppress survival signaling, and modulate cellular metabolism can be leveraged to reinforce cooperative therapeutic effects through carrier–payload co-localization (Table 1). In addition, the intrinsic antioxidant and cytoprotective

**Table 1** Therapeutic Implications of EGCG–Drug Interactions Relevant to the Design of EGCG-Building Nanocarriers

EGCG–Drug Interactions	Representative Examples	Major Mechanisms	Relevance for EGCG-Building Nanocarrier Design
<b>Enhanced efficacy</b>	DOX, cisplatin, erlotinib, sorafenib, apatinib, gemcitabine	P-gp inhibition, modulation of apoptotic signaling (p53, NF-κB), enhanced drug uptake (CTR1), metabolic pathway modulation	EGCG can act as a synergistic carrier component, enabling cooperative therapeutic effects between carrier and payload.
<b>Reduced toxicity</b>	DOX cardiotoxicity, cisplatin nephrotoxicity, bleomycin lung injury	Antioxidant activity, anti-inflammatory effects, mitochondrial protection, suppression of oxidative stress pathways	EGCG-based carriers may attenuate payload-associated toxic mechanisms while maintaining therapeutic efficacy.
<b>Reversal of drug resistance</b>	5-FU resistance, tamoxifen resistance, cisplatin-resistant tumors	Suppression of MDR-1/P-gp activity, epigenetic regulation, modulation of survival signaling pathways	EGCG incorporation may enable resistance-modulating nanocarriers that enhance intracellular drug retention.
<b>Molecular binding and pharmacokinetic interactions</b>	Bortezomib, sunitinib, irinotecan, digoxin	Direct chemical complexation, transporter modulation (P-gp, OATP), CYP-mediated metabolic interactions	Strong intermolecular interactions can be exploited for high drug loading, nanoscale assembly, and carrier–payload stabilization.

**Abbreviations:** EGCG, (–)-epigallocatechin-3-gallate; DOX, doxorubicin; 5-FU, 5-fluorouracil; OATP, organic anion transporting polypeptides; P-gp, P-glycoprotein.

properties of EGCG offer opportunities to mitigate treatment-related toxicity and improve the therapeutic index. EGCG-mediated modulation of drug resistance pathways, including efflux transport and survival signaling, may further enhance intracellular drug retention in resistant tumors.

Notably, intermolecular interactions responsible for unfavorable pharmacokinetic effects can be repurposed as a design principle in nanodelivery systems. In EGCG-building nanocarriers, such interactions promote nanoscale assembly and stabilize carrier–payload complexes. Therefore, rational design requires careful consideration of compatibility between EGCG and the payload to achieve balanced interaction strength, enabling stable assembly, controlled drug retention, responsive release, and favorable therapeutic synergy. These insights provide a conceptual framework for the EGCG-building nanocarrier systems discussed in the following sections.

## Unmodified EGCG as a Molecular Binder for Nanocomplex Formation

### Versatile Binding Properties of EGCG

EGCG exhibits versatile binding properties toward various biomolecules, including peptides, proteins, and nucleic acids, through multiple covalent and noncovalent interactions such as hydrophobic interactions, hydrogen bonding,  $\pi$ – $\pi$  stacking, and electrostatic.<sup>11</sup> The diverse therapeutic properties of EGCG have been attributed, at least in part, to its ability to interact with biological molecules and thereby modulate a variety of signal transduction pathways.<sup>17,64</sup> For instance, EGCG binds to a variety of proteins mainly through hydrophobic interactions,<sup>65</sup> while its polyphenolic rings can interact with aromatic and proline residues of proteins through  $\pi$ – $\pi$  stacking.<sup>66</sup> These interactions can contribute to the regulation of multiple signaling pathways.<sup>17,64</sup> In addition, the oxidized ortho-quinone form of EGCG can react with nucleophilic thiol groups in proteins.<sup>67</sup> The hydroxyl groups of EGCG also serve as hydrogen-bond donors, allowing strong interactions with proteins and nucleic acids.<sup>68</sup> EGCG has been reported to enter the nucleus and bind to DNA and RNA in CpG-rich regions,<sup>69</sup> suggesting that EGCG–nucleic acid interactions may contribute to the regulation of gene-related functions.

EGCG can also coordinate with various metal cations, including  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Fe}^{3+}$ , and  $\text{Al}^{3+}$ , through its polyphenolic moieties, thereby forming metal–polyphenol complexes and nanostructures.<sup>70</sup> Coordination interactions between phenolic moieties and metal ions are fundamental to natural phenomena such as plant pigmentation and nutrient cycling, with the stoichiometry of the resulting complexes, including mono-, bis-, or tris-coordinated forms, governed by pH, metal ion valence, and metal-to-phenolic group ratios.<sup>10</sup> EGCG–metal complexes have attracted broad interest for biomedical applications because of their facile one-step formation, biocompatibility, and stability in systemic circulation.<sup>11</sup>

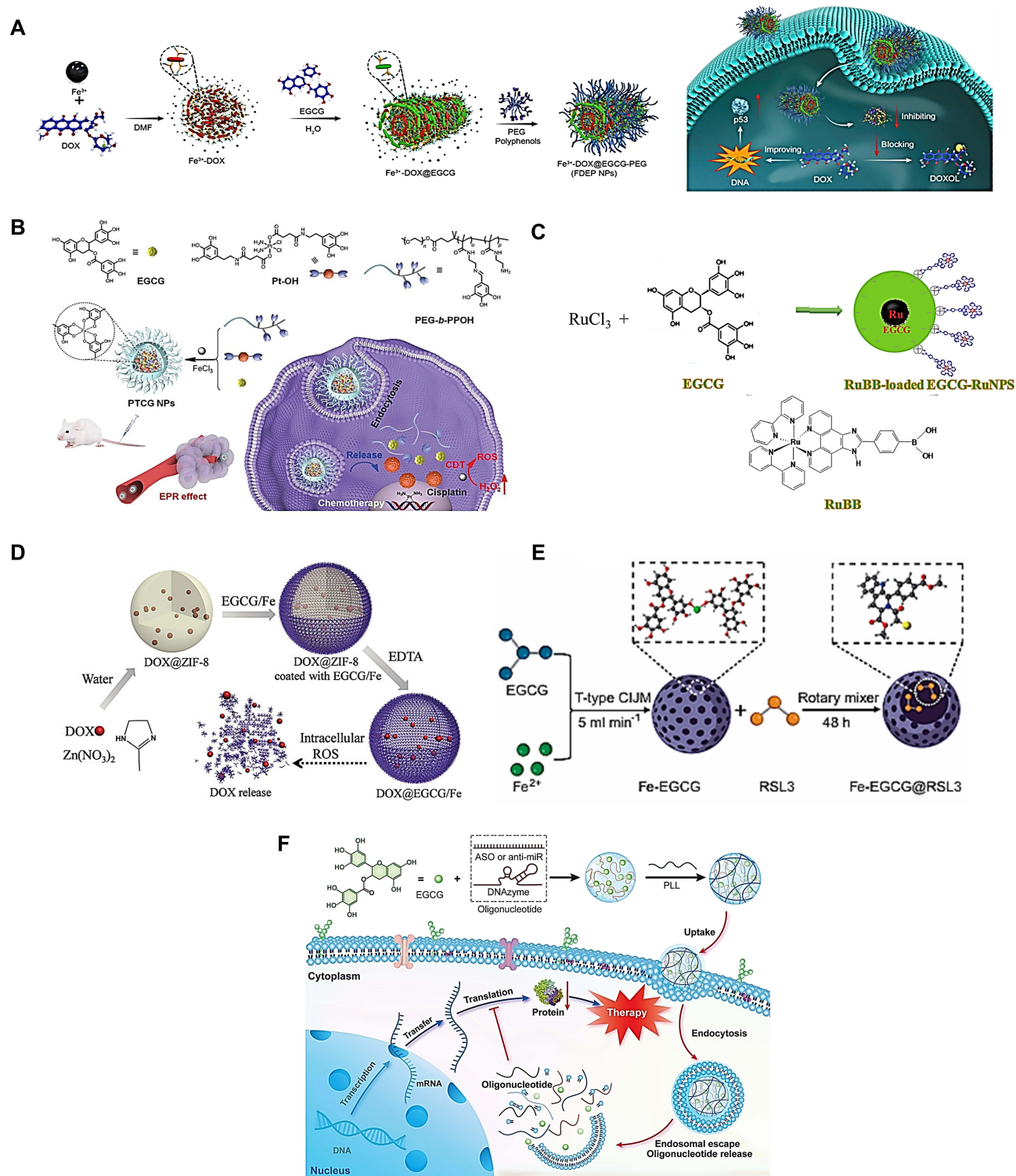
Furthermore, the pyrogallol and galloyl moieties of EGCG can form dynamic covalent linkages with boronate groups through boronate–catechol complexation.<sup>71</sup> The structural similarity between EGCG and many multiring aromatic small

molecule drugs also favors EGCG–drug association through  $\pi$ – $\pi$  stacking, which can be reinforced by hydrogen bonding, hydrophobic interactions, and/or electrostatic interactions.<sup>72</sup> These binding properties may also underlie antagonistic or pharmacokinetic interactions observed when EGCG is co-administered with certain drugs, particularly in the gastrointestinal (GI) tract or systemic circulation. Several studies have reported that EGCG can alter the pharmacokinetics and pharmacodynamics of therapeutic agents through direct or indirect mechanisms, thereby affecting their absorption, bioavailability, or activity.<sup>73</sup> Nevertheless, these same interaction mechanisms can be advantageously exploited in nanocarrier design. EGCG-mediated binding can promote efficient loading of active pharmaceutical ingredients (APIs) into nanoscale assemblies, stabilize payloads within confined nanostructures, protect them during exposure to the GI tract or systemic circulation, and ultimately improve pharmacokinetic performance.

## Noncovalent EGCG–Drug Nanocomplexes Driven by Molecular Binding

Noncovalent EGCG–drug nanocomplexes represent the most direct strategy for constructing EGCG-building nanocarriers. In these systems, unmodified EGCG participates in nanocarrier formation through reversible molecular interactions, including hydrogen bonding,  $\pi$ – $\pi$  stacking, hydrophobic interactions, electrostatic interactions, and metal–phenolic coordination. These interaction-driven assemblies can incorporate structurally diverse payloads under mild aqueous conditions, thereby reducing the need for large amounts of inert carrier materials. At the same time, their performance depends strongly on the balance between complex stability and stimulus-responsive dissociation, which determines drug retention during circulation and release at the target site. The following examples illustrate how noncovalent EGCG-mediated binding has been used to construct nanocomplexes for small molecule drugs, metal-coordinated systems, and nucleic acid delivery.

Shan et al developed a self-assembled NP in which DOX was loaded through EGCG/Fe<sup>3+</sup> coordination, and the resulting complex was further encapsulated with high molecular weight polyphenol-conjugated poly(ethylene glycol) (PEG) for evaluation in glioma xenograft mice (Figure 3A).<sup>74</sup> The NP formulation exhibited prolonged systemic circulation, increased tumor accumulation, and significant suppression of tumor growth in a uppsala 87 malignant glioma (U87MG) xenograft model. In addition, the NPs mitigated DOX-induced cardiotoxicity and hematological toxicity by EGCG-mediated inhibition of CBR1 expression, thereby reducing the formation of doxorubicinol, a key DOX metabolite implicated in drug resistance and cardiotoxicity.<sup>74</sup> A similar strategy was used to construct hybrid phenolic complexes composed of EGCG, a 5-hydroxydopamine-modified platinum(IV) prodrug (Pt-OH), Fe<sup>3+</sup>, and a polyphenol-modified block copolymer (PEG-*b*-PPOH) (Figure 3B).<sup>75</sup> Incorporation of gadolinium ions (Gd<sup>3+</sup>) endowed the NPs with magnetic resonance imaging (MRI) contrast for noninvasive in vivo tracking, creating a bifunctional nanomedicine for both drug delivery and imaging. Wang et al developed an oral delivery system in which EGCG and 5-FU, a first-line chemotherapeutic agent for colon cancer, were complexed with gelatin and chitosan to form NPs.<sup>76</sup> The NPs loaded with 5-FU and EGCG exhibited controlled drug release, improved cellular internalization, and prolonged systemic circulation, which collectively resulted in enhanced antitumor and pro-apoptotic effects in vivo compared with free drug formulations. Zhou et al prepared EGCG/ruthenium (Ru) NPs loaded with luminescent Ru complexes [Ru(2,2'-bipyridine)<sub>2</sub>(4-B)](ClO<sub>4</sub>)<sub>2</sub>·2H<sub>2</sub>O (RuBB) for liver cancer treatment (Figure 3C).<sup>77</sup> RuBB-loaded EGCG/Ru NPs showed monodisperse, homogeneous and spherical morphology, improved stability, and selective accumulation in 67LR-overexpressed liver cancer cells (SMMC-7721) due to the targeting ability of EGCG. The NPs were nontoxic in normal cells (L-02) and showed direct ROS-dependent cytotoxic, pro-apoptotic, and anti-invasive effects in SMMC-7721 cells. Also, the NPs demonstrated high antitumor efficacy in tumor-bearing nude mice. Wang et al developed DOX-loaded EGCG/Fe NPs using zeolitic imidazolate framework-8 (ZIF-8) particles as sacrificial templates (Figure 3D).<sup>78</sup> DOX was initially incorporated into ZIF-8 via a coprecipitation process, followed by deposition of EGCG/Fe layers onto the particle surface. Subsequent removal of the ZIF-8 core with EDTA yielded hollow EGCG/Fe NPs encapsulating DOX. These NPs exhibited strong ROS scavenging capability and underwent structural disassembly upon oxidation of EGCG during ROS neutralization, thereby triggering DOX release. Elevated endogenous ROS levels in tumor cells further accelerated NP degradation and intracellular drug release, resulting in superior tumor growth inhibition compared with free DOX, while showing minimal acute toxicity to normal tissues. Chen et al developed a multifunctional nanocomplex composed of EGCG, Fe<sup>3+</sup>, and DOX through metal–phenolic coordination, enabling combined tumor therapy, imaging, and



**Figure 3** Drug–EGCG nanocomplexes via noncovalent bonding. **(A)** DOX-loaded EGCG/Fe<sup>3+</sup>/PEG NP and its intracellular mechanism.<sup>74</sup> **(B)** Pt(IV) prodrug-loaded EGCG/Fe<sup>3+</sup>/PEG-b-PPOH NP.<sup>75</sup> **(C)** RuBB-loaded EGCG/Ru NP.<sup>77</sup> **(D)** DOX-loaded EGCG/Fe NP by ZIF-8 template.<sup>78</sup> **(E)** RSL3-loaded Fe/EGCG NP.<sup>80</sup> **(F)** Oligonucleotide-loaded EGCG/ε-poly-L-lysine NP.<sup>81</sup> Reproduced with permission.

**Abbreviations:** DOX, doxorubicin; EGCG, (–)–epigallocatechin-3-gallate; NP, nanoparticle; PEG, poly(ethylene glycol); PEG-b-PPOH, polyphenol modified PEG block copolymer; PLL, ε-poly-L-lysine; Pt, platinum; ZIF-8, zeolitic imidazolate framework-8.

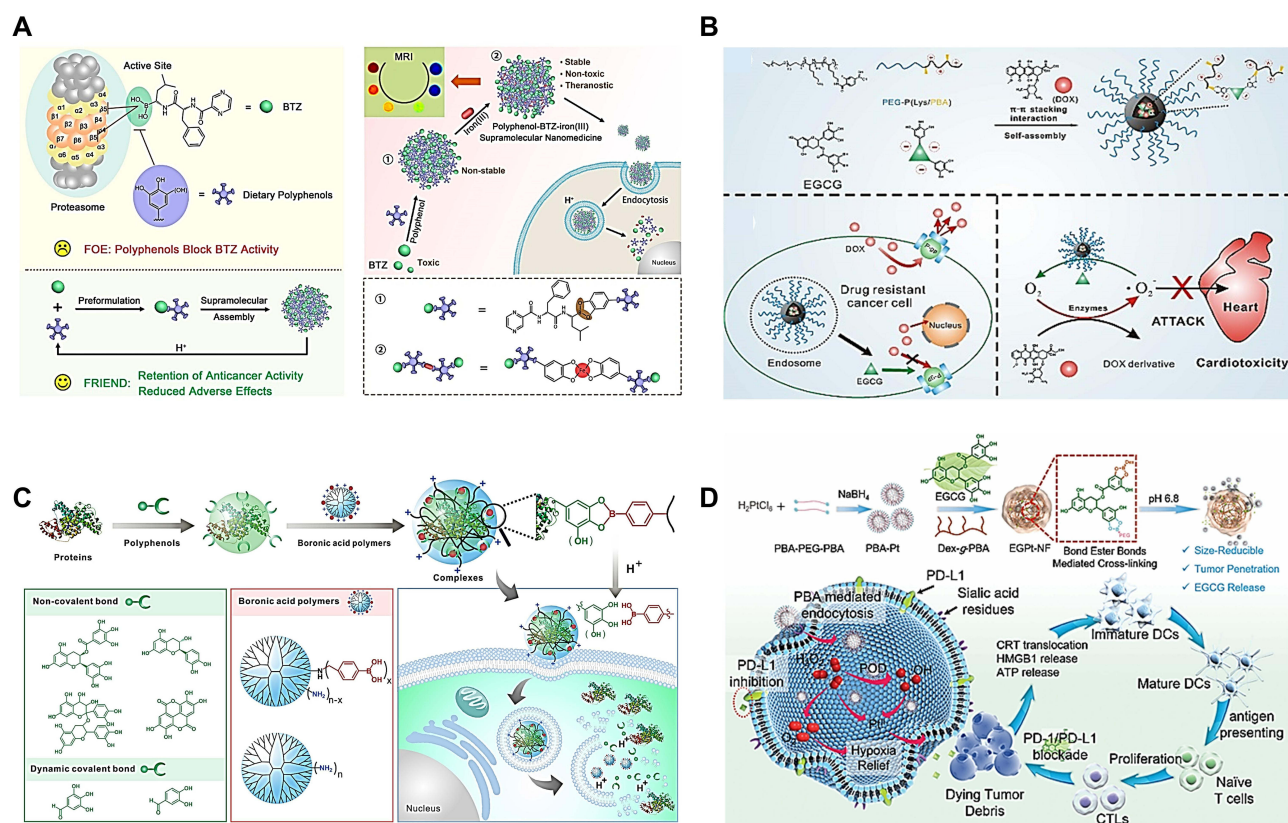
metastasis suppression.<sup>79</sup> The nanocomplex preferentially accumulated in tumor tissue via the enhanced permeability and retention (EPR) effect and released DOX within tumor cell endosomes as the coordination network destabilized under mildly acidic conditions. Following dissociation, EGCG functioned as a therapeutic adjuvant by inhibiting EMT and reducing matrix metalloproteinase expression, thereby suppressing metastatic progression. Meanwhile, Fe<sup>3+</sup> served as an effective magnetic resonance imaging contrast agent, allowing noninvasive visualization of nanocomplex distribution. Both in vitro and in vivo studies confirmed enhanced antitumor efficacy, reduced metastasis, and concurrent diagnostic capability. Building on this strategy, Zhang et al developed a self-assembled nanomedicine by coordinating Fe<sup>2+</sup> with EGCG and encapsulating the ferroptosis inducer RSL3, resulting in Fe-EGCG@RSL3 NP (Figure 3E).<sup>80</sup> EGCG served multiple roles including chelating iron, stabilizing the NP architecture, and contributing antioxidant effects. In subcutaneous and orthotopic bladder cancer mouse models, the NP accumulated in tumors and significantly inhibited tumor growth compared with RSL3 or EGCG alone after intravesical administration. Fe-EGCG@RSL3 integrated ferroptosis induction with immunomodulation, supporting its potential as a multifunctional nanomedicine.

Nanocomplexes of EGCG and biomolecules such as nucleic acids and proteins have also been developed. Ding et al reported NPs co-loaded with small interfering RNA (siRNA) and protamine via complexation with EGCG, and then encapsulated by HA and tumor-homing cell-penetrating peptides grafted on the surface for triple-negative breast cancer treatment.<sup>82</sup> The NPs have demonstrated superior selectivity and tumor growth inhibition compared with EGCG alone in MDA-MB-231 tumor-bearing xenograft mice. Beyond cancer therapy, Shen et al have reported core-shell NPs prepared by complexation of siRNA with EGCG, followed by coating low molecular weight polymers to form the shell for inflammatory bowel disease treatment.<sup>83</sup> The NPs achieved selective inhibition of target gene expression in vitro and in vivo and effectively mitigated chronic intestinal inflammation in an experimental model of inflammatory bowel disease. EGCG facilitated siRNA condensation into NPs, reducing reliance on highly cationic polymers whose toxicity often increases with transfection efficiency. Using the same technique, EGCG formed complexes with several types of single-strand oligonucleotides, including antisense oligonucleotides, anti-miRNA, and DNazyme, which were further coated with the low molecular weight cationic polymer  $\epsilon$ -poly-*L*-lysine to enhance cellular internalization (Figure 3F).<sup>81</sup> The resulting core-shell structured NPs showed improved cargo stability and achieved efficient intracellular delivery in vitro. In another approach, a noncationic NP for mRNA delivery was developed by the sequential mixing of PEG, mRNA, and EGCG to form agglomerates, followed by introduction of metal ions to stabilize the NP through metal/EGCG complexation.<sup>84</sup> Among various polyphenols examined, EGCG produced the highest transfection of HEK 293T cells, likely attributed to its high loading capacity. Intravenous administration of the NP enabled predominant protein expression and gene editing in the brain, liver, and kidney, while organ tropism could be tuned by varying NP composition.

## Boronate–Catechol Dynamic Conjugation for EGCG-Mediated Nanocomplex Formation

Boronate–catechol dynamic conjugation provides a more chemically defined and stimuli-responsive mode of EGCG-mediated nanocomplex formation. Because the catechol or galloyl groups of EGCG can form reversible boronate ester linkages with boronic acid-containing drugs or polymers, this strategy enables stable complexation under selected conditions and dissociation in response to environmental changes such as pH. Importantly, interactions that are unfavorable in simple co-administration, such as EGCG-mediated inactivation of boronate-containing drugs, can be repurposed for controlled nanocarrier assembly and tumor-responsive release. The representative systems described below demonstrate how boronate–catechol chemistry can be used to improve drug retention, trigger intracellular release, and integrate EGCG-derived bioactivity with payload function.

Wang et al used metal coordination interaction and boronate–catechol interaction with four types of polyphenols (catechin, EGCG, TA, and procyanidin) to form BTZ-loaded NPs for cancer therapy (Figure 4A).<sup>85</sup> EGCG can form a cyclic boronate–catechol diester bond with BTZ, an interaction that inactivates BTZ during simple co-administration. In this nanocarrier design, however, the same interaction was deliberately exploited to construct a pH-responsive supramolecular nanomedicine. Ferric ions were incorporated into the NPs through metal–phenolic coordination to



**Figure 4** Drug-EGCG nanocomplexes via boronic acid–catechol dynamic conjugation. **(A)** BTZ-loaded EGCG/Fe<sup>3+</sup> NP.<sup>85</sup> **(B)** Formation and proposed mechanism by which DOX-loaded EGCG/PEG-P(Lys/PBA) NPs overcome multidrug resistance and reduce cardiotoxicity.<sup>86</sup> **(C)** Protein-loaded polyphenol/boronate polymer NP.<sup>87</sup> **(D)** PBA-Pt/EGCG/Dex-g-PBA nano-framework (EGPt-NF) for immunogenic cell death induction together with PD-L1 checkpoint blockade immunotherapy.<sup>88</sup> Reproduced with permission.

**Abbreviations:** BTZ, bortezomib; Dex, dextran; DOX, doxorubicin; EGCG, (–)-epigallocatechin-3-gallate; NP, nanoparticle; PBA, phenylboronic acid; PEG, poly(ethylene glycol).

improve structural stability and introduce bioimaging capability. The fabricated NPs exhibited pH-responsive release behavior, minimizing premature BTZ leakage under physiological conditions while enabling rapid drug liberation under acidic tumor conditions. This system effectively triggered apoptosis in cancer cells and significantly inhibited tumor growth in both subcutaneous and bone tumor models, with minimal systemic toxicity. This example illustrates how an EGCG–drug interaction that is generally considered detrimental can be repurposed to achieve controlled drug delivery and improved therapeutic efficacy. A polyion complex (PIC) micelle encapsulating DOX and EGCG was prepared via a combination of electrostatic interactions and phenylboronic acid–catechol binding between poly(ethylene glycol)-*block*-poly(lysine-*co*-lysine-phenylboronic acid) (PEG-PLys/PBA) and EGCG, while DOX was incorporated into the micellar core via  $\pi$ – $\pi$  stacking interactions with EGCG (Figure 4B).<sup>86</sup> The PIC micelles remained stable under physiological conditions through phenylboronic acid–catechol complexation, whereas the acid-labile nature of this interaction enabled pH-triggered dissociation in the micellar core, resulting in coordinated release of EGCG and DOX and enhanced synergistic effects. In addition, the combination of EGCG and DOX protected cardiomyocytes from DOX-mediated cardiotoxicity through the ROS scavenging activity of EGCG and overcame multidrug resistance by suppressing P-gp activity. Collectively, this system demonstrates the potential of boronate–catechol-stabilized EGCG-based micelles to improve DOX delivery while reducing cardiotoxicity and multidrug resistance. Lui et al developed polyphenol-based NPs for cytosolic protein delivery using EGCG, (+)-catechin, ellagic acid, or procyanidin (Figure 4C).<sup>87</sup> These polyphenols formed nanocomplexes with proteins such as bovine serum albumin (BSA), R-phycoerythrin and ribonuclease A via hydrogen bonding and hydrophobic interactions. EGCG–BSA complexation was reported to be exothermic, and the EGCG/BSA complex retained the secondary structure of the protein. The pyrogallol groups on the nanocomplex

surface were further decorated with boronate-containing polymers, such as boronic acid-conjugated dendrimers and boronic acid-modified polylysine. Under acidic conditions, pH-responsive cleavage of boronate–catechol bonds promoted protein release from the nanocomplexes and facilitated endosomal/lysosomal escape, thereby enhancing intracellular protein delivery. Sun et al reported a phenolic-based, tumor-permeable nanoframework (EGPt-NF) constructed through pH-reversible borate ester linkages mediated by EGCG, which crosslinked phenylboronic acid-modified platinum NPs (PBA-Pt) with dextran grafted with phenylboronic acid (Dex-g-PBA) (Figure 4D).<sup>88</sup> The resulting EGPt-NF effectively enhanced dendritic cell maturation while suppressing PD-L1 expression in tumor cells. In addition, the nanoframework alleviated tumor hypoxia, thereby promoting cytotoxic T-lymphocyte infiltration and increasing interferon- $\gamma$  secretion. The enhanced tumor immunogenicity was attributed to the synergistic interplay between PBA-Pt as an inducer of immunogenic cell death and EGCG as a PD-L1 inhibitory component.

Representative unmodified EGCG-mediated nanocomplexes based on noncovalent binding, metal coordination, and boronate–catechol dynamic conjugation are summarized in Table 2, highlighting their payloads, binding mechanisms, reported loading values, and major functional advantages.

**Table 2** Representative Unmodified EGCG-Mediated nanocomplexes

System	Payload	Carrier Component	Main Binding Mechanism	Drug Loading	Major Advantages	Ref.
Pt(IV) prodrug-loaded EGCG/ $\text{Fe}^{3+}$ /PEG- <i>b</i> -PPOH NP	Pt(IV) prodrug	EGCG with $\text{Fe}^{3+}$ and polyphenol-modified block copolymer	Metal coordination (polyphenol/ $\text{Fe}^{3+}$ ), hydrophobic interaction	LE > 90%; LC > 30%	Combined chemo- and chemodynamic therapy, pH/redox-responsive release, reduced Pt toxicity.	Ren et al, 2020 <sup>75</sup>
DOX-loaded EGCG/ $\text{Fe}^{3+}$ /PEG NP	Doxorubicin	EGCG with $\text{Fe}^{3+}$ and PEG-based polyphenol component	Metal coordination (polyphenol/ $\text{Fe}^{3+}$ ), $\pi$ - $\pi$ stacking	Not specified	Prolonged circulation, increased tumor accumulation, enhanced antitumor efficacy, reduced DOX-associated cardiotoxicity	Shan et al, 2019 <sup>74</sup>
RSL3-loaded Fe/EGCG NP	RSL3	EGCG coordinated with $\text{Fe}^{2+}$	Metal coordination (EGCG/ $\text{Fe}^{2+}$ )	Not specified	Ferroptosis induction, tumor microenvironment remodeling, immunomodulation, enhanced bladder cancer therapy	Zhang et al, 2025 <sup>80</sup>
Oligonucleotide-loaded EGCG/ $\epsilon$ -poly-L-lysine NP	Antisense oligonucleotide, anti-miRNA, DNase	EGCG with low molecular weight cationic polymer	EGCG–oligonucleotide interaction through hydrogen bonding, $\pi$ - $\pi$ stacking, hydrophobic interaction, and polymer-assisted condensation	Not specified	Improved oligonucleotide stability, enhanced cellular internalization, reduced reliance on highly cationic polymers	Shen et al, 2020 <sup>81</sup>
DOX-loaded EGCG/PEG-P (Lys/PBA) NP	Doxorubicin	EGCG incorporated into phenylboronic acid-containing polymer micelles	Boronate–catechol binding between EGCG and PBA; $\pi$ - $\pi$ stacking between EGCG and DOX; electrostatic complexation	LE 55%; LC 12%	Overcomes MDR via P-gp inhibition, reduces DOX cardiotoxicity via EGCG ROS scavenging	Cheng et al, 2016 <sup>86</sup>
PBA-Pt/EGCG/Dex-g-PBA nano-framework (EGPt-NF)	PBA-Pt	EGCG crosslinking PBA-Pt and Dex-g-PBA	pH-reversible boronate ester linkage between EGCG and PBA groups	Not specified	Tumor penetration, immunogenic cell death induction, PD-L1 suppression, enhanced antitumor immune response	Sun et al, 2022 <sup>88</sup>

**Abbreviations:** Dex, dextran; DOX, doxorubicin; EGCG, (–)-epigallocatechin-3-gallate; LC, Loading content (w/w); LE, Loading efficiency; NP, nanoparticle; PBA, phenylboronic acid; PEG, poly(ethylene glycol); PEG-*b*-PPOH, polyphenol modified PEG block copolymer; P-gp, P-glycoprotein; Pt, platinum; ROS, reactive oxygen species.

## Chemically Modified EGCG Derivatives as Building Blocks for Hierarchically Organized Nanocarriers

Although unmodified EGCG-mediated nanocomplexes offer a simple and efficient strategy for payload association, their assembly generally relies on reversible equilibrium-driven interactions. As a result, these systems may undergo partial dissociation or structural rearrangement under physiological pH, ionic strength, dilution, or serum-rich conditions. Such assemblies can enhance drug binding and reduce excipient use, but they may provide limited control over higher-order organization such as well-defined core-shell or multilayered architectures. Because of their dynamic nature, these formulations may exhibit structural heterogeneity and batch-to-batch variability, which can complicate manufacturing consistency, shelf-life stability, and reproducible therapeutic performance. NPs with exposed EGCG or drug-rich surfaces may also be prone to protein adsorption in plasma, leading to protein corona formation, particle destabilization, aggregation, and accelerated recognition and clearance by the mononuclear phagocyte system. These effects may shorten systemic circulation and reduce therapeutic efficacy.

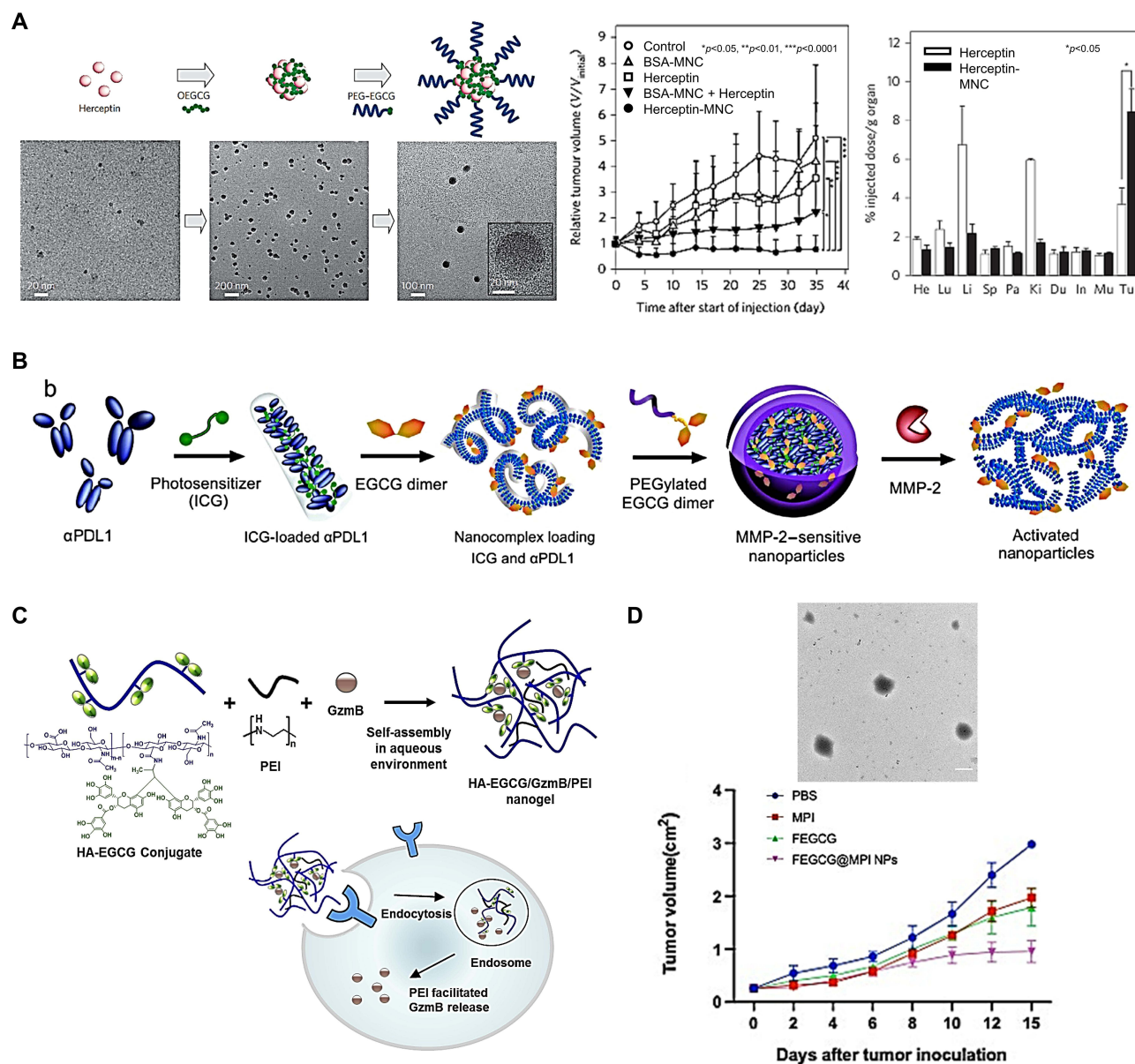
To improve thermodynamic and kinetic stability, chemically modified EGCG derivatives have been developed to enable programmed assembly with therapeutic payloads into more ordered nanostructures. Chemical modification of EGCG introduces molecular directionality and amphiphilic balance, enabling controlled hierarchical self-assembly into organized core-shell, micellar, or multilayered architectures with improved stability and tunable functionality. This approach can improve EGCG resistance to oxidation, enhance drug loading and release tunability, and support thermodynamic and pharmacokinetic robustness, which are important for reproducibility and therapeutic precision. This section reviews chemically modified EGCG-building nanocarriers in which engineered EGCG derivatives function as designed building blocks for hierarchical assembly, transforming EGCG from a transient molecular binder into a structural and functional component of multitasking nanocarriers. Several studies, including those from our group, have demonstrated therapeutically active nanocarriers based on modified EGCG derivatives that enable efficient and stable loading of diverse payloads and promote synergistically enhanced efficacy.<sup>72,89–96</sup> More recently, various engineered EGCG derivatives have been investigated to construct effective, safe, and versatile nanocarrier systems that exploit both the broad binding capacity and intrinsic therapeutic activity of EGCG.

## Chemically Modified EGCG-Based Nanocarriers for Protein and Peptide Delivery

Compared with small molecule pharmaceuticals, peptide and protein drugs are expanding rapidly and are expected to represent an increasingly important segment of the global drug market.<sup>97</sup> This growth reflects their advantages, including high target specificity, potent biological activity, and, in some cases, reduced off-target toxicity compared with conventional small molecule drugs.<sup>98</sup> However, effective delivery of protein and peptide therapeutics remains challenging because these biomacromolecules are highly susceptible to denaturation, enzymatic degradation, and loss of bioactivity during formulation, storage, and administration. Intracellular delivery is particularly difficult, as proteins and peptides must overcome cellular membrane barriers, avoid lysosomal degradation, and escape from endosomal compartments.<sup>99</sup> Accordingly, conventional protein delivery approaches, including PEGylation, emulsion-based formulations, covalent modification, and encapsulation in polymeric or lipid carriers, can suffer from low loading efficiency, reduced biological activity, complex formulation processes, or limited yield.

The pyrogallol and galloyl groups of EGCG can readily interact with proteins and peptides through noncovalent interactions, enabling self-assembled nanocomplexes to form under mild aqueous conditions. Chemically modified EGCG carriers are therefore particularly attractive for protein and peptide delivery because they allow reversible complexation while avoiding extensive covalent modification of fragile biomacromolecules. Compared with conventional protein delivery approaches that may compromise protein activity or formulation yield, EGCG-derived carriers can provide a gentle complexation strategy for encapsulating and stabilizing fragile proteins and peptides. By combining multivalent EGCG-protein interactions with protective polymer or polysaccharide shells, these systems can improve loading, preserve bioactivity, and enhance systemic or intracellular delivery. The following examples highlight how EGCG-derived carriers have been engineered to stabilize protein and peptide therapeutics and promote carrier-payload synergy.

In a pioneering study performed by Chung et al, a micellar nanocomplex (MNC) carrier comprising two EGCG derivatives has been developed to encapsulate proteins in a spatially ordered nanostructure for cancer therapy (Figure 5A).<sup>89</sup> One component was oligomerized EGCG (OEGCG), which was designed to possess greater oxidative stability than native EGCG and to form a stable core complex with proteins through strengthened multidentate binding. The other component was PEG-conjugated EGCG (PEG-EGCG), which was designed to anchor onto the preformed protein/OEGCG core complex through EGCG moieties and form an inert hydrophilic PEG shell. This shell protects the core from biological environments and prolongs the blood half-life of the nanocomplex. The MNC loaded Herceptin, a trastuzumab antibody against HER2/neu (erbB2), mainly through hydrophobic interactions between EGCG moieties and the protein, yielding monodisperse nanocomplexes of approximately 90 nm with high loading efficiency (~100%)



**Figure 5** Chemically modified EGCG-based nanocarriers for protein and peptide delivery. **(A)** Herceptin-loaded OEGCG/PEG-EGCG MNC and its enhanced antitumor efficacy and tumor-selective biodistribution.<sup>89</sup> **(B)** Anti-PD-L1/ICG-loaded dEGCG/PEG-EGCG NP.<sup>100</sup> **(C)** GzmB-loaded HA-EGCG/PEI nanogel.<sup>91</sup> **(D)** TEM images and anti-tumor efficacy of MPI-loaded FEGCG NP (scale bar = 100 nm).<sup>101</sup> Reproduced with permission. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.0001$  by one-way ANOVA.

**Abbreviations:** EGCG, (-)-epigallocatechin-3-gallate; FEGCG, fluorinated EGCG; GzmB, Granzyme B; HA-EGCG, hyaluronic acid-conjugated EGCG; ICG, indocyanine green; MNC, micellar nanocomplex; MPI, melittin; NP, nanoparticle; OEGCG, oligomerized EGCG; PEG-EGCG, poly(ethylene glycol)-conjugated EGCG; PEI, poly(ethylenimine).

and loading content (64% (w/w)). Herceptin-loaded MNCs exhibited excellent stability under physiologically relevant conditions, including incubation at 37°C in PBS with serum for 15 days, extreme dilution up to 1000-fold, and exposure to enzymatic proteolysis. They also showed greater growth-inhibitory effects against HER2-overexpressing human cancer cell lines (BT-474, SK-BR3, and SKOV3) than free Herceptin, attributable to synergistic effects between the antibody and the carrier, as indicated by a combination index (CI) < 1. No inhibitory effects were observed in normal breast cell lines (MCF-10A and HMEC). In vivo, Herceptin-loaded and interferon  $\alpha$ -2a (IFN- $\alpha$ -2a)-loaded MNCs achieved superior antitumor efficacy, inducing pronounced tumor regression in BT-474 and HAK-1B-xenograft models, respectively, compared with free drug, carrier alone, or their sequential administration. The MNCs also exhibited markedly increased tumor accumulation, reduced distribution to off-target organs such as the liver, kidney, and lung, and a ~29-fold prolonged blood half-life relative to free protein drugs. Collectively, these results demonstrate that MNCs can improve protein delivery and therapeutic outcomes through carrier–drug synergy. Wang et al prepared an a matrix metalloproteinase protein 2 (MMP-2)-responsive nanocomplex loaded with anti-PD-L1 antibody and the photosensitizer indocyanine green (ICG) (Figure 5B).<sup>100</sup> In this system, anti-PD-L1 and ICG were complexed with EGCG dimers (dEGCG) and a PEG-EGCG conjugate containing MMP-2-cleavable peptide linkers. The nanocomplex was designed to accumulate at tumor sites and release both anti-PD-L1 and ICG in response to overexpressed MMP-2, thereby amplifying intratumoral ROS production under near-infrared (NIR) laser irradiation. This strategy promoted intratumoral infiltration of cytotoxic T cells and sensitized tumors to anti-PD-L1 blockade therapy. Treatment with the nanocomplex combined with NIR laser irradiation markedly inhibited tumor progression and reduced metastatic spread to the lungs and lymph nodes in murine models.

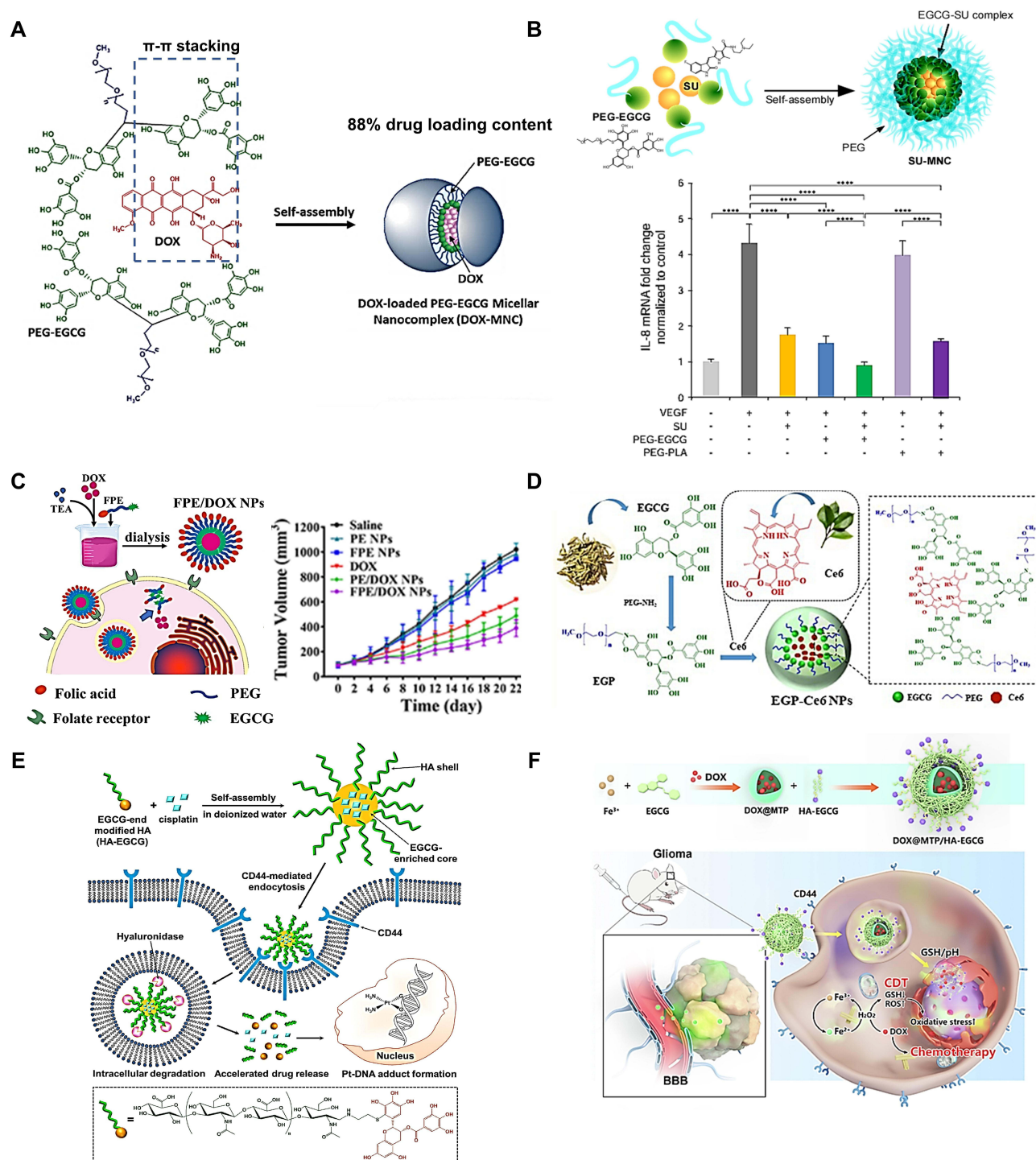
Cytosolic delivery is particularly important for intracellularly active proteins such as granzyme B (GzmB), but achieving efficient cytosolic access remains challenging because proteins must cross cellular membranes, avoid lysosomal degradation, and escape from endosomes.<sup>99</sup> Liang et al developed a hyaluronic acid-EGCG conjugate (HA-EGCG)-based nanocarrier for cytosolic delivery of GzmB, a cytotoxic effector protein released by cytotoxic T lymphocytes and natural killer cells to eliminate pathogen-infected, premalignant, and malignant cells (Figure 5C).<sup>91</sup> GzmB-loaded nanogels were formulated through noncovalent interactions between HA-EGCG and GzmB with the assistance of poly(ethylenimine) (PEI). The nanogels delivered GzmB into the cytosol of the cluster of determination 44 (CD44)-overexpressing cancer cells and induced CD44-targeted cancer cell killing. The observed cytotoxicity was attributed to GzmB-mediated apoptosis, indicating successful cytosolic delivery of functional GzmB. Sun et al developed melittin-loaded fluorinated EGCG NPs for cancer immunotherapy (Figure 5D).<sup>101</sup> Melittin (MPI) is a 26-amino-acid cytolytic peptide derived from bee venom that exhibits antitumor and immunomodulatory activities;<sup>102</sup> however, its clinical translation is hindered by pronounced hemolytic activity and systemic toxicity. To address these limitations, EGCG was modified with fluorinated linkers to generate fluorinated EGCG (FEGCG), thereby enhancing hydrophobic and lipophobic interactions. Through hydrophobic interactions and hydrogen bonding, FEGCG and MPI self-assembled into NPs (FEGCG@MPI NPs). In hepatoma models, these NPs modulated PD-L1 signaling via IRF and STAT1/pSTAT1 pathways and triggered apoptosis through regulation of Bcl-2 and Bax expression, reflecting synergistic actions of EGCG and MPI. Importantly, FEGCG@MPI NPs significantly reduced MPI-induced hemolysis, highlighting their potential as a safer and effective platform for antitumor immunotherapy.

## Chemically Modified EGCG-Based Nanocarriers for Small Molecule Drug Delivery

Small molecule drug delivery using chemically modified EGCG carriers mainly takes advantage of the molecular compatibility between EGCG and aromatic or hydrophobic drugs. Through  $\pi$ - $\pi$  stacking, hydrophobic interactions, hydrogen bonding, and coordination interactions, EGCG derivatives can promote drug association and organized nanocarrier formation in aqueous media. These features make chemically modified EGCG carriers particularly suitable for improving the loading, dispersion, and therapeutic performance of poorly soluble small molecule drugs. With this design principle, EGCG derivatives can self-assemble with various small molecule drugs to form spatially organized nanoarchitectures. In particular, small molecule drugs possessing multiring aromatic structures can form stable nano-complexes with high drug loading efficiency when combined with EGCG-building carriers, owing to their structural similarity to EGCG.

Liang et al developed highly stable MNCs with exceptionally high drug loading based on the self-assembly of DOX and PEG-EGCG conjugates (Figure 6A).<sup>72</sup> The MNC consisting of DOX/EGCG core surrounded by a PEG corona was constructed through favorable noncovalent interactions between EGCG and DOX, driven primarily by  $\pi$ - $\pi$  stacking of aromatic rings. This design enabled an exceptionally high drug loading content of up to 88% (w/w) and imparted strong thermodynamic and kinetic stability. The DOX-MNC achieved a 25-fold increase in intratumoral DOX accumulation at 24 h relative to free DOX, along with a 16-fold extension in blood half-life and a 27-fold increase in area under the concentration–time curve. The formulation produced pronounced tumor growth suppression in a human liver cancer (HAK-1B) xenograft model with minimal systemic toxicity, whereas free DOX and the clinically approved liposomal formulation DOXIL failed to show efficacy at their lethal doses of 10 mg/kg. Collectively, these results highlight the potential of PEG-EGCG-based MNCs as a safe and effective platform for DOX delivery in cancer therapy. As described above, SU strongly interacts with EGCG, and co-administration of EGCG can markedly impair SU bioavailability, raising caution regarding EGCG intake during SU treatment.<sup>29</sup> However, Yongvongsoontorn et al deliberately employed this EGCG–SU intermolecular interaction to construct an EGCG-building nanocarrier for SU delivery.<sup>93</sup> The SU-loaded MNC (SU-MNC) was developed through self-assembly of SU and PEG-EGCG (Figure 6B). SU-MNC effectively inhibited VEGF-stimulated proliferation of human umbilical vein endothelial cells (HUVECs) and suppressed tumor growth in human renal cell carcinoma (HRCC) xenograft models through carrier–drug synergy while exhibiting minimal systemic toxicity. Compared with free SU, SU-MNC prolonged blood half-life and increased intratumoral SU accumulation by 2.2-fold and 5.1-fold in wild-type and SU-resistant HRCC tumors, respectively, while reducing accumulation in normal tissues. SU-MNC reduced the minimum effective dose by 50-fold compared with free SU and exhibited no apparent adverse effects even at doses higher than the maximum tolerated dose of free SU. By contrast, SU-loaded PEG-*b*-poly(lactic acid) polymeric micelles, used as a conventional nanocarrier control, reduced toxicity but failed to enhance antitumor efficacy despite showing drug loading capacity and tumor-targeting performance comparable to SU-MNC. This study demonstrated that EGCG-building nanocarriers can expand the therapeutic window of small molecule anticancer drugs beyond the safety improvements conferred by tumor-targeted delivery alone. Moreover, SU-MNC significantly inhibited the growth of SU-resistant A498 renal cell carcinoma xenografts at a 28-fold lower dose than conventional free SU treatment, indicating its potential to overcome SU resistance. Chuan et al synthesized folic acid-conjugated PEG-EGCG (FA-PEG-EGCG) and formulated DOX-loaded NPs (DOX/FA-PEG-EGCG NPs) through self-assembly of DOX and FA-PEG-EGCG for targeted delivery to ovarian cancer (Figure 6C).<sup>103</sup> FA can bind specifically to folate receptors, enabling FA-modified NPs to enter tumor cells through receptor-mediated endocytosis. DOX/FA-PEG-EGCG NPs showed increased cellular uptake and anticancer efficacy in human ovarian cancer cells (SKOV3) and SKOV3 xenografts compared with NPs without FA modification. Liu et al enhanced the lipophilicity of EGCG by introducing 9-fluorenylmethoxycarbonyl (Fmoc) groups onto its phenolic hydroxyl moieties, enabling self-assembly with paclitaxel.<sup>104</sup> This carrier system significantly improved cellular uptake and tumor-site delivery of paclitaxel, leading to pronounced tumor growth suppression, increased apoptotic responses, and reduced metastatic progression. Chen et al constructed self-assembled photodynamic nanocarriers (EGP-Ce6 NPs) by assembling PEG-EGCG with chlorin e6 (Ce6), a photosensitizer, for carrier-enhanced photodynamic cancer therapy (PDT) (Figure 6D).<sup>105</sup> PEG-EGCG enabled efficient encapsulation of Ce6 into stable nanoplateforms through  $\pi$ - $\pi$  stacking and hydrogen bonding interactions. Compared with free Ce6, EGP-Ce6 NPs exhibited enhanced cellular internalization, increased ROS generation, and elevated apoptosis in cancer cells, leading to effective suppression of cell proliferation through photodynamic action. Three-dimensional multicellular spheroid studies further demonstrated deep NP penetration into the spheroid core and efficient destruction of tumor cells after light irradiation. The PEG-EGCG segment acted as a bioactive antioxidant carrier that improved Ce6 solubility and stability, reduced aggregation-caused quenching, enhanced cellular uptake, and thereby amplified PDT efficiency.

In recent years, safety concerns associated with exogenous synthetic materials have encouraged increasing attention to carrier designs based on endogenous or biodegradable materials. Although EGCG-building nanocarriers can reduce excipient burden by replacing inactive synthetic materials with pharmacologically active EGCG-building blocks that contribute to drug binding and structural stabilization, many formulations still use synthetic polymers such as PEG to achieve efficient drug delivery. PEG has long been regarded as a gold-standard material for increasing drug stability and circulation half-



**Figure 6** Chemically modified EGCG-based nanocarriers for small molecule drug delivery. **(A)** DOX-loaded PEG-EGCG MNC.<sup>72</sup> **(B)** SU-loaded PEG-EGCG MNC and its synergistic inhibitory effects on IL-8 mRNA expression.<sup>93</sup> **(C)** DOX-loaded FA-PEG-EGCG NP and its antitumor efficacy.<sup>103</sup> **(D)** Ce6-loaded PEG-EGCG NP.<sup>105</sup> **(E)** Cisplatin-loaded HA-EGCG MNC.<sup>92</sup> **(F)** DOX-loaded Fe<sup>3+</sup>/EGCG/HA-EGCG NP.<sup>106</sup> Reproduced with permission.

**Abbreviations:** CD44, cluster of determination 44; Ce6, chlorin e6; DOX, doxorubicin; EGCG, (-)-epigallocatechin-3-gallate; FA, folic acid; HA-EGCG, hyaluronic acid-conjugated EGCG; MNC, micellar nanocomplex; MTP, metal-tea polyphenol network; NP, nanoparticle; PEG-EGCG, poly(ethylene glycol)-conjugated EGCG; SU, sunitinib.

life; however, the emergence of PEG immunogenicity, as evidenced by anti-PEG serum antibodies, has raised concerns regarding reduced efficacy and severe adverse reactions in some PEGylated drugs.<sup>107</sup> In pursuit of improved biocompatibility, emerging designs have employed EGCG derivatives coupled to bio-sourced materials to construct inherently safer nanocarriers.

Hyaluronic acid (HA) is an endogenous polysaccharide with favorable biocompatibility and biodegradability, supporting its use in drug delivery applications.<sup>108,109</sup> HA can also bind to CD44, which is overexpressed on various cancer cells and tumor-associated angiogenic vascular cells, enabling receptor-mediated tumor targeting.<sup>109</sup> This active targeting mechanism may enhance tumor and tumor-vasculature specificity in addition to passive tumor accumulation. For example, Bae et al developed CD44-targeted MNCs constructed by self-assembly of HA-EGCG and cisplatin for ovarian cancer treatment (Figure 6E).<sup>92</sup> HA presented on the NP surface facilitated targeted cisplatin delivery to CD44-overexpressing cancer cells through receptor-mediated endocytosis, followed by enzyme-responsive drug release triggered by endosomal hyaluronidase. EGCG moieties contributed to favorable cisplatin loading and provided antioxidant protection against cisplatin-induced ROS-mediated toxicity. Pharmacokinetic and biodistribution studies revealed prolonged blood circulation and preferential tumor accumulation of the MNC compared with HA/cisplatin complexes and free cisplatin. The MNC exhibited superior antitumor efficacy over free cisplatin in both subcutaneous xenograft and peritoneal metastatic models of human ovarian cancer while showing no apparent systemic toxicity. Using the same HA-EGCG nanocarrier, sorafenib, daunorubicin (DNR), and gilteritinib were separately loaded into MNCs through self-assembly with HA-EGCG conjugates for acute myeloid leukemia (AML) treatment. Sorafenib-loaded MNCs significantly enhanced the antileukemic activity of sorafenib by selectively interfering with pro-survival mTOR signaling pathways.<sup>94</sup> Biodistribution analyses revealed that the MNC achieved approximately 11-fold higher accumulation in bone marrow compared with free sorafenib. In an AML patient-derived xenograft model, treatment with the MNC effectively eliminated leukemic blasts within the bone marrow and markedly prolonged survival while exhibiting minimal off-target toxicity. A DNR-loaded MNC was engineered to release DNR, an anthracycline used as first-line therapy for AML, under mildly acidic conditions (pH 5.5) resembling the endosomal environment.<sup>95</sup> Compared with free DNR, this MNC exhibited markedly enhanced cytotoxicity against multidrug-resistant leukemia cells, with median-effect analysis confirming strong synergistic activity. The chemosensitizing effect was attributed to increased nuclear accumulation of DNR, elevated intracellular ROS, and activation of caspase-dependent apoptosis. In a related system, gilteritinib, an FMS-like tyrosine kinase 3 (FLT3) inhibitor with limited stand-alone efficacy, was incorporated into an MNC and efficiently internalized by FLT3-mutant leukemia cells via CD44 receptor-mediated uptake.<sup>96</sup> Combination index analysis demonstrated pronounced synergism arising from the combination of HA-EGCG and gilteritinib, resulting in enhanced antileukemic efficacy compared with free drug. This improvement was associated with augmented ROS production and increased caspase-3/7 activation. Furthermore, Mu et al developed a nanodelivery platform based on HA-EGCG containing reducible disulfide linkages for chemodynamic therapy of glioblastoma (Figure 6F).<sup>106</sup> DOX-loaded metal-polyphenol networks (MTPs) were first formed through coordination between EGCG and Fe<sup>3+</sup>, followed by introduction of HA-EGCG via self-assembly to generate DOX@MTP/HA-EGCG. The system was designed so that MTPs dissociate in the acidic, glutathione (GSH)-rich intracellular environment, releasing DOX, EGCG, and Fe<sup>3+</sup>. EGCG subsequently reduces Fe<sup>3+</sup> to Fe<sup>2+</sup>, enabling continuous Fenton conversion of H<sub>2</sub>O<sub>2</sub> into hydroxyl radicals (•OH), thereby enhancing the chemotherapeutic effect of DOX. In addition, disulfide linkages within the HA-EGCG carrier depleted abnormally high intracellular GSH levels in tumor cells, further intensifying oxidative stress. The nanocomplexes selectively accumulated in glioblastoma tissue through CD44 receptor-mediated targeting and were retained in tumors for extended durations. Consequently, DOX@MTP/HA-EGCG significantly suppressed tumor progression and extended survival in tumor-bearing mice by integrating chemodynamic therapy with enhanced chemotherapy.

Yi et al developed NPs composed of covalently assembled catechins (EGCG ≥80% (w/w)) and hair keratin in the presence of formaldehyde as a biocompatible, colloiddally stable, and stimuli-responsive nanocarrier for DOX delivery.<sup>110</sup> The DOX-loaded NPs showed GSH-responsive drug release due to cleavage of disulfide bonds in keratin under reducing conditions and achieved enhanced anticancer efficacy with negligible systemic toxicity compared with free DOX in an HT-29 human colon cancer xenograft mouse model.

To improve the extremely low oral bioavailability of lycopene, a natural antioxidant, Li et al employed OEGCG as a carrier for oral lycopene delivery.<sup>111</sup> OEGCG NPs containing lycopene were fabricated using a nanoprecipitation technique and subsequently coated with chitosan to generate an outer shell. The chitosan-coated OEGCG/lycopene NP system displayed pH-responsive release, with sustained lycopene release in acidic gastric media and accelerated release in simulated intestinal fluid. In vivo pharmacokinetic evaluation in mice demonstrated improved lycopene absorption

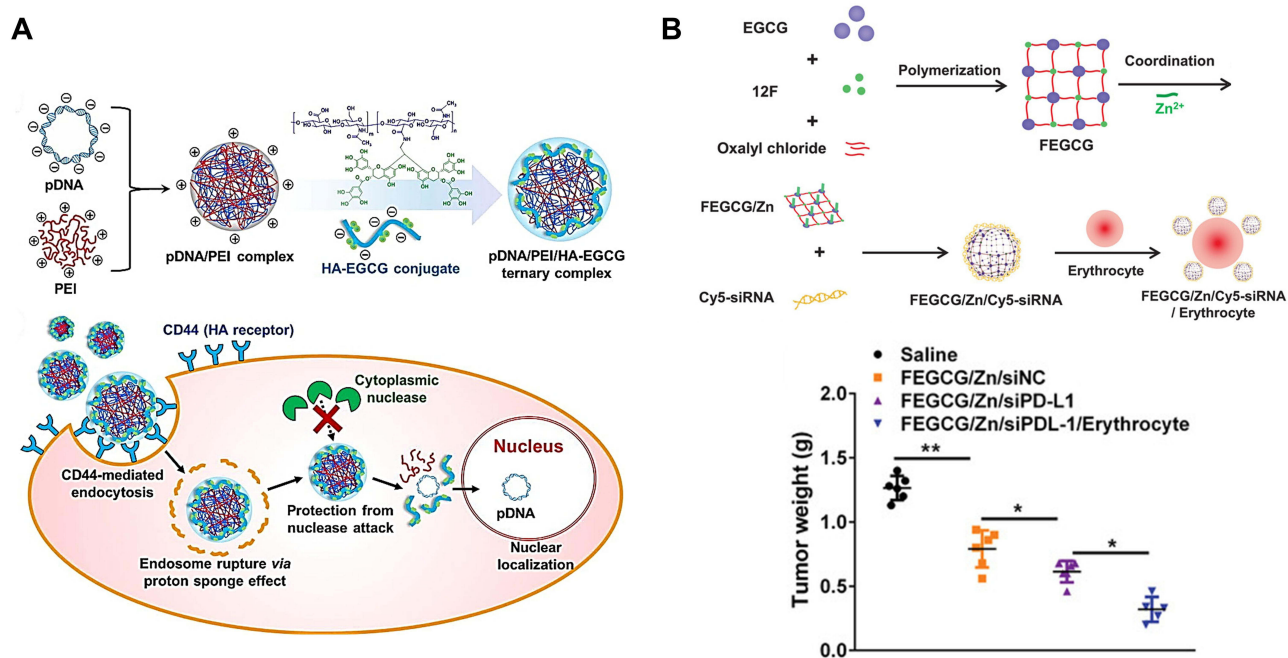
with OEGCG/chitosan NPs compared with PLGA/chitosan-based systems, supporting their suitability for oral delivery applications.

## Chemically Modified EGCG-Based Nanocarriers for Nucleic Acid Delivery

Although gene therapy has emerged as a powerful therapeutic approach for diverse diseases by modulating pathogenic pathways at the genetic level, its clinical application remains limited by the lack of efficient and safe nucleic acid delivery systems. Conventional polymeric carriers typically compact DNA or RNA through electrostatic interactions, which often require polymers with high molecular weights or dense cationic charge.<sup>112</sup> However, such strongly cationic materials can induce cytotoxicity, membrane disruption, inflammatory responses, and limited biocompatibility.

EGCG-based carriers provide an alternative strategy for nucleic acid delivery by exploiting the intrinsic binding affinity of EGCG toward DNA and RNA. EGCG can interact with nucleic acids through hydrogen bonding,  $\pi$ - $\pi$  stacking, hydrophobic interactions, and other noncovalent forces, enabling nanocomplex formation while potentially reducing reliance on highly cationic polymers. In particular, chemically modified EGCG architectures can further improve complex stability, serum resistance, and targeting capability. These features may support safer and more efficient delivery of plasmid DNA, siRNA, and other nucleic acid therapeutics. The following examples illustrate how EGCG-building nanocarriers have been engineered to overcome key barriers in nucleic acid delivery.

For example, HA-EGCG was used to stabilize preformed plasmid DNA (pDNA)/PEI complexes through the strong affinity of EGCG for nucleic acids, forming a ternary nanocomplex for targeted gene delivery (Figure 7A).<sup>90</sup> The pDNA/PEI/HA-EGCG nanocomplex showed enhanced resistance to nuclease attack, partly due to the enzyme-inhibitory effect of EGCG, and promoted successful endosomal escape, demonstrating its ability to overcome major barriers in gene therapy. The nanocomplex also facilitated delivery into CD44-overexpressing colon cancer cells (HCT-116), which are typically difficult to transfect, even in serum-containing media. Compared with pDNA/PEI/HA nanocomplexes, the HA-EGCG-containing nanocomplex showed enhanced stability, CD44-targeting capability, and higher transfection efficiency both in vitro and in vivo. Wu et al developed PD-L1 siRNA-loaded FEGCG/Zn/erythrocyte NPs for cancer immunotherapy (Figure 7B).<sup>113</sup> Fluorinated, zinc-coordinated EGCG NPs (FEGCG/Zn) were generated by incorporating fluorine



**Figure 7** Chemically modified EGCG-based nanocarriers for nucleic acid delivery. **(A)** pDNA-loaded PEI/HA-EGCG nanocomplex.<sup>90</sup> **(B)** PD-L1 siRNA-loaded FEGCG/Zn/erythrocyte NP.<sup>113</sup> Reproduced with permission. \* $p < 0.05$ , \*\* $p < 0.01$  by one-way ANOVA analysis.

**Abbreviations:** CD44, cluster of determination 44; EGCG, (-)-epigallocatechin-3-gallate; FEGCG, fluorinated EGCG; HA-EGCG, hyaluronic acid-conjugated EGCG; NP, nanoparticle; pDNA, plasmid DNA; PEI, poly(ethylenimine); siRNA, small interfering RNA.

moieties and  $Zn^{2+}$  ions into EGCG, enabling the assembly of nanostructures capable of carrying diverse cargos, including small molecule chemotherapeutics such as sorafenib, gemcitabine, and DOX, as well as nucleic acids, peptides, and proteins. These NPs were subsequently anchored onto erythrocytes to extend systemic circulation. Erythrocyte hitchhiking enhanced intratumoral accumulation of PD-L1 siRNA, while co-delivery with FEGCG/Zn potentiated T cell-mediated cancer cell killing, likely through blockade of the PD-1/PD-L1 inhibitory axis that suppresses infiltrating  $CD8^+$  T cell activity. Collectively, these findings indicate that FEGCG/Zn can function both as a PD-L1 inhibitory component and as a versatile carrier for immune biomolecule delivery via cell-based transport.

Representative chemically modified EGCG-based nanocarriers for protein, small molecule, and nucleic acid delivery are summarized in Table 3, highlighting how EGCG modification enables more organized nanocarrier architectures with improved loading, stability, targeting, and therapeutic performance.

## EGCG-Building Nanocarriers versus Conventional Encapsulation Strategies

The examples discussed above demonstrate that EGCG-building nanocarriers are conceptually distinct from conventional encapsulation-based delivery systems. Conventional nanocarriers have contributed substantially to drug delivery by improving drug solubility, pharmacokinetics, biodistribution, and controlled release. Although these systems vary widely in formulation design and include several clinically established platforms, their therapeutic contribution is mainly derived from the loaded drug, whereas the carrier itself primarily serves delivery functions.

A key formulation constraint in conventional nanocarriers is the drug loading dilemma. In many systems, the API constitutes only a small fraction of the total NP mass, meaning that most of the administered NP dose consists of pharmacologically inert carrier materials rather than active ingredients.<sup>6</sup> Although such materials, including lipids,

**Table 3** Representative Chemically Modified EGCG-Based Nanocarriers

System	Payload	EGCG Component	Main Binding Mechanism	Drug Loading	Major Advantages	Ref.
Herceptin-loaded OEGCG/PEG-EGCG MNC	Trastuzumab; IFN- $\alpha$ -2a	OEGCG and PEG-EGCG	EGCG–protein hydrophobic interactions	LE ~100%; LC 64%	Protein stabilization, improved thermodynamic/kinetic stability, tumor selectivity, blood half-life, and tumor growth inhibition via carrier–drug synergy.	Chung et al, 2014 <sup>89</sup>
DOX-loaded PEG-EGCG MNC	Doxorubicin	PEG-EGCG	EGCG–DOX $\pi$ - $\pi$ stacking	LE up to 88%; LC up to 88%	Ultrahigh drug loading, excellent thermodynamic/kinetic stability, improved PK, safety, and tumor inhibition effects	Liang et al, 2018 <sup>72</sup>
SU-loaded PEG-EGCG MNC	Sunitinib	PEG-EGCG	EGCG–SU hydrophobic interaction	LE 93%; LC 14%	Improved anti-angiogenic effects via carrier–drug synergy, tumor-targeted delivery, expanded therapeutic window, overcoming resistance	Yongvongsoontorn et al, 2019 <sup>93</sup>
DOX-loaded FA-PEG-EGCG NP	Doxorubicin	Folic acid-conjugated PEG-EGCG	EGCG–DOX association	LE 70%; LC 15%	Folate receptor-targeted delivery, enhanced cellular uptake, improved antitumor efficacy	Chuan et al, 2021 <sup>103</sup>
Ce6-loaded PEG-EGCG NP	Chlorin e6	PEG-EGCG	EGCG–Ce 6 $\pi$ - $\pi$ stacking and hydrogen bonding	LE 89%; LC 44%	Improved Ce6 solubility/stability, enhanced cellular uptake, photodynamic therapy	Chen et al, 2020 <sup>105</sup>
Cisplatin-loaded HA-EGCG MNC	Cisplatin	HA-EGCG	EGCG–Cisplatin association	LE 41%; LC 44%	CD44-targeted delivery, reduced organ toxicity, improved antitumor efficacy	Bae et al, 2017 <sup>92</sup>
PD-L1 siRNA-loaded FEGCG/Zn/erythrocyte NP	PD-L1 siRNA	Fluorinated EGCG	EGCG– $Zn^{2+}$ coordination, siRNA complexation, erythrocyte hitchhiking	LE up to 96%; LC up to 64%	Delivery of diverse biomolecules, PD-L1 downregulation, erythrocyte-hitchhiking for enhanced tumor delivery	Wu et al, 2022 <sup>113</sup>

**Abbreviations:** CD44, cluster of determination 44; Ce6, chlorin e6; DOX, doxorubicin; EGCG, (–)-epigallocatechin-3-gallate; FA, folic acid; HA-EGCG, hyaluronic acid-conjugate EGCG; LC, Loading content (w/w); LE, Loading efficiency; MNC, micellar nanocomplex, NP, nanoparticle; OEGCG, oligomerized EGCG; PEG-EGCG, poly (ethylene glycol)-conjugated EGCG; SU, sunitinib.

synthetic polymers such as PEG, and inorganic components, are generally considered biocompatible, their cumulative exposure may contribute to carrier-associated toxicity, immunogenicity, or undesired tissue accumulation.<sup>7,8</sup>

To address the low-loading limitation of conventional carriers, minimal-carrier and carrier-free nanomedicines, including prodrug assemblies, drug–drug conjugates, and drug-rich self-assembled systems, have also been explored.<sup>114,115</sup> These strategies can substantially increase drug content by reducing inactive excipients, in some cases to 15–95% (w/w); however, they may also introduce new challenges, including colloidal instability, premature drug release, complex synthesis, and limited batch-to-batch reproducibility.

In contrast, EGCG-building nanocarriers use EGCG as a carrier-forming and pharmacoeactive component. Through multivalent interactions, including  $\pi$ – $\pi$  stacking, hydrogen bonding, hydrophobic interactions, metal coordination, and dynamic covalent bonding, EGCG can support the incorporation of structurally diverse payloads and contribute to nanocarrier assembly. This interaction-driven design may reduce reliance on inert carrier materials while enabling the carrier component to participate not only in drug loading and stabilization but also in therapeutic activity. In addition, the antioxidant, anti-inflammatory, anticancer, chemosensitizing, and resistance-modulating activities of EGCG may cooperate with the payload, distinguishing EGCG from auxiliary excipients or simply co-loaded therapeutic agents.

Another important distinction is payload adaptability. In conventional nanocarriers, carrier composition and formulation parameters often need to be optimized for each payload because drug loading depends strongly on drug-specific physicochemical properties and compatibility with the carrier matrix. By contrast, the multivalent interaction capacity of EGCG can enable adaptable loading of structurally diverse payloads through multiple favorable interactions.

A concise comparison of conventional encapsulation strategies and EGCG-building nanocarriers is provided in Table 4. As summarized, EGCG-building nanocarriers represent an emerging pharmacoeactive nanocarrier platform with potential to serve as an alternative to inert carrier-based DDS by integrating delivery and therapeutic functions.

**Table 4** Comparison of EGCG-Building Nanocarriers and Conventional Encapsulation Strategies

Feature	Conventional Encapsulation Strategies	EGCG-Building Nanocarriers
<b>Design strategy</b>	Drugs are encapsulated into inert carrier matrices such as liposomes, polymeric micelles, polymeric nanoparticles, inorganic carriers.	EGCG functions as a pharmacoeactive and carrier-forming component through drug binding, self-assembly, metal coordination, or chemical conjugation.
<b>Drug incorporation and payload adaptability</b>	Drug loading relies on passive entrapment, hydrophobic partitioning, or electrostatic adsorption and often requires payload-specific optimization.	Interaction-driven loading occurs through $\pi$ – $\pi$ stacking, hydrogen bonding, hydrophobic interactions, metal coordination, or boronate ester formation, allowing adaptable loading of diverse payloads.
<b>Drug loading and carrier burden</b>	Often limited by carrier capacity and colloidal stability, requiring substantial inert excipients.	May enhance drug association and reduce inert carrier burden via favorable EGCG–payload interactions.
<b>Therapeutic contribution</b>	Primarily derived from the encapsulated drug; the carrier mainly provides delivery functions.	Derived from both the payload and EGCG carrier component through additive or synergistic effects.
<b>Release behavior</b>	Governed by diffusion, matrix degradation, membrane disruption, or environmental responsiveness.	Governed by EGCG–payload interaction strength and stimulus-responsive dissociation such as pH, redox, enzymatic activity, or competing ligands.
<b>Stability and crystallization</b>	Stability depends on carrier degradation, drug leakage, and drug–matrix compatibility; crystallization depends on matrix amorphicity and drug–polymer miscibility.	Stability depends on EGCG oxidation, pH sensitivity, and complex dissociation; EGCG-mediated complexation may suppress payload crystallization.
<b>Safety considerations</b>	Inert excipients may contribute to excipient-related toxicity, immunogenicity, or tissue accumulation.	Reduced inert excipient burden, but oxidation state, nonspecific biomolecular interactions, and concentration-dependent toxicity require evaluation.
<b>Pharmacokinetic considerations</b>	Generally minimal from inert carrier materials, although carrier materials can affect biodistribution and clearance.	EGCG may modulate transporters, metabolic enzymes, drug-binding proteins, or co-administered drugs, potentially altering drug disposition.
<b>Scalability and reproducibility</b>	Relatively established for selected carrier classes; scalable manufacturing processes are available for some platforms.	Largely preclinical; reproducible control of EGCG/payload complexation, oxidation state, and chemical structure requires further standardization.
<b>Clinical translation status</b>	Several formulations are in clinical use or advanced trials, with relatively defined regulatory pathways for approved excipients.	Predominantly preclinical; no clinical-stage EGCG-building nanocarrier has been reported, and regulatory classification remains undefined.

**Abbreviation:** EGCG, (–)-epigallocatechin-3-gallate.

The physicochemical and translational issues that must be addressed to realize this potential are discussed in the following section.

## Physicochemical Consideration, Translational Challenges, and Future Perspectives

EGCG-building nanocarriers represent a promising pharmacoactive delivery platform because EGCG can function simultaneously as a drug-binding element, structural carrier component, and therapeutic contributor. By integrating these roles, EGCG-building systems can improve drug loading, stabilize payloads within nanoscale assemblies, reduce reliance on pharmacologically inert excipients, and promote cooperative therapeutic effects between the carrier and payload. Chemically modified EGCG derivatives further enable more organized nanostructures with improved stability, tunable release behavior, and enhanced pharmacokinetic performance. This shift in carrier function, from serving merely as an inert excipient to acting as a therapeutic contributor, represents a significant conceptual advancement in nanomedicine design and may help address long-standing constraints such as low drug loading and modest therapeutic benefit. Nevertheless, these advantages remain largely preclinical, and several physicochemical, biological, and translational challenges must be addressed before clinical application.

Besides EGCG, other polyphenol-based nanocarriers have also been studied, and their formulation properties differ substantially depending on the molecular characteristics of the polyphenol used. For instance, curcumin is a representative pharmacoactive polyphenol that has been widely investigated for nanomedicine applications because of its anticancer, anti-inflammatory, and antioxidant activities.<sup>14</sup> However, curcumin is highly hydrophobic and poorly water-soluble, and its crystallization or aggregation can limit formulation stability and bioavailability. By comparison, EGCG is relatively more water-compatible and contains catechol and galloyl groups that enable diverse interactions with therapeutic payloads. A defining advantage of EGCG-building nanocarriers is that structurally diverse drugs can be complexed or assembled into nanostructures in aqueous media through favorable EGCG–drug interactions. These interaction-driven assemblies can facilitate efficient drug loading without requiring large amounts of synthetic polymers or organic solvents, thereby supporting a simpler and potentially less excipient-intensive formulation strategy. Nevertheless, EGCG is more susceptible to oxidation and pH-dependent degradation in aqueous and physiological environments. Thus, the key formulation challenges differ among polyphenol-based systems: curcumin-based systems often require strategies to improve solubilization and suppress crystallization, whereas EGCG-building systems require precise control of oxidation, interaction dynamics, and biological fluid-induced complex dissociation.

In this context, solubility, crystallization, and aggregation behavior also require systematic evaluation. Free EGCG is relatively water-soluble compared with highly hydrophobic polyphenols such as curcumin, but many therapeutic payloads incorporated into EGCG-building nanocarriers are poorly water-soluble aromatic drugs. EGCG-mediated complexation can improve apparent aqueous dispersibility by promoting nanoscale assembly through aromatic stacking, hydrogen bonding, hydrophobic interactions, or coordination bonds. In some systems, EGCG-based carriers may also suppress drug crystallization by maintaining payloads in an amorphous, molecularly associated, or nanoscale dispersed state within the nanostructure.<sup>116</sup> However, this benefit is formulation-dependent. Insufficiently controlled EGCG–payload interactions may result in partial crystallization, aggregation, or precipitation during storage, dilution, or exposure to biological fluids, thereby altering drug loading, release kinetics, biodistribution, and toxicity. Therefore, future characterization should include not only particle size and drug loading but also payload crystallinity, amorphous stability, aggregation behavior, colloidal stability, and physical stability under storage and physiologically relevant conditions.

A central challenge is the intrinsic chemical instability of EGCG. As a polyphenolic compound, EGCG can undergo autoxidation and react with oxygen or metal ions, and it may degrade upon exposure to light, elevated temperature, pH variations, or enzymatic activity.<sup>22</sup> This instability can complicate manufacturing because oxidation may occur during conjugation or NP formation, producing heterogeneous reaction by-products and leading to variable molecular structures, inconsistent drug-to-carrier ratios, and batch-to-batch variability. For example, oxidation-driven self-assembly strategies, often involving metal ions or oxidative enzymes, have been widely explored because they enable facile NP formation,

but the precise chemical identities of oxidized intermediates are often poorly defined, and structural heterogeneity remains insufficiently characterized.<sup>117</sup> Given that the antioxidant, anticancer, and anti-inflammatory activities of EGCG are structure-dependent, controlling its oxidation state is essential for reproducible therapeutic performance. In vivo, EGCG is also vulnerable to oxidation after administration, producing quinones or other reactive intermediates that may form unwanted adducts with biomolecules, potentially leading to off-target effects or premature loss of activity.<sup>118</sup> While EGCG's redox behavior can be therapeutically advantageous, for example by participating in redox cycling or enhancing ROS levels in tumors, it may simultaneously cause unintended biological outcomes. Importantly, conjugation of EGCG to polymers or assembly into hierarchically organized structures has been shown to markedly improve oxidation resistance compared with free EGCG.<sup>22,119</sup> In organized structures, EGCG may be physically shielded within hydrophobic domains or sterically protected by polymer shells, limiting exposure to oxidative triggers. These observations are promising, yet systematic studies examining oxidation kinetics, degradation pathways, and in vivo chemical stability of EGCG within nanostructures remain limited. Therefore, validation of EGCG structural integrity under storage, physiological, and disease-specific conditions will be important for further development.

EGCG–payload interaction dynamics are another important determinant of nanocarrier performance. The multimodal interactions of EGCG enable efficient loading of diverse payloads, ranging from hydrophobic small molecule drugs to hydrophilic biomacromolecules such as proteins and nucleic acids. These interactions can enable high drug loading and reversible association with fragile biomolecules, helping to preserve their structure and activity, which is often challenging for conventional polymeric or lipid carriers. However, the same interaction-driven design requires careful control. Although strong EGCG–drug binding promotes drug encapsulation and prevents premature leakage during circulation, excessively strong binding may hinder payload release at the disease site. Conversely, weak or unstable interactions may lead to premature dissociation during dilution or exposure to biological fluids. To balance robust drug loading with responsive release, careful selection of drugs with well-defined interaction modes, together with rational carrier design, is required.

The broad binding capacity of EGCG may also influence biological interactions after administration. EGCG does not exclusively bind therapeutic payloads; it can also interact with endogenous proteins, nucleic acids, lipophilic molecules, transporters, and metabolic enzymes. When EGCG moieties are exposed on nanoparticle surfaces, interactions with circulating proteins may contribute to protein corona formation, altered biodistribution, immunological recognition, or unintended biological activity. Hydrophilic shells such as PEG or polysaccharides are therefore commonly used to shield EGCG–payload complexes and reduce nonspecific interactions. However, some unshielded or minimally shielded EGCG-based assemblies formed through oxidative or metal-coordination crosslinking have shown efficient delivery and antitumor efficacy without apparent acute toxicity, suggesting that the biological consequences of surface-exposed EGCG remain system-dependent and incompletely understood. Further studies on nanoparticle morphology, surface chemistry, protein corona formation, and in vivo fate are needed to support predictable biological performance.

The synergistic therapeutic effect enabled by EGCG-building nanocarriers represents one of their most transformative advantages. Besides enabling drug loading and delivery, EGCG directly participates in therapy by modulating signaling pathways, altering redox balance, inhibiting multidrug resistance transporters, and protecting normal tissues from drug-induced toxicity. These actions may enable enhanced therapeutic outcomes at lower drug doses and expand therapeutic windows for otherwise toxic drugs. Although numerous studies have reported improved efficacy in vitro and in vivo using EGCG-building nanocarriers, only a limited number have quantitatively and mechanistically evaluated synergy through combination index analysis, pathway elucidation, or computational assessment. Because synergy underpins the rationale for EGCG-building nanocarriers in addressing the limited efficacy of traditional low-loading formulations, robust and mechanistically grounded evidence of such synergy is indispensable for advancing these systems toward clinical translation and regulatory approval.

In addition, EGCG-containing carriers may influence drug disposition, particularly when they produce high local or systemic EGCG exposure. Because EGCG can modulate drug transporters and metabolic enzymes and can directly bind certain therapeutic agents,<sup>50</sup> EGCG-building nanocarriers should be evaluated not only as delivery systems but also as potential modifiers of pharmacokinetics and biodistribution. This consideration is particularly important for drugs with narrow therapeutic windows, limited solubility, transporter-dependent absorption or clearance, or known sensitivity to

catechol/boronate interactions. Comparative pharmacokinetic studies using free drug, free EGCG plus drug, blank EGCG-building carrier, drug-loaded EGCG-building nanocarrier, and, where relevant, co-administered drugs would help distinguish nanocarrier-mediated delivery effects from EGCG-mediated pharmacokinetic interactions.

Safety considerations are also polyphenol-specific and dose-dependent. Although polyphenols are often perceived as biocompatible natural compounds, their biological activities can change at pharmacological concentrations. Curcumin and other polyphenols have been reported to show formulation- and dose-dependent cytotoxic or pro-oxidant effects under certain conditions.<sup>120</sup> Similarly, EGCG can exert antioxidant or pro-oxidant effects depending on concentration, redox environment, metal ion availability, and cellular context, and high systemic exposure has been associated with hepatotoxicity concerns.<sup>21</sup> Therefore, EGCG-building nanocarriers should be evaluated based on EGCG-equivalent dose, release kinetics, oxidation state, tissue exposure, and repeated dose safety, rather than assuming safety solely from the dietary origin of EGCG. Such evaluation should also consider whether high EGCG-equivalent exposure from the carrier alters the disposition or toxicity of the loaded drug or concomitantly administered medications.

Long-term safety and manufacturability remain major translational considerations. Repeated administration may raise concerns about accumulation of non-degradable or slowly eliminated components, particularly in formulations containing inorganic materials used for coordination, imaging, catalysis, or chemodynamic therapy.<sup>121</sup> Although many NPs containing inorganic materials have demonstrated useful potential for catalysis, bioimaging, and targeting, safety remains a well-recognized barrier to their clinical translation.<sup>122</sup> Immunogenic carrier segments, including certain polymers, peptides, or targeting ligands, may also induce immune activation, reduce therapeutic efficacy, or cause immediate or delayed adverse reactions after repeated exposure. Although many short-term preclinical studies have shown acceptable safety, comprehensive evaluation of pharmacokinetics, metabolism, biodegradation, immunogenicity, organ accumulation, and chronic toxicity will be necessary. From a manufacturing perspective, chemically modified EGCG systems require rigorous control of chemical structure, substitution degree, purity, oxidation state, batch-to-batch consistency, and scalable synthesis, in addition to the EGCG stability issues discussed above.

Finally, the route of administration will strongly affect clinical feasibility. Most EGCG-building nanocarriers have been evaluated by parenteral injection, whereas non-invasive routes may be desirable for chronic diseases because they can improve patient convenience and adherence. Oral delivery is particularly challenging because nanocarriers must maintain structural integrity in the gastrointestinal tract, withstand acidic and enzymatic environments, and cross the intestinal epithelium. These requirements are especially demanding for protein and peptide payloads. Only a limited number of EGCG-building nanocarriers have demonstrated improved oral bioavailability of small molecule drugs. Further development of oral or other non-invasive systems will require protection of both EGCG moieties and payloads from degradation, together with nanostructure engineering strategies such as mucoadhesive design, surface charge optimization, and absorption enhancement.

Taken together, the clinical translation of EGCG-building nanocarriers will require coordinated advances in EGCG molecular engineering, mechanistic understanding of EGCG–payload and EGCG–biomolecule interactions, standardized physicochemical characterization, scalable manufacturing, and rigorous pharmacokinetic and safety evaluation. With continued progress in these areas, EGCG-building systems have strong potential to advance from promising preclinical platforms to clinically meaningful pharmacoactive nanocarriers.

## Conclusions

EGCG-building nanocarriers represent an emerging class of pharmacoactive delivery systems that integrate structural and therapeutic functions within a single platform. By exploiting the multivalent binding capacity and intrinsic bioactivity of EGCG, these systems can promote efficient payload association, reduce reliance on pharmacologically inert carrier materials, and enable cooperative therapeutic effects between the carrier and payload. Unlike many conventional nanocarriers, in which therapeutic performance is primarily determined by the loaded drug, EGCG-building architectures allow the carrier component itself to contribute to drug stabilization, controlled release, resistance-modulation, toxicity reduction, and therapeutic efficacy.

Current evidence remains largely preclinical, with many studies focused on cancer therapy, but the concept may be extendable to other disease areas when EGCG–payload interactions, carrier stability, and biological behavior are

appropriately controlled. Several challenges may explain the current translational gap. In relatively simple EGCG–drug nanocomplexes or metal–phenolic assemblies, oxidation sensitivity, dynamic EGCG–payload interactions, and biological fluid-induced dissociation may affect formulation reproducibility, stability, and release behavior. Chemically modified EGCG systems may partially address these limitations through more controlled molecular design and hierarchical assembly, but they require rigorous characterization of chemical structure, substitution degree, purity, oxidation state, batch-to-batch consistency, scalability, and degradation behavior.

Future development will require precise control of EGCG chemistry, standardized characterization of drug loading, release profiles, surface properties, colloidal stability, oxidation state, and degradation behavior, together with rigorous pharmacokinetic, biodistribution, immunogenicity, and toxicity evaluation. Particular attention should also be given to the potential influence of EGCG-containing carriers on the disposition and safety of loaded drugs and concomitantly administered medications. With these advances, EGCG-building systems may progress from promising preclinical platforms to clinically meaningful pharmacoactive nanocarriers capable of improving therapeutic efficacy while reducing inert carrier burden.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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