Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) *2025 26(7):633-656*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Review

https://doi.org/10.1631/jzus.B2400040

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EGCG as a therapeutic agent: a systematic review of recent advances and challenges in nanocarrier strategies

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Abstract: Epigallocatechin-3-gallate (EGCG), a bioactive polyphenol abundant in green tea, has garnered significant attention for its diverse therapeutic applications, ranging from antioxidant and anti-inflammatory effects to potential anticancer properties. Despite its immense promise, the practical utilization of EGCG in therapeutic settings as a medication has been hampered by inherent limitations of this drug, including poor bioavailability, instability, and rapid degradation. This review comprehensively explores the current challenges associated with the application of EGCG and evaluates the potential of nanoparticle-based formulations in addressing these limitations. Nanoparticles, with their unique physicochemical properties, offer a platform for the enhanced stability, bioavailability, and targeted delivery of EGCG. Various nanoparticle strategies, including polymeric nanoparticle, micelle, lipid-based nanocarrier, metal nanoparticle, and silica nanoparticle, are currently employed to enhance EGCG stability and pharmacological activity. This review concludes that the particle sizes of most of these formulated nanocarriers fall within 300 nm and their encapsulation efficiency ranges from 51% to 97%. Notably, the pharmacological activities of EGCG-loaded nanoparticles, such as antioxidative, anti-inflammatory, anticancer, and antimicrobial effects, are significantly enhanced compared to those of free EGCG. By critically analyzing the existing literature and highlighting recent advancements, this article provides valuable insights into the promising prospects of nanoparticle-mediated EGCG formulations, paving the way for the development of more effective and clinically viable therapeutic strategies.

Key words: Epigallocatechin-3-gallate (EGCG); Nanoparticle; Nanocarrier; Nanosystem; Nanoformulation; Stability; Biological activity

1 Introduction

Within the catechin family, epigallocatechin-3-gallate (EGCG) stands out as a highly potent antioxidant. While sharing structural similarities with other catechins, EGCG contains an additional gallic acid moiety, amplifying its antioxidant and anti-inflammatory abilities. Within the flavonoid family, EGCG is derived from the flavan-3-ol subgroup. Notably, during its synthesis, it undergoes structural modification where the original hydroxyl (–OH) group at position 3 on the tetrahydropyran moiety is replaced by a galloyl group. This results in the incorporation of a benzenediol ring (A), a tetrahydropyran moiety (C), a pyrogallol ring (B), and a galloyl group (D), collectively forming the distinctive chemical structure of EGCG (Botten et al., 2015), as illustrated in Fig. 1. The antioxidative property of EGCG is attributed to its potent ability to scavenge various free radicals (Chandra and Arora, 2018; He et al., 2018), to inhibit metal-mediated oxidation (Zwolak, 2021), as well as to stimulate the synthesis of endogenous antioxidant enzymes, amplifying the cellular defense against oxidative stress (Wada et al., 2019).

The above antioxidative properties of EGCG contribute to a diverse range of biological activities, such as anti-inflammatory, anti-cancer, cardioprotective, and neuroprotective effects, making it a promising candidate for therapeutic applications for inflammatory or

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Received Jan. 24, 2024; Revision accepted June 10, 2024;
Crosschecked June 19, 2025; Published online June 30, 2025

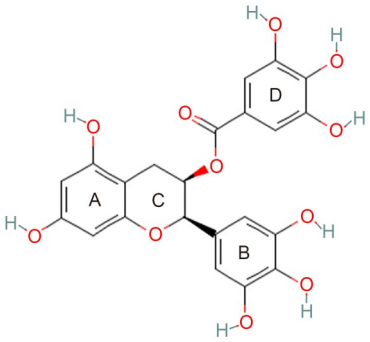

Fig. 1 Two-dimensional (2D) structure image of CID 65064 (epigallocatechin-3-gallate (EGCG)). A: benzenediol ring; B: pyrogallol ring; C: tetrahydropyran moiety; D: galloyl group.

oxidative stress-associated diseases (Alam et al., 2022; Furniturewalla and Barve, 2022; Mohd Sabri et al., 2022; Parn et al., 2022; Youn et al., 2022; Khor et al., 2023). Over the past decades, the protective effects of EGCG against metabolic disorders have garnered significant interest, particularly concerning its roles in modulating carbohydrate and lipid metabolism, as evidenced by its inhibitory effects on α-glucosidase, α-amylase, and lipase (Jiang et al., 2021; Wen et al., 2022; Ma et al., 2024).

Nevertheless, the practical application of EGCG as a therapeutic agent has been hindered by its poor stability in the intestinal environment, low permeability and active efflux, as well as rapid degradation (Cai et al., 2018; Cano et al., 2019). EGCG is prone to degradation under harsh conditions (alkaline medium, enzymatic degradation) because of its susceptibility to oxidation, which underscores the importance of preventing its uncontrolled degradation within biological systems. Such degradation can lead to inconsistent drug release kinetics, jeopardizing the therapeutic efficacy and patient outcomes, potentially resulting in inadequate treatment and unintended side effects. The encapsulation of EGCG within nanocarriers has been shown to effectively mitigate its degradation by providing a protective environment to shield the molecule from external factors such as pH changes and enzymatic activity. In addition, surface modifications and coatings can be applied to nanocarriers to further enhance their stability and protect the EGCG encapsulated within them, which helps regulate drug release kinetics and prevent premature degradation. Overall, nanocarriers serve as effective tools for controlling drug degradation and ensuring the stability and efficacy of the encapsulated EGCG under various physiological conditions. This review aims to critically assess and consolidate the current state of research on nanoparticle-mediated strategies for formulating EGCG, with a focus on overcoming the inherent limitations of this drug to unlock its full therapeutic potential.

1.1 EGCG: limitations as a therapeutic agent

Achieving optimal drug bioavailability and absorption is a pivotal aim in drug development and formulation. Drug bioavailability and therapeutic effects are profoundly influenced by various factors, including solubility, permeability, and the intricacies of first-pass metabolism.

1.1.1 Poor stability under intestinal conditions

Orally consumed EGCG undergoes a drastic pH change in the body, from a strongly acidic condition in the stomach (pH 2) to an alkaline environment in the intestine (pH 8). EGCG is unstable under alkaline condition and quickly undergoes degradation via oxidation (Zhu et al., 1997; Cano et al., 2019). The structural vulnerability of EGCG lies in its pyrogallol ring that comprises three hydroxyl groups, rendering its high susceptibility to autooxidation, poor stability, and rapid degradation (Severino et al., 2009). Autooxidation occurs in the alkaline medium of the intestine together in the presence of molecular oxygen. Two hydrogen atoms of the hydroxyl groups are snatched away by the oxygen molecule, resulting in the simultaneous formation of hydrogen peroxide and several intermediate products of pyrogallol oxidation (Omoruyi et al., 2020). This leads to the impaired integrity of the structure of EGCG and its poor bioavailability in the systemic circulation.

1.1.2 Low permeability and active efflux

The absence of a specific carrier or receptor for EGCG on the surface of small intestinal epithelial cells necessitates reliance on passive diffusion, comprising both paracellular and transcellular transports, as the primary route of EGCG absorption (Cai et al., 2018). However, eight hydroxyl groups on the benzenediol, pyrogallol, and galloyl groups in EGCG could form hydrogen bonding with water molecules, leading to high hydrophilicity and resulting in poor membrane permeability across biological membranes (Dahan and Miller, 2012). Besides, EGCG absorptions

into the small intestine encounter active hindrance from efflux transporters such as P-glycoprotein (P-gp). These transporters actively pump EGCG out of the cells, leading to its poor bioavailability (Dai et al., 2020a). This limitation in permeation across the small intestine prevents a substantial amount of EGCG from reaching target tissues and executing its therapeutic functions effectively.

1.1.3 Rapid metabolism

EGCG undergoes a series of metabolic activities upon ingestion. Esterase enzymes, present in the saliva, hydrolyze the ester bond between the tetrahydropyran moiety and the galloyl group in EGCG, causing the formation of a degalloylated EGCG derivative (Higdon and Frei, 2003). Subsequent metabolic processes in the small intestine and liver, including methylation, sulphation, and glucuronidation, lead to the biotransformation of EGCG into *O*-methylated, sulphated, and glucuronidated conjugates (Rietveld and Wiseman, 2003; Mokra et al., 2022). These metabolites exhibit different structures and biological activities as compared to their parent compound, therefore their efficacy in achieving therapeutic outcomes may not reach that of the original compound. This underscores the potential impact of metabolism on the therapeutic effectiveness of EGCG (Xu et al., 2004; Dai et al., 2020a).

1.2 Nanocarriers as stability and biological activity enhancers

While EGCG shows great promise as a therapeutic agent, addressing the above limitations is essential for its successful development and application in clinical settings. Researchers continue to explore innovative formulations and strategies to overcome these challenges and harness the potential benefits of EGCG in various health conditions. This review aims to discuss the existing nanoparticle strategies, including polymeric nanoparticle, micelle, lipid-based nanocarrier, metal nanoparticle, and silica nanoparticle, emphasizing their roles in optimizing the therapeutic efficacy of EGCG via various experimental models.

Nanocarriers are nano-sized structures, typically ranging from tens to hundreds of nanometers in size, to encapsulate therapeutic agents such as drugs, proteins, or nucleic acids for targeted drug delivery. They can be designed using various materials such as lipids, polymers, or inorganic substances, each offering unique advantages in terms of stability, biocompatibility, and drug release kinetics (Table 1). Once loaded with the

Table 1 Advantages and disadvantages of different nanocarriers

Type	Advantage(s)	Disadvantage(s)
Polymeric nanoparticle	Higher stability than lipid-based nanocarrier, controlled release behavior, and incorporation of biodegradable materials	Toxicity issue caused by prolonged retention of synthetic polymer, and difficulty in scaling up
Micelle	Enhanced solubility of lipophilic drug, small particle size, biocompatibility, and biodegradability	Instability below critical micelle concentration (CMC)
Liposome	Encapsulation of both hydrophilic and lipophilic drugs, as well as protection against drug degradation	Drug leakage, low drug loading, and large particle size
Solid lipid nanoparticle	Low toxicity, biodegradability, and targeted drug delivery	Lipid polymorphism-induced drug leakage and initial burst release behavior
Nanostructured lipid carrier	Enhanced physical stability, high drug loading capacity, and biocompatibility	Selective drug choice
Gold nanoparticle	Large surface area, being less invasive and exhibiting localized plasmon surface resonance (LPSR) phenomenon	Weak optical signal
Silver nanoparticle	Low toxicity and biocompatibility	Off-target drug delivery
Selenium nanoparticle	High stability	Synthesis method-dependent biocompatibility
Zinc oxide nanoparticle	Large surface area, high photostability, and enhanced redox capacity	Off-target drug delivery
Silica nanoparticle	Tunable particle size, excellent compatibility within living systems, and large surface area	Scattered particle size distribution

Extracted from: Talluri et al., 2015; Kahraman et al., 2017; Khan and Roy, 2019; Sharma et al., 2019; Lu et al., 2021; Huang et al., 2022; Milligan and Saha, 2022; Sampath et al., 2024.

desired drug, nanocarriers can be administered through various routes such as oral, intravenous, or topical, depending on the target tissue and the desired therapeutic outcome. Upon reaching the target site, nanocarriers can passively accumulate via enhanced permeability and the retention (EPR) effect or actively target specific cells or tissues through surface modifications or ligand conjugation. Once internalized by the target cells, nanocarriers release the encapsulated drug either through diffusion, degradation, or triggered release mechanisms, resulting in localized therapeutic effects while minimizing potential systemic toxicity.

Various nanocarriers, each with distinct structures and compositions, have been constructed and investigated to encapsulate EGCG (Table 2). These serve as protective vehicles, addressing the limitations of EGCG and facilitating its efficient delivery to target sites. In this paper, we carried out an extensive search for studies delving into the exploration and comparative analysis of EGCG-loaded nanocarriers.

2 Search strategy

Data collection was conducted by entering the key terms ("EGCG" OR "Epigallocatechin-3-gallate" OR "Epigallocatechin gallate") AND ("Micelle" OR "Liposome" OR "Nanoparticle" OR "Nanotube" OR "Silica" OR "Dendrimer" OR "Niosome" OR "Nanosuspension" OR "Nanomicelle" OR "Nanocrystal" OR "Nanosphere" OR "Nanocapsule" OR "Metal nanoparticle") AND ("in vitro" OR "in vivo") into the Scopus database. The search was constrained to articles published between 2018 and 2023, focusing on the document type. Full-text articles published in English and relevant to EGCG, featuring a single active ingredient, utilizing at least one in vitro or in vivo experimental model, and including functional studies or measured therapeutic effects (determination of biological or pharmacological activity), were included in the final review. The initial search of the database yielded 132 records. Following screening by title and abstract, 117 full-text articles were analyzed. Among these, 78 papers were excluded, leaving 39 papers meeting the inclusion criteria that were included in this review (Fig. 2). The key findings are illustrated in Table 2 and Fig. 3.

3 Main findings

In this paper, the database search revolved around exploring various nanocarrier systems employed for the formulation of EGCG, which found five types of nanocarriers, namely, polymeric nanoparticle, micelle, lipid-based nanocarrier, metal nanoparticle, and silica nanoparticle. Each nanocarrier was examined for its unique structural features and advantages in encapsulating EGCG. The studies selected highlight the potential of these nanocarrier systems to enhance the stability, bioavailability, therapeutic efficacy, and safety profile of EGCG-loaded formulations, providing a comprehensive overview of the current advancements in EGCG nanoparticle technology.

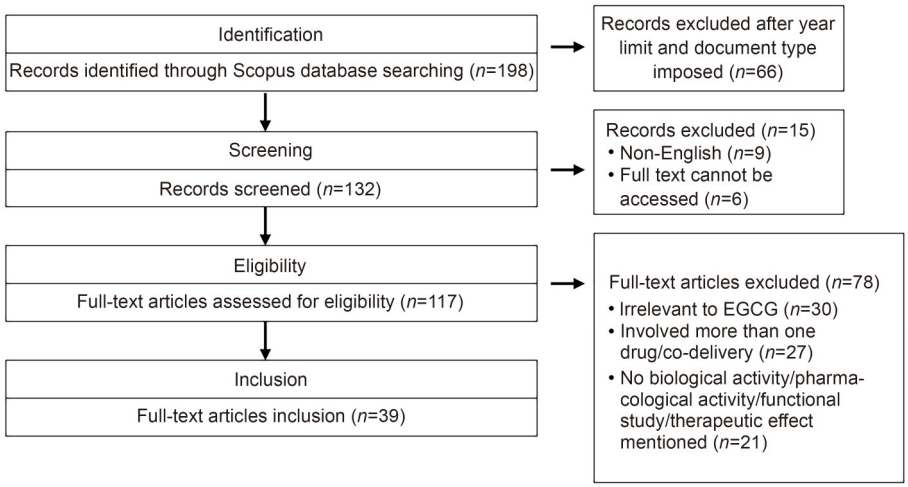

Fig. 2 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart of study selection.

Table 2 Characteristics and biological effects of EGCG-loaded nanocarrier systems

Type	Composition	Production method	Particle size (nm)	Zeta potential (mV)	Encapsulation efficiency (%)	Experimental model	Biological effect (as compared to free EGCG)	Reference
Polymeric nanoparticle	Type-A gelatin, poly-γ-glutamic acid	Solvent injection	155.1±7.3	−23.9±0.9	51.2–72.4	Human colorectal adenocarcinoma cells (Caco-2)	Enhanced antioxidant activity	Zhang WJ et al., 2023
	PLGA, Poloxamer-407	Double emulsion/ solvent evaporation	134±4		58±5	Lung adenocarcinoma epithelial cell line (A549) and HDF cells	Enhanced anticancer activity	Minnelli et al., 2023
	Hordein	Liquid–liquid dispersion	160±10	20.7±0.4	91.2±0.2	Human liver cancer cell line (HepG2)	Enhanced antioxidant activity	He et al., 2020; Song et al., 2022
	CSSPS	Mixing followed by centrifugation and ultrafiltration	152.00±3.35	19.00±0.86	87.53±0.27	In vitro normal cells (HUVECs) and various tumor cell lines (HCT-116, MCF-7, HepG2, K562, A549, and DU145), *Listeria monocytogenes*, *Escherichia coli*, and *Staphylococcus aureus*, ex vivo salmon	Enhanced antioxidant, antitumor, and antimicrobial activities	Zhou et al., 2022
	Glycine, formaldehyde, Pluronic F-127	One-step polyphenolic condensation reaction (Mannich condensation)	72.4±9.7	−38		In vitro RAW264.7 cell line, mouse peritoneal macrophages extracted from BALB/c mice, in vivo chronic periodontitis rat	Enhanced anti-inflammation, antioxidant, and anti-osteoclastogenic effects	Tian et al., 2022
	Pluronic F-68, PBCA	Self-polymerization method	156.03±4.82	−31.05±2.41	90.32±3.45	Silica-induced pulmonary fibrosis Sprague Dawley rat model	Enhanced anti-fibrosis effect	Yao et al., 2022
	PBCA, EtOAc	Interfacial polymerization	EGCG-PBCA NP water (50.9±3.1); EGCG-PBCA NP oil (55.7±2.8)	EGCG-PBCA NP water (−21.7±1.3); EGCG-PBCA NP oil (−24.6±3.0)	EGCG-PBCA NP water (76.30±1.81); EGCG-PBCA NP oil (74.60±2.32)	*Bacillus subtilis*, *Staphylococcus sureus*, *E. coli*, and *Micrococcus tetragenus*	Enhanced anti-bacterial activity	Hu et al., 2021

To be continued

Table 2 (continued)

Type	Composition	Production method	Particle size (nm)	Zeta potential (mV)	Encapsulation efficiency (%)	Experimental model	Biological effect (as compared to free EGCG)	Reference
Polymeric nanoparticle	Chitosan	Nanoprecipitation	362.93±28.36	40.87±0.64		Gram-negative strain (*Pseudomonas fluorescens* ATCC 13525) and Gram-positive strain (*S. aureus* ATCC 25923)	Enhanced antibacterial and antioxidant effects	Moreno-Vásquez et al., 2021
	Lysozyme, pectin	Mixing	About 200	−28.50±1.42	71.77±8.01	N2 WT *Caenorhabditis elegans*	Enhanced antioxidant activity	Zhang et al., 2021
	Hyaluronan, fucoidan, PEG, gelatin	Mixing and centrifugation	217.00±14.00	−33.60±1.30	52.08±5.37	RAW264.7 cells	Enhanced anti-inflammation effect	Ho et al., 2020
	PLGA, folate peptide	Nanoprecipitation followed by conjugation with folate peptide	169.0±5.6	−25.60±3.81	52.30±2.05	In vitro breast adenocarcinoma cell lines (MDA-MB-231 and MCF-7), in vivo Sprague Dawley rats, and MDA-MB-231 tumor-bearing nude mice	Enhanced antitumor activity	Kazi et al., 2020
	Chitosan, β-Lg	Ionic cross linking	157.20±5.15	30.51±5.31	76.29±1.45	Human colorectal adenocarcinoma cells (Caco-2)	Enhanced cellular antioxidant activity	Dai et al., 2020b
	PVP, $FeCl_3 \cdot 6H_2O$	Ultrasonication and dialysis	3.2±1.2	−10		Rat pheochromocytoma cells (PC12)	Enhanced anti-fibrillation of Aβ40	Liu et al., 2019
	PLGA-PEG, Tween 80 (surfactant), EtOAc (oil phase)	W/O/W double emulsion-solvent evaporation	168.5±9.9	−23.3±5.3	>95	In vitro astrocytes, mouse brain microvascular endothelial cells (bEnd.3) and rat pheochromocytoma cells (PC12), in vivo WT C57BL/6J mice, ex vivo rat NPCs	Enhanced anti-seizure and neuroprotection effects	Cano et al., 2018; Kühne et al., 2019
	PLGA and Pluronic F-127	Emulsion/solvent evaporation	129.4±15.5		86.27±2.42	NLCs	Enhanced antioxidant activity	Hoyos-Ceballos et al., 2018

To be continued

Table 2 (continued)

Type	Composition	Production method	Particle size (nm)	Zeta potential (mV)	Encapsulation efficiency (%)	Experimental model	Biological effect (as compared to free EGCG)	Reference
Polymeric nanoparticle	PLA, PEG	Double emulsion solvent evaporation	317.8	−24.5	96.25±1.01	Male Swiss Albino Wistar rats induced with aluminum chloride and neuroblastoma cell line (SH-SY-5Y)	Enhanced anti-fibrillation, neuroprotection and antioxidant effects	Singh et al., 2018a, 2018b
	Type A gelatin, hyaluronic acid	Magnetic stirring	253.4±7.3	9.2±1.8	97.8±0.5	In vitro HCECs, in vivo Wistar rats and New Zealand White rabbits with healthy eyes	Enhanced anti-inflammation effect	Huang et al., 2018
	ES100, PLGA	Emulsion evaporation	91.3±0.8	−21.3	80.8±1.6	Sprague Dawley rats	Enhanced renal protection	Zhang and Zhang, 2018
Micelle	EGCG, Fmoc-Cl, Pluronic F-68	Esterification followed by solvent evaporation	163.10±2.54	−17.07±0.25		Breast cancer cells (4T1)	Enhanced anticancer activity	Liu et al., 2023
	Tween 80 and Span 80	Direct dissolution				In vitro Henrietta Lacks (HeLa) cancer cells, in vivo Wistar rats	Enhanced anticancer activity	Rosita et al., 2019
Lipid-based nanocarrier								
Liposome	SPC, cholesterol, glucose ligand	Thin-film hydration and sonication	158.70±1.30	2.37±0.53	73.05±1.00	Rat adrenal pheochromocytoma cells (PC12) and mouse brain microvascular endothelial cells (bEnd.3)	Enhanced antioxidant activity	Xia et al., 2023
	DPPG (sodium salt), DPPC, cholesterol	Thin-film hydration	105	−25.5	90.5	Transfection cell line (HEK293T)	Enhanced anti-hypertension effect	Haddad et al., 2023
	PC, PS, cholesterol, and α-tocopherol (vitamin E)	Thin-film hydration	142.9–161.5		60.2–76.8	In vitro BV2 cells, in vivo LPS-induced Parkinson's disease rats	Enhanced anti-inflammation effect	Cheng et al., 2021

To be continued

Table 2 (continued)

Type	Composition	Production method	Particle size (nm)	Zeta potential (mV)	Encapsulation efficiency (%)	Experimental model	Biological effect (as compared to free EGCG)	Reference
Liposome	DOPE, POPC, and CHEMS, magnesium salt, Poloxamer-407	Reverse-phase evaporation (REV)	205.2±8.9	−17.6±4.1	95.0±4.8	Adult human retinal pigment epithelial cells (ARPE-19)	Enhanced antioxidant activity	Minnelli et al., 2018
Solid lipid nanoparticle	Glycerol, Sofitsan S100, Lipoid S75, cationic lipids (DDAB), ascorbic acid, Poloxamer-188 (P188)	Multiple emulsion (W/O/W)	143.700± 0.450	25.700±1.420		Human epithelial colorectal adenocarcinoma (Caco-2), human lung fibroblast (SV-80), human retina retinoblastoma (Y-79), human liver hepatocellular carcinoma (HepG2), and human breast adenocarcinoma (MCF-7)	Enhanced anti-proliferation effect	Silva et al., 2019
	GMS, stearic acid, lecithin soy, Pluronic F-68, bombesin	Double emulsification-evaporation followed by conjugation with bombesin	163.4±3.2	−25.2±2.8	67.2±3.5	In vitro MDA-MB-231 human breast cancer cell lines and B16F10 mouse melanoma cells, in vivo tumor-bearing female C57/BL6 mice	Enhanced anticancer, anti-angiogenic, and antitumor effects	Radhakrishnan et al., 2019
Nanostructured lipid carrier	Solid lipid (Precirol ATO 5), liquid lipid (Mygliol 812), surfactant (Tween 60), FA	High-shear homogenization and ultra-sonication	313	−30	85	Breast carcinoma cell lines (MCF-7, MDA-MB-231, and MCF-7TAM) and human normal mammary epithelial cells (MCF10A)	Enhanced anticancer activity	Farabegoli et al., 2022
Metal nanoparticle								
Gold	Chitosan, cysteamine, $HAuCl_4$	Gold reduction (EGCG-ChAuNPs); Turkevitch method (EGCG-CystAuNPs)	EGCG-ChAuNPs (125±13); EGCG-CystAuNPs (111±1)	EGCG-ChAuNPs (36±6); EGCG-CystAuNPs (−24±1)	EGCG-ChAuNPs (60±2); EGCG-CystAuNPs (78.0±1.3)	Human pancreatic cancer cell line (BxPC3)	Enhanced anticancer activity	Cunha et al., 2022

To be continued

Table 2 (continued)

Type	Composition	Production method	Particle size (nm)	Zeta potential (mV)	Encapsulation efficiency (%)	Experimental model	Biological effect (as compared to free EGCG)	Reference
Gold	$HAuCl_4·4H_2O$	Gold reduction	38.6–135.2	−30.4 to −6.4		Cancer cells (MDA-MB-231 and HeLa) and embryonic mouse fibroblast cell line (NIH3T3)	Enhanced antioxidant and anticancer effects	Gan et al., 2022
	$HAuCl_4$	Gold reduction	33.8±2.2	−24.9±0.3	92.6±0.6	Ex vivo venous blood samples collected from male volunteers, in vivo Ehrlich's tumor-bearing mice	Enhanced anticancer and antitumor effects	Safwat et al., 2020
	$NaAuCl_4$	Gold reduction	35			Human HCC HepG2 cells	Enhanced anticancer and antitumor effects	Mostafa et al., 2020
	$HAuCl_4·3H_2O$	Gold reduction	90.3	−72.57		Human normal and cancer cell lines (MCF-10A, hTERT-HPNE, RWPE1, 231MDA-MB-, MIA PaCa, and PC3), normal immortalized keratinocytes (HaCaT), A375SM cell line	Enhanced anticancer effect	Chavva et al., 2019
	$HAuCl_4$	Direct reduction	35.6	−19.5		In vitro BMMs, in vivo LPS-induced mouse calvarial bone erosion	Enhanced anti-osteoclastogenic and antioxidant effects	Zhu et al., 2019
Silver	$AgNO_3$, $C_6H_5Na_3O_7·2H_2O$, $NaBH_4$	Seed growth-mediated method followed by incubation and stirring	32±11	−67±2		In vitro human VK2-E6/E7 vaginal epithelial cells (ATCC® CRL-2616), Vero cells (ATCC® CCL-81) and HaCaT keratinocytes, in vivo HSV-1- & HSV-2-infected C57BL/6 mice	Enhanced antiviral effect	Krzyzowska et al., 2023
	AGG, SA, gelatin, glycerol, $CaCl_2$, $AgNO_3$	Solution mixing and casting	217±10	−2.60 to −1.59		In vitro *E. coli* K12 (MTCC-1302), *Pseudomonas aeruginosa* (MTCC-424), *B. subtilis* (MTCC-441), and *S. aureus* (lab strain), in vivo wound-bearing Wistar rat	Enhanced anti-bacterial and wound-healing effects	Kar et al., 2019

To be continued

Table 2 (continued)

Type	Composition	Production method	Particle size (nm)	Zeta potential (mV)	Encapsulation efficiency (%)	Experimental model	Biological effect (as compared to free EGCG)	Reference
Selenium	Na_2SeO_3	Mixing and magnetic stirring	89.3	−30.6		PTZ-treated male albino Swiss mice	Enhanced anti-convulsant, antioxidant, and anti-inflammation effects	Alrashdi et al., 2023
	Selenious acid	Dialysis	91.3±35.7			In vitro rat pheochromocytoma cells (PC12), BV2 microglia, in vivo SCI Sprague-Dawley rats	Enhanced anti-inflammation and neuroprotection effects	Wang et al., 2022
Zinc oxide	Zinc oxide	Co-crystallization	409.5±9.2	−20.03±0.23		Normal fibroblast cells (WI-38) and prostate cancer cells (PC-3)	Enhanced anticancer activity	Samutprasert et al., 2018
Silica nanoparticle	AS1411 aptamer, chitosan, silica	Ammonia-based catalysis (mesoporous silica nanoparticle preparation) followed by ultrasonication and centrifugation	257	7.14±5.90 (before conjugation), and −11.40±3.28 (surface charge after conjugation of the aptamer)	80	Ovarian cancer cell lines (SKOV-3)	Enhanced anticancer activity	Alizadeh et al., 2020

AGG: aminated guar gum; $AgNO_3$: silver nitrate; BMMs: bone marrow macrophages; $CaCl_2$: calcium chloride; ChAuNPs: chitosan-coated gold nanoparticles; CystAuNPs: cysteine-coated gold nanoparticles; CHEMS: cholesteryl hemisuccinate; $C_6H_5Na_3O_7\cdot 2H_2O$: sodium citrate; CSSPS: cationic soluble soybean polysaccharide; DDAB: dimethyldioctadecylammonium bromide; DOPE: 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; DPPC: 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DPPG: 1,2-dipalmitoyl-sn-glycerol-3-phosphate-rac-(1-glycerol); EGCG: epigallocatechin-3-gallate; ES100: Eudragit S100; EtOAc: ethyl acetate; FA: folic acid; $FeCl_3\cdot 6H_2O$: iron(III) chloride hexahydrate; Fmoc-Cl: 9-fluorenylmethoxycarbonyl chloride; GMS: glycerol mono-stearate; $HAuCl_4$: tetrachloroauric(III) acid; HCC: hepatocellular carcinoma; HCECs: human corneal epithelium cells; HDF: human dermal fibroblast; HSV: herpes simplex virus; HUVECs: human umbilical vein endothelial cells; β-Lg: β-lactoglobulin; LPS: lipopolysaccharide; $NaAuCl_4$: sodium-tetrachloroaurate; $NaBH_4$: sodium borohydride; Na_2SeO_3: sodium selenite; NLCs: nerve-like cells; NP: nanoparticle; NPCs: neural progenitor cells; PBCA: poly(*n*-butyl cyanoacrylate); PC: L-α-phosphatidylcholine; PEG: polyethylene glycol; PLA: polylactic acid; PLGA: poly(lactic-co-glycolic acid); POPC: 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; PS: phosphatidyl-serine; PTZ: pentylenetetrazole; PVP: polyvinylpyrrolidone; SA: sodium alginate; SCI: spinal cord injury; SPC: soybean phospholipids; W/O/W: water-in-oil-in-water; WT: wild-type.

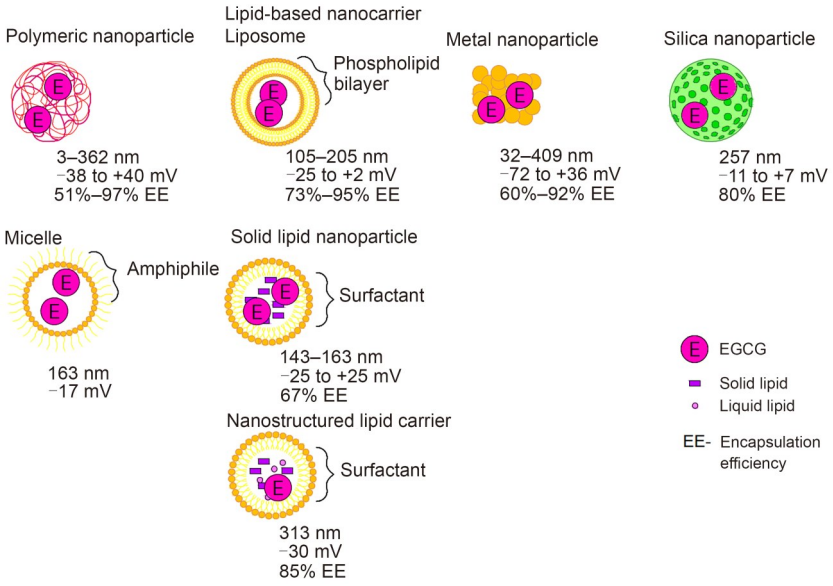

Fig. 3 Illustration of various epigallocatechin-3-gallate (EGCG) nanocarriers.

3.1 Polymeric nanoparticles and EGCG

A polymeric nanoparticle is defined as a colloidal particle made up of repeated subunits, with dimensions falling within the nanometer range. Synthetic polymers such as polyethylene glycol (PEG), poly (lactic-co-glycolic acid) (PLGA), poly(*n*-butyl cyanoacrylate) (PBCA), and polyvinylpyrrolidone (PVP) have been utilized as nanocarriers for EGCG (Singh et al., 2018a, 2018b; Liu et al., 2019; Hu et al., 2021; Minnelli et al., 2023). These synthetic polymers offer precise control over nanoparticle properties such as size, shape, and surface characteristics. Nevertheless, prolonged retention of these synthetic polymers within biological systems may induce certain toxicity issues, prompting a gradual shift towards the application of natural alternatives like chitosan, gelatin, hordein, and soybean polysaccharides in the EGCG-nanocarrier formulation (He et al., 2020; Moreno-Vásquez et al., 2021; Zhou et al., 2022; Zhang WJ et al., 2023).

The EGCG-loaded polymeric nanoparticles discussed in this study are in the size range of 3–362 nm, indicating a notable degree of variance. However, the overall size range falls within acceptable limits (Table 2). The above variation could be attributed to the varying interactions between different polymeric ingredients utilized and loaded with EGCG. Stronger chemical interactions between EGCG and polymeric ingredients tend to pull the outer polymeric shell closer to the core, resulting in smaller particle sizes. The studies discussed in this paper reveal that the encapsulation efficiency of polymeric nanoparticles spans from 46% to 97%, highlighting their efficacy as potent EGCG delivery vehicles. The production method also plays a crucial role in developing an effective nanocarrier. When utilizing identical polymeric components (PLGA and PEG), the nanoprecipitation technique yields a 49% encapsulation efficiency, whereas the double emulsion-solvent evaporation method achieves a significantly higher efficiency of 95% (Cano et al., 2018; Alserihi et al., 2021).

Encapsulating EGCG within a polymeric nanoparticle yields enhanced anti-inflammatory effects, as evidenced by the reduced expression of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1β and the increased expression of anti-inflammatory markers such as IL-10 and arginase-1 (Arg-1). Moreover, this formulation exhibits superior antioxidant activity compared to its free form, characterized by an increased capacity for scavenging reactive oxygen species (ROS) (Tian et al., 2022). These augmented biological effects can be attributed to the enhanced stability of EGCG and protection against drug degradation provided by nanoparticle encapsulation. Besides, the improved cellular uptake and permeability of EGCG across Caco-2 cells, coupled with the suppression of multidrug resistance protein 2 (MRP2) and P-gp-mediated efflux transport, contribute to the increased intracellular

retention of EGCG, thereby amplifying its therapeutic effectiveness (Zhang MY et al., 2023; Zhang WJ et al., 2023).

3.2 Micelles and EGCG

A micelle has a spherical structure with a core-shell configuration, formed by the self-aggregation of amphiphilic molecules at the critical micelle concentration (CMC) and critical micelle temperature (CMT) (Koopaie, 2020). Micelles can be mainly categorized into two types: (1) regular micelles with hydrophilic shell and hydrophobic core and (2) inverse micelles with hydrophobic shell and hydrophilic core. The choice of solvent determines the type of micelle to be synthesized (Perumal et al., 2022).

Most nano-systems encapsulate drugs within the center of nanoparticles, utilizing pharmaceutical excipients as carriers. However, a novel delivery platform integrating micelles has been developed by transforming the role of EGCG from bioactive natural ingredient to bioactive drug carrier, thereby enhancing its bioavailability. This involves structural modification through the conjugation of EGCG with 9-fluorenylmethoxycarbonyl (Fmoc) moiety, yielding EGCG-Fmoc. Owing to its amphiphilic nature, EGCG-Fmoc can undergo self-assembly in the medium and form a micellar system. The EGCG-Fmoc micelle is characterized as a spherical particle with small particle size (approximately 163 nm) and homogenous distribution (approximately 0.09). Its relatively small size takes advantage of the EPR effect, facilitating penetration into tumor cells. The negative zeta potential found on the surface of micelle prevents particle aggregation, indicating its stability-enhancing impact. The anti-proliferation effect of EGCG-Fmoc micelle on a breast cancer cell line was significantly improved as compared to EGCG alone, suggesting the enhanced bioavailability and therapeutic effects of EGCG through the self-assembly system. Lower half-maximal inhibitory concentration (IC_{50}) was found in EGCG-Fmoc (45.21 μg/mL) than in EGCG (63.88 μg/mL), signifying the enhanced anti-cancer effect achieved by the EGCG-Fmoc micelle. The self-aggregated EGCG-Fmoc micellar system demonstrated an exceptional advantage, allowing the co-delivery of EGCG with other pharmaceutical ingredients without the need of an inert carrier (Liu et al., 2023).

An EGCG-loaded reverse micelle has been synthesized using Tween 80 and Span 80. Unfortunately, the study did not provide details on key characterizations such as particle size, surface charge, and encapsulation efficiency. However, the reverse micelle approach effectively increased the cytotoxicity of EGCG against HeLa cells and demonstrated deeper penetration into rat skin, owing to the enhanced lipophilicity of EGCG (Rosita et al., 2019).

3.3 Lipid-based nanocarriers and EGCG

The utilization of lipids as formulating materials for nanocarriers ensures biocompatibility, making them particularly suited to drug delivery applications. Three types of lipid-based nanocarriers, namely, liposome, solid lipid nanoparticle (SLN), and nanostructured lipid carrier (NLC), have been examined in this review to highlight their unique features and potential applications in EGCG delivery.

3.3.1 Liposomes and EGCG

A liposome is a spherical vesicle comprising an aqueous core enclosed by a phospholipid bilayer. The presence of this bilayer enables the biocompatibility of liposome and facilitates its transport across the plasma membrane (Dymek and Sikora, 2022). Compared to micelles, liposomes typically have a larger diameter, primarily due to the enlargement of the overall particle size caused by the presence of the outer bilayer. One of the key advantages of liposomes is their versatility in encapsulating various types of drugs. Both hydrophilic and lipophilic drugs can be efficiently loaded into liposomes. Hydrophilic drugs are encapsulated within the aqueous core of the liposome, where they are solubilized and protected from degradation. On the other hand, lipophilic drugs can be incorporated into the phospholipid bilayer, where they are stably embedded (Laddu et al., 2021; Nsairat et al., 2022).

All liposomal formulations discussed in this review utilize phospholipids, glycerols, and cholesterols as their primary ingredients for formulation. Among the various methods for liposome synthesis, thin-film hydration has emerged as a popular choice, with three out of four studies opting for this technique. The results indicate favorable outcomes, as the size achieved through thin-film hydration (ranging from 105 to 161 nm) is smaller than that obtained through reverse-phase evaporation (205 nm). This size difference may also be attributed to the incorporation of high molecular weight and additional ingredients (1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE),

1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), cholesteryl hemisuccinate (CHEMS), magnesium salt, and Poloxamer-407) in this anionic liposome formulation (Minnelli et al., 2018). However, it is important to note that the size of 205 nm still falls within an acceptable range. Furthermore, reverse phase evaporation demonstrated superior encapsulation efficiency, with 95% of EGCG encapsulated within the liposomal core, marking the highest among all liposomal formulations discussed.

The attenuation of oxidative stress-induced cellular damage and the reduced levels of ROS suggest that the antioxidant efficacy of EGCG is heightened when formulated within liposomes compared to its natural form (Xia et al., 2023). The slower release rate of encapsulated EGCG from the liposome extends its presence and circulation within the body, thereby augmenting its therapeutic impact (Minnelli et al., 2018). Further evidence of this effect was provided by the amplified inhibition of the transforming growth factor-β (TGF-β) signaling pathway, which was associated with pulmonary arterial hypertension (PAH). This effect was observed with liposomal EGCG but not with free EGCG at 1 μmol/L (Haddad et al., 2023).

3.3.2 Solid lipid nanoparticles and EGCG

SLN is a spherical particle characterized by a surfactant monolayer enveloping a solid lipid core. Its structure resembles that of a liposome, albeit with a notable difference: the phospholipid bilayer is replaced by a surfactant monolayer, and the drug is entrapped within this solid lipid matrix. Emulsification is required to blend the immiscible solid lipid and the surfactant, resulting in the formation of an emulsion. Various ingredients have been explored for their suitability in formulating SLN as a nanocarrier for EGCG, such as glyceryl monostearate, stearic acid, lecithin soy, Sofitsan S100, and Lipoid S75.

Researchers have developed a positively charged SLN formulation encapsulating EGCG, employing ingredients such as glycerol, Sofitsan S100, Lipoid S75, and cationic lipids (dimethyldioctadecylammonium bromide (DDAB)). The anti-proliferative effect of this formulation was evaluated across various cell lines, with notable outcomes observed specifically in fibroblast SV-80 cells and characterized by a lower IC_{50} value following 48 h of incubation and reduced cell viability. However, the researchers suggested that the enhanced anti-proliferative effect may not be anticipated in other cell lines, which could be attributed to the superior antioxidant property and protective effects of the formulation on these cell lines (except SV-80). As a result, comparable cell viability was observed between the group treated with EGCG-DDAB-SLN and the group treated solely with EGCG (Silva et al., 2019).

A research group has selected glycerol monostearate (GMS), stearic acid, and soy lecithin as lipid sources for synthesizing EGCG-SLN. After formulation optimization, a preparation with 5% EGCG to lipid mass ratio (particle size: 157 nm; polydispersity index (PDI): 0.268; drug encapsulation efficiency: 67.2%) was chosen as the optimum for subsequent assessments. Notably, a formulation with 3% EGCG to lipid mass ratio was considered as a better option due to its smaller particle size (112 nm), lower PDI (0.140), and higher encapsulation efficiency (89.0%). However, the authors do not explicitly state the rationale behind selecting the 5% EGCG to lipid mass ratio preparation as the optimum choice. The anti-proliferation ability of EGCG-SLN was assessed against a cancer cell line. Reduced breast cancer cell viability and lowered IC_{50} value of EGCG-SLN indicated the improved cytotoxicity of EGCG towards cancer cells, which can be related to drug encapsulation within the lipid formulation, leading to increased stability and enhanced therapeutic effects (Radhakrishnan et al., 2016).

To further enhance the specific targeting of EGCG-SLN, a research group developed bombesin-conjugated EGCG-SLN. Bombesin, a tumor-specific peptide molecule, acts as a ligand targeting and interacting specifically with overexpressed gastrin-releasing peptide receptor (GRPR) in breast cancer. The conjugation of bombesin onto EGCG-SLN is anticipated to significantly improve the anti-tumor and anti-cancer efficacy of EGCG. Compared to the non-conjugated formulation, bombesin-conjugated EGCG-SLN exhibited larger particle size (163 nm) and reduced zeta potential (due to neutralization of negative charge on SLN surface), proving the successful interaction between bombesin and the lipid particle. In vitro cytotoxicity results revealed (1) lower percentage of cells viable in the conjugated EGCG-SLN group, (2) less EGCG-SLN required to exert half of its maximal inhibitory effect, and (3) increased cell apoptosis. Additionally, negligible wound closure in cancer cells was

observed, indicating the improved anti-angiogenic effect of EGCG. These in vitro outcomes aligned with the in vivo assessment results, where conjugated EGCG-SLN (1) extended the lifespan of tumor-bearing mice, (2) retained normal body weight, and (3) reduced tumor growth. The incorporation of bombesin onto the EGCG-SLN surface increases its target-specific ability towards cancer cells. This implies enhanced cellular uptake and internalization through receptor (bombesin)-mediated endocytosis in the conjugated formulation, further augmenting the therapeutic benefits of EGCG (Radhakrishnan et al., 2019).

3.3.3 Nanostructured lipid carriers and EGCG

Issues have been identified with SLN, including low drug-loading capacity and drug expulsion during storage. In response to these challenges, an NLC has been presented. NLC is a colloidal spherical particle encapsulating a lipid blend (solid and liquid lipids). The combination of solid and liquid lipids introduces imperfections into the lipid matrix, enhancing its capacity to accommodate drugs. Moreover, the amorphous nature of the lipid matrix in NLC prevents drug expulsion caused by crystallization, a common occurrence in the crystalline matrix of SLN, which contributes to the preservation of NLC storage stability (Müller et al., 2002).

A combination of Precirol ATO 5 (solid lipid), Mygliol 812 (liquid lipid), and Tween 60 (surfactant) was utilized in the synthesis of NLC, which was further functionalized with folic acid (FA). The resulting NLC exhibited a size of 313 nm, PDI of 0.2, and zeta potential of −30 mV, indicating the successful synthesis of a highly stable formulation, which achieved a notable encapsulation efficiency of 85%. This EGCG-loaded formulation demonstrated significant cytotoxic effects on three types of breast carcinoma cells, as evidenced by reduced cell viability and the controlled proliferation of cancer cells. Conversely, human normal mammary epithelial cells (MCF10A) treated with EGCG-loaded formulation showed no sign of cytotoxicity, displaying cell viability comparable to the control group. This indicated the ability of the formulation to selectively target cancer cells, possibly attributed to the FA functionalization on the surface of nanocarrier, targeting the overexpressed folate receptor found in various cancer cell subtypes (Farabegoli et al., 2022). This targeting mechanism ensures the safety of the formulation towards normal cells while effectively exerting anti-cancer effects.

3.4 Metal nanoparticles and EGCG

A metal nanoparticle has a nano-sized structure composed of metallic elements such as gold (Au), silver (Ag), copper (Cu), and zinc (Zn). These nanoparticles have attracted considerable attention in drug formulation due to their customizable physical and chemical properties, surface modification capability, biocompatibility, and stability (Klębowski et al., 2018; Yaqoob et al., 2020).

3.4.1 Gold nanoparticles and EGCG

Among the reviewed articles, gold nanoparticles (AuNPs) stand out as the most prominent and commonly used ingredient in formulating EGCG-metal nanoparticles (Table 2). This preference is largely due to their inertness and low toxicity compared to other metal types (Hammami et al., 2021). AuNPs possess the remarkable ability to be precisely tailored into diverse shapes and structures, including nanospheres, nanorods, and nanocubes. This morphological versatility allows for fine-tuning of their physicochemical properties, such as surface area, plasmonic characteristics, and stability (Hu et al., 2020). The widespread applications of AuNPs in the medical field stem from their (1) excellent biocompatibility (therefore low toxicity), (2) high inertness, and (3) potential for surface modification (Pissuwan et al., 2020).

All the formulated gold-EGCG nanoparticles listed in Table 2 exhibit small particle sizes below 150 nm. This characteristic is likely a contributing factor to their enhanced membrane penetration and therapeutic efficacy. One study synthesized AuNPs using two different methods (gold reduction and the Turkevitch method), followed by conjugation with EGCG. In the gold reduction method, chitosan serves as the reducing agent and is mixed with chloroauric acid ($HAuCl_4$) solution to form EGCG-chitosan-coated AuNPs (ChAuNPs). In the Turkevitch method, $HAuCl_4$ is reduced by sodium citrate and functionalized with cysteamine, yielding EGCG-cysteine-coated AuNPs (CystAuNPs). The particle sizes of EGCG-ChAuNPs and EGCG-CystAuNPs are 125 nm and 111 nm, respectively, implying the effect of reducing agent on particle size (Cunha et al., 2022). The Turkevich method has been evaluated as effective for producing

spherical particles of <30 nm. However, as the size of the AuNPs increases beyond 30 nm, the particles lose their spherical shape coupled with a wider size distribution, indicating the incompatibility of this method with larger nanoparticles (Dong et al., 2020). This is especially evident in the case of CystAuNPs, which have a size of 54 nm and a PDI value of 0.6, indicating their heterogeneity. Conjugation with EGCG could increase the size of nanoparticles but significantly reduce the PDI to 0.2, suggesting that the addition of EGCG facilitates control over the properties of AuNPs. However, most studies included in this review did not assess their encapsulation efficiency; therefore, the challenge remains to accurately determine the extent to which EGCG is loaded onto the nanoparticles, thereby limiting our understanding of the efficiency of EGCG encapsulation in these formulations.

Loading EGCG onto AuNPs has enhanced its anticancer effects, as evidenced by (1) the decreased viability of cancer cells, (2) the increased apoptosis in cancer cells, (3) the reduced expression of anti-apoptotic proteins including B-cell lymphoma 2 (BCL2) and BCL extra large (BCL-xL), and (4) the heightened expression of the pro-apoptotic proteins such as BCL2-associated X protein (Bax) (Chavva et al., 2019; Mostafa et al., 2020; Cunha et al., 2022). This improvement can be attributed to (1) enhanced stabilization, (2) increased cellular uptake, (3) reduced P-gp-mediated efflux, and (4) controlled release of EGCG from the gold nanoformulation (Chavva et al., 2019).

3.4.2 Silver nanoparticles and EGCG

Silver nanoparticles (AgNPs) have emerged as versatile nanomaterials with diverse bio-applications, notably as potent agents against bacterial and viral infections. One study employed a chemical reducing agent, namely sodium citrate, for the production of EGCG-modified AgNPs (EGCG-AgNPs) via a seed growth-mediated method (Krzyzowska et al., 2023). While this kind of chemical synthesis method offers advantages such as simplicity and cost-effectiveness, the use of chemical reducing agents may not be environmentally friendly and poses unforeseen risks to biological systems. In response to these drawbacks, the utilization of biological agents has emerged as a promising alternative. Another study, which utilized aminated guar gum (AGG) as the reducing agent for the synthesis of hydrogel-silver-EGCG (HG-Ag-EGCG), exemplifies an environment-friendly approach while demonstrating the potency of HG-Ag-EGCG as an antibacterial agent (Kar et al., 2019).

Research shows that reduction with sodium citrate yields superior results in characterization. The particle sizes and zeta potentials of EGCG-AgNPs and HG-Ag-EGCG were 32 nm and 217 nm and −67 mV and −2.60 mV, respectively. The significantly smaller particle size may offer advantages in cellular penetration and uptake, while the 25-fold larger absolute zeta potential may contribute to the much higher stability of EGCG-AgNPs via electrostatic repulsion, preventing particle aggregation. Nevertheless, these differences do not affect the biological effects of HG-Ag-EGCG. Several outcomes were observed, including (1) reduced bacterial growth curve, (2) increased wound closure percentage, (3) higher vascular endothelial growth factor (VEGF), and (4) reduced levels of pro-inflammatory cytokine (IL-6) compared to HG-EGCG (Kar et al., 2019). Similarly, enhanced antiviral response was noted in EGCG-AgNPs compared to its free counterpart, as evidenced by (1) inhibition of herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2) infections, (2) reduced attachment and penetration of HSV-1 and HSV-2 to human keratinocytes, and (3) activated early antiviral response (Krzyzowska et al., 2023).

3.4.3 Selenium nanoparticles and EGCG

The development of selenium nanoparticles (SeNPs) has unveiled their promising biological applications, including antimicrobial, antioxidant, and anticancer properties as well as their utility in drug delivery systems, owing to their biocompatibility and bioavailability (Sampath et al., 2024). However, preclinical trials on rodent models have indicated potential adverse effects of SeNPs, such as weight loss and liver toxicity, emphasizing the need to establish effective therapeutic dosages while mitigating the side effects (Ryabova et al., 2024).

The particle size of SeNPs in two studies fell between 89 and 91 nm, showing consistent results despite variations in the starting materials and production methods (Wang et al., 2022; Alrashdi et al., 2023) (Table 2). In one study, mice with pentylenetetrazole (PTZ)-induced acute epileptic seizures were treated with EGCG or EGCG-SeNPs. The results showed reduced seizure duration and increased seizure latency in the EGCG-SeNPs-treated group, indicating enhanced

anti-convulsant effects, along with augmented antioxidant and anti-inflammatory functions. These effects could be attributed to the enhanced cellular uptake of EGCG through its incorporation into high surface area and nanosized SeNPs, thereby augmenting its therapeutic effects (Alrashdi et al., 2023).

Another study demonstrated the antioxidant and anti-inflammatory properties of EGCG-SeNPs using models of oxidative stress induced by hydrogen peroxide (H_2O_2) and inflammation induced by lipopolysaccharide (LPS). The neuroprotective effects were evidenced by (1) higher Basso, Beattie, and Bresnahan (BBB) scores, (2) improved integrality of spinal cord structure with decreased lesion voiding, and (3) enhanced demyelination and nerve fiber preservation (Wang et al., 2022).

3.4.4 Zinc oxide nanoparticles and EGCG

Zinc oxide nanoparticles (ZnO NPs) are chemically inert, possess a large surface area, exhibit high photostability, and demonstrate an enhanced redox capacity, making them highly versatile for applications in drug delivery (Nagar et al., 2022; Zhou et al., 2023). While ZnO NPs have been deemed generally safe by the US Food and Drug Administration (FDA), they still possess dose-dependent toxicity risks (Nagar et al., 2022; Pushpalatha et al., 2022). Therefore, the future development of ZnO NPs should be accompanied by a thorough scrutiny of their potential hazardous effects, toxicity mechanisms, and impacts on human health.

Owing to the low bioavailability of EGCG, researchers have sought to develop EGCG-zinc oxide co-crystalline nanoparticles (EGCG-ZnO), harnessing their potential as effective anticancer agents. These negatively charged particles, with a relatively large size of 409 nm, have been successfully synthesized. The selective anticancer property of hybrid EGCG-ZnO has been demonstrated by the reduced viability of cancer cells without affecting the viability of normal cells when treated with the same concentration of EGCG-ZnO. Essentially, a safe concentration (12.5 μg/mL (Samutprasert et al., 2018)) of EGCG-ZnO particle effectively killed cancer cells without causing any harm to normal cells. This effectiveness may stem from the synergism exhibited by the hybrid particles upon their simultaneous uptake into cancer cells, whereas the same phenomenon could not be observed in the simple physical mixture of EGCG and ZnO due to differences between EGCG and ZnO in their cellular penetration ability and penetration pathways. Consequently, simultaneous uptake is not achievable, which constrains the potential of EGCG-ZnO to achieve synergistic anticancer effects (Samutprasert et al., 2018).

3.5 Silica nanoparticles and EGCG

The favorable properties of silica nanoparticles (SiNPs), such as tunable particle size, excellent compatibility within living systems, and large surface area, have led to their widespread adoption (Huang et al., 2022). SiNPs have been successfully utilized in various applications including drug delivery systems, biomedical imaging, photodynamic and photothermal therapies, and bone regeneration (Selvarajan et al., 2020; Li et al., 2021). However, it is important to note that SiNPs may induce toxicity concerns in organisms, necessitating comprehensive toxicity evaluations during both development and specific application phases (Huang et al., 2022).

The Stöber method, commonly employed for the production of SiNPs, involves the combination of tetraethyl orthosilicate (TEOS) with a mixture of water, alcohol, and ammonia. Subsequent removal of water or alcohol molecules from the silicic acid molecules results in the formation of Si–O–Si condensate. Initially, primary SiNPs aggregate upon reaching a supersaturation point, followed by crystalline growth, yielding stable SiNPs (Li et al., 2021). A mesoporous silica nanoparticle (MSN) was synthesized using an ammonia-based catalysis technique, with TEOS as the primary component. This nanoparticle was then coated with chitosan (CS) and further functionalized with the AS1411 aptamer (Ap). The resultant entity efficiently loaded EGCG onto its structure, dubbed as SiO_2@CS-EGCG-Ap. Its particle size was measured as 257 nm, with PDI approaching 1, indicating considerable heterogeneity. Incorporating the aptamer altered the surface charge of nanoparticle from +7.14 to −11.40 mV, a significant shift affirming successful conjugation with the targeting ligand. Notably, 80% of EGCG was effectively encapsulated, showcasing the high efficiency of SiO_2@CS NPs. SKOV-3, an ovarian cancer cell line, served as the focal point of this investigation. SiO_2@CS-EGCG-Ap demonstrated higher cellular uptake (50.0%) compared to its unconjugated

counterpart (29.6%), attributed to the aptamer-specific recognition of nucleolin on the cell surface, facilitating macropinocytosis. This heightened uptake translates into enhanced anticancer effects, as evidenced by (1) a lower IC_{50}, (2) suppressed cell proliferation, (3) diminished cancer cell viability, (4) increased nuclear fragmentation, and (5) reduced expression of extracellular signal-regulated kinase 2 (ERK2) and human telomerase reverse transcriptase (hTERT), both pivotal in cellular growth and proliferation (Alizadeh et al., 2020).

4 Summary, challenges, and prospects

From the reviewed studies on advanced formulations of EGCG, it seems that polymeric nanoparticles emerge as the most well-studied and optimal choice of EGCG-loaded nanocarriers. This preference can be attributed to their relatively small size, high encapsulation efficiency, and favorable zeta potential compared to other nanocarriers. Moreover, the good safety profiles of EGCG-polymeric nanoparticles have been vigorously demonstrated across numerous studies (Table 3). In the comparison between various polymeric nanoparticles discussed in the involved studies (Table 2), one configuration stands out: EGCG enclosed within PBCA/Pluronic F-68 nanoparticle. This leads the pack primarily due to its favorable particle size (156 nm), stable surface charge potential (−31 mV), and impressive encapsulation efficiency (90%). While certain studies may boast higher encapsulation efficiency (Huang et al., 2018; Xia et al., 2023), they often compromise other critical factors, such as zeta potential. Nonetheless, the choice of nanocarriers is highly dependent on the specific disease model and its desired therapeutic outcomes, and the main goal is to achieve optimized efficacy while mitigating any risks of potential toxicity.

Nanocarriers are often constructed (1) from biocompatible materials to minimize the risk of immune response, (2) from biodegradable materials to minimize long-term accumulation effects, (3) with good membrane penetration via its appropriate surface properties (size, charge, and surface chemistry), (4) to allow surface modifications facilitating receptor-mediated uptake, and (5) to enable controlled release in response to the diffusion coefficient, physiological stimuli (pH, presence of enzymes or biomolecules), dissolution and degradation rates. Nevertheless, a significant gap exists in the literature regarding the comprehensive evaluation of EGCG-loaded nanocarriers. Specifically, exploration has been limited regarding (1) how the design and construction of delivery vehicles facilitate membrane penetration, (2) the potential acute and long-term effects stemming from the high load capacity of the nanocarriers, (3) thorough toxicity assessments of the nano-complex in biological system, and (4) the microstructure and interface characteristics of EGCG nanocarriers.

Among the analyzed studies, four investigated the membrane internalization mechanisms of EGCG nanocarriers. These carriers exhibit the ability to permeate intestinal epithelial cells and enter systemic circulation. Two of these studies illustrated the intestinal absorption of EGCG-polymeric nanoparticles by disrupting tight junctions of the membrane, thereby facilitating their passage through the paracellular pathway (Huang et al., 2020; Zhang WJ et al., 2023). Furthermore, two studies demonstrated the cellular uptake of EGCG AuNPs via laminin receptors (Chavva et al., 2019; Gan et al., 2022). More research is needed to provide further insights into how EGCG-loaded nanocarriers enhance membrane permeability, including the clarification of the roles played by their microstructure and interface characteristics.

Among the discussed studies, 12 out of 39 studies assessed the toxicity profile of EGCG-loaded nanocarriers using various cell lines, while only one study performed this in an animal model (Wistar rats) (Kar et al., 2019). These studies reported low cytotoxicity and high cell viability, and no adverse effects on the liver or kidney function of Wistar rats (Table 3). The findings indicate that the selection of chemical constituents and excipients in these studies is appropriate and the EGCG-loaded nanocarriers exhibit a favorable safety profile. The utilization of biocompatible and biodegradable materials with well-established safety profiles is prioritized in pharmaceutical formulation, including the construction of EGCG nanoparticle formulations reviewed in this study.

Potential toxicity due to the high load capacity of nanocarriers could be mitigated by implementing a controlled release strategy that minimizes exposure to high concentrations of EGCG. Nonetheless, such toxicity is unlikely to occur, as the dose-dependent

Table 3 Toxicity assessment of the EGCG-loaded nanocarriers

Composition	Experimental model	Toxicity assay/dosage	Finding(s)	Reference
Polymeric nanoparticle				
PLGA, Poloxamer-407	HDF cells	Cytotoxicity MTT assay (20–80 μmol/L)	Low cytotoxicity in 20−80 μmol/L	Minnelli et al., 2023
CSSPS	HUVECs	Cytotoxicity MTT assay (10–100 μg/mL)	High cell viability in 10–100 μg/mL	Zhou et al., 2022
Chitosan, β-Lg	Caco-2 cell	Cytotoxicity MTT assay (25–125 μg/mL)	High cell survival rate in 25–125 μg/mL	Dai et al., 2020b
PLGA-PEG, Tween 80 (surfactant), ethyl acetate (oil phase)	Astrocytes and bEnd.3 cells	Cytotoxicity Alamar Blue assay (0.08–2.50 mg/mL)	>80% cell viability at <1.25 mg/mL	Cano et al., 2018
PLGA/PF127	NLCs	Cytotoxicity Fluorescent microscopy and/or flow cytometry (assessment of the ROS generation and mitochondrial membrane potential, 40–100 μg/mL PLGA/PF127 NPs and 10–50 μmol/L EGCG)	No significant ROS production or alteration in mitochondrial membrane potential in the concentration range of 40–100 μg/mL PLGA/PF127 NPs and 10–50 μmol/L EGCG	Hoyos-Ceballos et al., 2018
Type A gelatin, hyaluronic acid	HCECs	Cytotoxicity CCK-8 assay and live/dead staining (2–200 μg/mL)	High cell viability in 2–20 μg/mL	Huang et al., 2018
Liposome				
SPC, cholesterol, glucose ligand	Mouse brain microvascular endothelial (bEnd.3) cells	Cytotoxicity MTT assay (2.5–160.0 μmol/L)	High cell viability up to 160 μmol/L	Xia et al., 2023
DOPE, POPC, CHEMS, magnesium salt, Poloxamer-407	Adult human retinal pigment epithelial (ARPE-19) cells	Cytotoxicity MTT assay (22–66 μmol/L EGCG and 35–110 μg/mL lipid)	High cell viability in the range of 22–66 μmol/L EGCG and 35–110 μg/mL lipid	Minnelli et al., 2018
Gold nanoparticle				
$HAuCl_4·4H_2O$	NIH3T3 cells (embryonic mouse fibroblast cell line)	Cytotoxicity CCK-8 assay (2.5–10.0 μmol/L)	High cell viability in 2.5–10.0 μmol/L	Gan et al., 2022
$HAuCl_4$	BMMs	Cytotoxicity CCK-8 assay (5–25 μmol/L)	High cell viability in 5−25 μmol/L	Zhu et al., 2019
Silver nanoparticle				
AGG, SA, gelatin, glycerol, $CaCl_2$, $AgNO_3$	In vitro murine skin keratinocyte cell line (MSC-P5); in vivo wound-bearing Wistar rat	Cytotoxicity MTT assay (dosage not stated)	In vitro 75%–80% cell viability; in vivo, no histo-architecture alteration on liver or kidney, normalized liver or kidney function (comparable serum levels of urea, creatinine, AST, and ALT to the control group)	Kar et al., 2019
Zinc oxide nanoparticle				
ZnO	Normal fibroblast cells (WI-38)	Cytotoxicity MTT assay (0.0275–0.4400 μg/mL EGCG and 3.125–50.000 μg/mL ZnO)	High cell viability in the range of 0.0275–0.1100 μg/mL EGCG and 3.125–12.500 μg/mL ZnO	Samutprasert et al., 2018

AGG: aminated guar gum; $AgNO_3$: silver nitrate; ALT: alanine transaminase; AST: aspartate aminotransferase; BMMs: bone marrow macrophages; $CaCl_2$: calcium chloride; CCK-8: cell counting kit-8; CHEMS: cholesteryl hemisuccinate; CSSPS: cationic soluble soybean polysaccharide; DOPE: 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; EGCG: epigallocatechin-3-gallate; $HAuCl_4$: tetrachloroauric(III) acid; $HAuCl_4·4H_2O$: hydrogen tetrachloroaurate(III) tetrahydrate; HCECs: human corneal epithelium cells; HDF: human dermal fibroblast; HUVECs: human umbilical vein endothelial cells; β-Lg: β-lactoglobulin; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; NLCs: nerve-like cells; PEG: polyethylene glycol; PF127: Pluronic F-127; PLGA: poly(lactic-co-glycolic acid); POPC: 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; NPs: nanoparticles; ROS: reactive oxygen species; SA: sodium alginate; SPC: soybean phospholipids; ZnO: zinc oxide.

analysis of EGCG is well established and the determination of maximum tolerable dose for either rodent models or human trials is possible based on previous concrete findings (Parn et al., 2022; Siblini et al., 2023). Moreover, several studies reviewed in this paper have shown that EGCG-loaded polymeric and lipid nanoparticles exhibit controlled release of EGCG in simulated gastric and intestinal fluid conditions, maintaining low toxicity and high cell viability (Cano et al., 2018; Hoyos-Ceballos et al., 2018; Minnelli et al., 2018, 2023). Future assessments should include comprehensive toxicity studies involving multiple in vivo models over longer periods, detailed dose–response analyses, and mechanistic studies to understand the interactions between nanocarriers and biological systems. Certainly, long-term monitoring in both animal and human trials is essential to evaluate the safety, efficacy, and potential delayed or cumulate adverse effects.

In addition, it is crucial to apply standardized evaluation methods for EGCG nanocarriers in the future to ensure consistency and reliability across different research endeavors. Beyond standardizing particle size and distribution, surface charge (zeta potential), drug encapsulation efficiency, in vitro cell viability, and uptake across studies discussed in this article, additional assessments such as drug release kinetics, in vivo biodistribution and pharmacokinetics, immunogenicity, and biocompatibility, targeting efficiency in disease models, as well as stability and shelf-life studies, are needed for a comprehensive understanding of the properties and performance of nano-delivery vectors. As nanoparticles move towards clinical translation, scalability and manufacturing processes should also be standardized to ensure reproducibility and quality control. Moreover, variations in individuals' genetic background and polymorphisms may exert significant influence on the response to EGCG nanocarriers, particularly its pharmacokinetic and pharmacodynamic profiles, presenting a substantial challenge in the assessment of efficacy and safety in human trials and clinical settings. In addition, it has been demonstrated that EGCG may influence various drug pharmacokinetic and pharmacodynamic profiles (Tan et al., 2021; Siew-Keah et al., 2023). Therefore, it is mandatory to perform a systematic re-assessment of drug–drug interactions of both the free form of EGCG and EGCG loaded in nanoparticles. On the other hand, it would be beneficial to conduct a comparative study assessing the impact of each nanocarrier on the stability and biological activity of EGCG. All parameters, including the preparation method and drug-to-excipient ratio, should be standardized, with the only variable being the excipient used in each carrier—given that these nanocarriers are differentiated by their distinct excipients. Such an approach would allow for a relatively equitable comparison of the structural and physicochemical properties as well as pharmacokinetic indexes. In order to ensure the advancement of future clinical trials, addressing these challenges is imperative. Strategies must be devised to navigate the intricacies of genetic diversity, perhaps via tailored dosing regimens, patient stratification based on genetic markers, or the integration of personalized medicine approaches.

Acknowledgments

This work was supported by the Ministry of Higher Education (MOHE), Malaysia, through the Fundamental Research Grant Scheme (No. FRGS/1/2022/SKK10/UTAR/02/1) and the Universiti Tunku Abdul Rahman, Malaysia, through UTAR-Research Fund (No. IPSR/RMC/UTARRF/2024-C1/L04).

Author contributions

Chee Ning WONG was involved in investigation, writing – original draft, editing, and visualization. Siew-Keah LEE was involved in conceptualization, writing – review & editing, and supervision. Yang Mooi LIM, Kai Bin LIEW, Yik-Ling CHEW, and Ang-Lim CHUA were involved in investigation, final review, and proof-reading. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Chee Ning WONG, Yang Mooi LIM, Kai Bin LIEW, Yik-Ling CHEW, Ang-Lim CHUA, and Siew-Keah LEE declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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