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Review

Overcoming Multidrug Resistance in Cancer: Mechanisms and Therapeutic Potential of Epigallocatechin Gallate

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Abstract

The initial effectiveness of anticancer treatment is often undermined by tumor cell adaptation to therapeutic pressure. Epigallocatechin-3-gallate (EGCG), the principal catechin in green tea, has shown potential to restore drug sensitivity in resistant cancer cells. Previous reviews have broadly described its anticancer activities. Here, we focus on experimentally established acquired drug-resistant cancer models, distinguishing evidence for resistance reversal from general enhancement of anticancer drug activity. We also examine EGCG derivatives and nanoplatform-based delivery systems, alongside epidemiological and early clinical findings. Studies in resistant models indicate that EGCG can reduce drug efflux, inhibit pro-survival signaling, promote apoptosis, alter epigenetic regulation, and enhance drug-induced DNA damage. EGCG can also suppress epithelial–mesenchymal transition, cancer stem cell-like properties, and invasive phenotypes. Structural modification and delivery systems may improve the stability, bioavailability, tumor targeting, and therapeutic efficacy. However, evidence for reversal remains largely preclinical, and direct clinical validation in patients with treatment-resistant cancers is lacking. Further development requires formulations that achieve adequate tumor exposure and studies that establish whether the effects observed in experimental models translate into improved treatment responses in drug-resistant cancers.

Keywords: epigallocatechin gallate (EGCG); drug resistance; cancer; drug efflux; apoptosis; cancer stem cells

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1. Introduction

Cancer remains a leading cause of mortality worldwide despite substantial advances in surgery, radiotherapy, chemotherapy, and targeted therapies. A major obstacle to successful treatment is the development of therapeutic resistance, which arises through diverse mechanisms including enhanced drug efflux, activation of pro-survival signaling pathways, evasion of apoptosis, metabolic reprogramming, and acquisition of cancer stem cell-like properties. These adaptive changes not only reduce treatment efficacy but also facilitate tumor progression and metastasis, ultimately contributing to poor clinical outcomes. Accordingly, identifying strategies capable of overcoming drug resistance remains a central challenge in oncology [1,2].

Phytochemicals have attracted considerable attention as potential adjuncts to conventional cancer therapy because they can modulate multiple cellular processes. Among these compounds, catechins, a class of flavan-3-ols, have been extensively investigated for their anti-inflammatory, antioxidant, and anticancer properties. The major catechins in green tea include epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate, epigallocatechin, and epicatechin [3]. EGCG is the most abundant of these catechins in green tea and is also found in oolong and black teas [4]. Structurally, EGCG is a flavan-3-ol with a galloyl group esterified to the hydroxyl group at C-3 of epigallocatechin [5].

Preclinical studies have documented the effects of EGCG on tumor growth [3] and treatment response [6]. Epidemiological and clinical studies have explored its relevance to cancer prevention and potential clinical applications [7–9]. At the cellular level, EGCG has been reported to modulate pathways involved in cell survival [10], oxidative stress responses [3], and apoptosis [11]. For example, studies in cultured prostate cancer cells have reported reduced Akt phosphorylation [12], altered cell-cycle progression, and induction of apoptosis following EGCG treatment [13].

Beyond its effects in treatment-sensitive cancer models, EGCG has also been investigated in cells with acquired drug resistance. In these models, EGCG has been reported to downregulate drug efflux transporters [14], modulate pro-survival signaling [15], inhibit epithelial–mesenchymal transition (EMT)-associated invasion [16], and suppress cancer stem cell (CSC)-like properties [6]. The evidence accumulated across models of acquired drug resistance warrants a focused assessment of EGCG. The chemical instability and limited oral bioavailability have also motivated research on its derivatives and delivery systems [10].

Previous reviews have broadly addressed the cancer-preventive effects [3], anticancer mechanisms [11], and pharmacological properties of EGCG [10]. Here, we focus on experimental evidence from established acquired drug-resistant cancer models, covering both restoration of drug sensitivity and the effects of EGCG on resistance-associated processes. We also examine EGCG derivatives and delivery systems and discuss the relevance and limitations of available human evidence for overcoming acquired drug resistance.

Literature search and selection: We searched MEDLINE for original studies published from January 2000 to October 2026 examining EGCG, its analogs, or EGCG-based delivery systems in established models of acquired drug resistance in cancer. Studies assessing drug sensitivity or resistance-related cellular and molecular effects were included; those using only treatment-sensitive models were excluded from the core analysis.

2. Molecular Mechanisms of Catechins in Drug-Resistant Cancer Cells

Preclinical studies have examined the effects of EGCG on multiple processes that contribute to acquired drug resistance. Figure 1 summarizes the proposed mechanisms discussed in this section.

2.1. Inhibition of Drug Efflux and Enhancement of Drug Accumulation

A major mechanism underlying acquired resistance to chemotherapy is the overexpression of ATP-binding cassette (ABC) transporters, which actively export cytotoxic agents from cancer cells and reduce intracellular drug accumulation [17]. Among these transporters, P-glycoprotein (P-gp), encoded by the ABCB1 (MDR1) gene, breast cancer resistance protein (BCRP), encoded by ABCG2, and multidrug resistance-associated proteins play central roles in the multidrug resistance (MDR) phenotype [17]. Increasing evidence indicates that EGCG can counteract this mechanism by modulating the expression and functional activity of these efflux pumps, thereby enhancing intracellular drug retention [14,18].

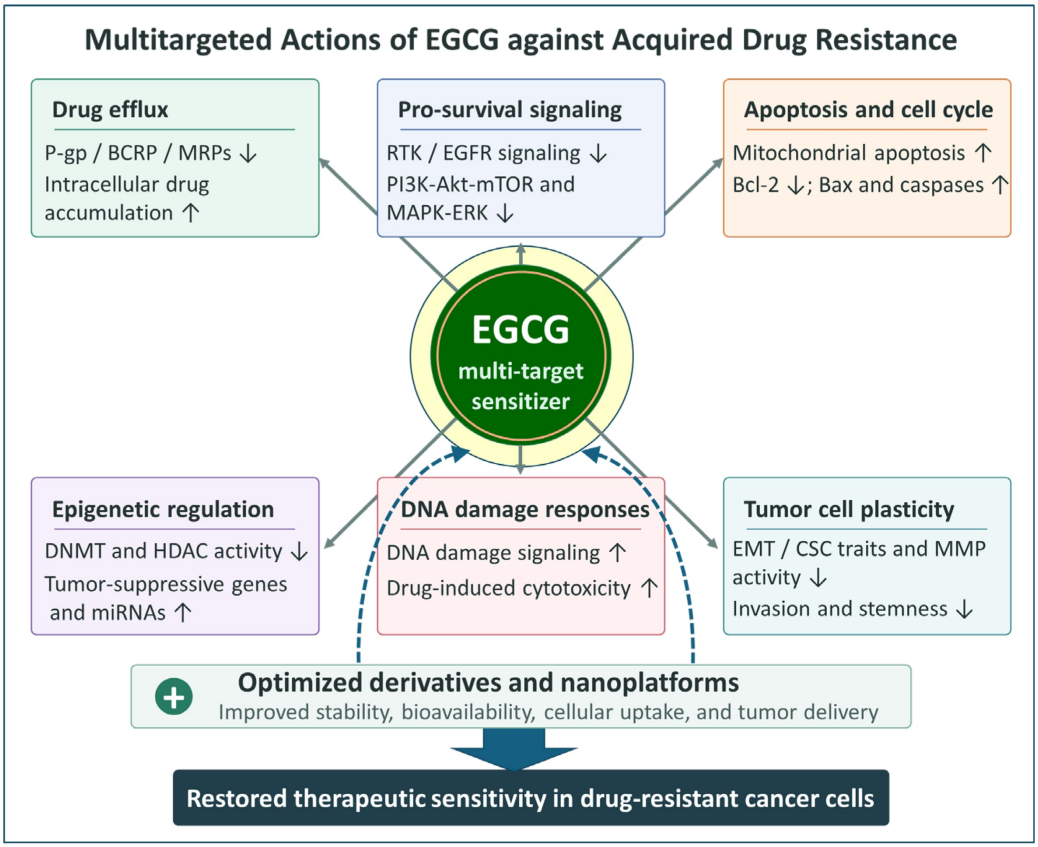


Figure 1. Multi-targeted mechanisms by which EGCG attenuates acquired drug resistance in cancer cells. EGCG modulates multiple resistance-associated processes, including drug efflux, pro-survival signaling, apoptosis and cell-cycle regulation, epigenetic regulation, DNA damage responses, and tumor cell plasticity. Optimized EGCG derivatives and nanoplatforms may improve stability, bioavailability, cellular uptake, and tumor delivery, thereby supporting the restoration of therapeutic sensitivity in drug-resistant cancer cells. The arrows at the bottom of the figure indicate that optimized EGCG derivatives and nanoplatforms may help restore drug sensitivity in resistant cancer cells. The arrows ↑ and ↓ indicate an increase and a decrease, respectively

2.1.1. Downregulation of MDR Transporter Expression

Several studies have demonstrated that EGCG suppresses the expression of key MDR-associated transporters. In tamoxifen-resistant breast cancer models, EGCG reduced P-gp protein levels to approximately half of control levels without altering ABCB1 mRNA expression, suggesting post-transcriptional regulation [14]. In 5-fluorouracil-resistant SGC-7901/FU and MGC-803/FU cells, EGCG downregulated ABCB1 mRNA and P-gp protein levels, with stronger effects in resistant cells than in their parental counterparts [19]. This suppression was also confirmed in xenograft tumors in vivo [19]. Consistently, in 5-fluorouracil- and Adriamycin-resistant carcinoma cells, EGCG decreased the expression of efflux-associated genes such as ABCB1 and lung resistance protein [20]. In cisplatin-resistant CAR cells, EGCG reduced ABCB1 expression, accompanied by decreased phosphorylation of Akt and STAT3 [15].

2.1.2. Functional Inhibition of Efflux Transporter Activity

In addition to transcriptional regulation, EGCG can interfere with the functional activity of efflux transporters. In P-gp-overexpressing multidrug-resistant KB-A-1 cells, EGCG significantly inhibited P-gp-mediated efflux of doxorubicin, resulting in a concentration-dependent increase in intracellular drug accumulation without altering MDR1 mRNA

expression [18], suggesting that resistance reversal in this model occurs primarily through functional inhibition of transporter activity. Consistent with this observation, EGCG and tea polyphenols enhanced intracellular doxorubicin levels in resistant KB-A-1 cells by increasing drug influx, reducing efflux, and inhibiting P-gp ATPase activity [21]. Notably, these resistance-reversal effects were largely restricted to MDR cells, as EGCG markedly reduced the IC50 of doxorubicin in resistant KB-A-1 cells but had little effect in parental KB-3-1 cells [22].

Additional studies further support the ability of EGCG to enhance intracellular drug retention through functional modulation of efflux transporters without altering transporter expression. In multidrug-resistant cells MCF-7/ADR, EGCG alone or in combination with curcumin did not affect P-gp protein levels, yet combination treatment markedly increased intracellular accumulation of rhodamine-123, curcumin, and doxorubicin, indicating functional modulation of transporter activity [23]. This enhanced intracellular drug retention was accompanied by increased caspase activation and PARP cleavage, together with downregulation of Bcl-2 and Survivin [23]. Similarly, although EGCG alone exerted only modest inhibition of P-gp activity in CEM/ADR5000 leukemia cells, it significantly enhanced doxorubicin-induced cytotoxicity when used in combination [24], suggesting that even modest inhibition of P-gp activity can substantially increase chemosensitivity. EGCG may also target multiple efflux transporters. For example, EGCG inhibited BCRP-mediated drug efflux, as demonstrated by increased intracellular accumulation of the BCRP substrate mitoxantrone without altering BCRP expression [14].

2.2. Suppression of Pro-Survival Signaling Pathways

In addition to modulating drug efflux systems, EGCG has been widely reported to sensitize drug-resistant cancer cells by suppressing key survival signaling pathways that support proliferation, stress adaptation, and resistance to cell death [25]. Many chemoresistant tumors exhibit hyperactivation of receptor tyrosine kinases (RTKs) and downstream signaling pathways, including the PI3K/Akt/mTOR and MAPK/ERK pathways [1]. EGCG interferes with these signaling networks at multiple levels, thereby attenuating survival signaling and restoring drug sensitivity [25].

Several studies indicate that EGCG targets RTK signaling pathways upregulated in resistant cancer cells. For example, tamoxifen-resistant MCF-7 cells display markedly elevated EGFR expression and phosphorylation compared with parental cells [16]. EGCG treatment significantly reduced EGFR levels in a dose-dependent manner, accompanied by decreased EGFR membrane localization and suppression of downstream ERK signaling. Notably, these inhibitory effects were more pronounced in resistant cells than in parental MCF-7 cells [16]. Similarly, EGCG inhibited phosphorylation of KIT, the major oncogenic driver in gastrointestinal stromal tumors, in both imatinib-sensitive and resistant cells, leading to suppression of downstream Akt and MAPK signaling pathways [26]. In non-small-cell lung cancer models, EGCG also downregulated Axl and Tyro3 expression at both the mRNA and protein levels in parental and cisplatin-resistant cell lines [27].

Beyond receptor-level inhibition, EGCG has also been shown to suppress major intracellular survival pathways. In multiple resistant cancer cell models, EGCG treatment reduced phosphorylation of Akt at Ser473 in a dose-dependent manner [28]. Inhibition of Akt signaling triggered nuclear translocation of the transcription factor FOXO3a and increased expression of the cell-cycle inhibitor p27^Kip1, ultimately contributing to growth suppression [28]. Importantly, expression of constitutively active Akt abolished the growth-inhibitory effects of EGCG, demonstrating that suppression of Akt signaling is a central mechanism underlying the growth-inhibitory effects of EGCG [28]. Consistent with this

mechanism, EGCG also inhibited phosphorylation of Akt and STAT3 in cisplatin-resistant oral cancer cells [15].

EGCG further modulates downstream metabolic and growth-control pathways. In trastuzumab-resistant (SKTR) and lapatinib-resistant (SKLR) HER2-positive SK-BR-3 breast cancer models, combined treatment with EGCG and the mTOR inhibitor temsirolimus abolished mTOR expression, indicating potent inhibition of mTOR-driven growth signaling [29]. Similarly, in EGFR-inhibitor-resistant lung cancer sublines (H1975 GR and H1975 AR), EGCG combined with gefitinib or osimertinib suppressed phosphorylation of ERK, Akt, and mTOR while activating AMP-activated protein kinase signaling, suggesting metabolic regulation of survival pathways [30].

In addition to classical survival pathways, EGCG has been reported to interfere with stress-adaptation mechanisms. Transcriptomic analyses revealed downregulation of stress-response genes such as HSPA1B, HSPA1L, and USP5 in drug-resistant BEL7404/ADM and BEL7402/5-FU cells [20].

EGCG can also disrupt pro-angiogenic survival signaling. In gastric cancer cells resistant to 5-fluorouracil, EGCG suppressed phosphorylation of TFAP2A and reduced VEGF secretion without altering total TFAP2A levels, indicating inhibition of the TFAP2A/VEGF axis both in vitro and in xenograft tumors [19].

2.3. Induction of Apoptosis and Cell-Cycle Arrest

A major mechanism by which EGCG reverses drug resistance is the restoration of apoptotic responsiveness and induction of cell-cycle arrest [23]. Many resistant cancer cells evade cytotoxic therapy by suppressing apoptotic signaling [1] and upregulating anti-apoptotic proteins such as Bcl-2, Survivin, and XIAP. Evidence from multiple drug-resistant cancer models indicates that EGCG restores apoptotic responsiveness by activating mitochondrial apoptotic pathways and shifting the balance between pro- and anti-apoptotic proteins [14,15].

Activation of the intrinsic mitochondrial apoptotic pathway has been reported in multiple drug-resistant cancer models. In tamoxifen-resistant MCF-7Tam cells, EGCG induced dose-dependent apoptosis accompanied by increased Bax expression and reduced Bcl-2 levels [14]. Similar effects were reported in cisplatin-resistant CAR cells, a subline established from human tongue squamous cell carcinoma CAL27 cells by repeated cisplatin exposure [15]. In these cells, EGCG induced apoptosis through activation of caspase-9 and caspase-3, together with modulation of Bax and Bcl-2 expression [15]. EGCG also induced apoptosis in drug-sensitive H69 and drug-resistant H69VP small-cell lung cancer cells, as evidenced by DNA fragmentation and TUNEL staining [31].

EGCG-induced apoptosis is also associated with suppression of anti-apoptotic proteins. In gastrointestinal stromal tumor cells, EGCG triggered anoikis-like apoptosis accompanied by downregulation of Survivin and XIAP [26]. In HER2-targeted therapy-resistant breast cancer models, EGCG also enhanced PARP cleavage and apoptotic signaling, accompanied by increased terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL)-positive cells in xenograft tumors [29]. In Hep3B sublines with acquired resistance to lenvatinib or sorafenib, EGCG inhibited cell proliferation and induced apoptosis [32]. Protein array analysis after 48 h of exposure to 10 μg/mL EGCG (approximately 21.8 μM) showed reduced levels of paraoxonase-2 (PON2) and heat shock protein 27 (HSP27) in the resistant sublines [32].

Importantly, EGCG exhibits enhanced pro-apoptotic effects when combined with anticancer agents or other bioactive compounds. In multidrug-resistant MCF-7/ADR cells, 2 μM EGCG alone induced little apoptosis, but co-treatment with 2 μM EGCG and 10 μM curcumin for 48 h increased apoptosis compared with curcumin alone [23]. This finding

illustrates that EGCG can enhance an apoptotic response at a concentration with little pro-apoptotic activity on its own in the same resistant model. Similar synergistic effects have been reported for combinations with 5-fluorouracil [6], cisplatin [33], EGFR inhibitors [30], and other phytochemicals [23].

EGCG also induces cell-cycle perturbations in drug-resistant cancer cells, with arrest occurring at different cell-cycle checkpoints. EGCG induced G2 arrest in resistant cells and enhanced G2 arrest when combined with 5-fluorouracil [6]. In other studies, EGCG triggered G1 arrest with upregulation of p21 and reduced expression of CDK2 and CDK6 [30]. Transcriptomic analyses further showed modulation of genes associated with cell-cycle progression and checkpoint regulation, including Cyclin G1, Cyclin G2, RB1, and GADD34 [20].

2.4. Epigenetic Modulation of Drug Resistance

Beyond its effects on drug transporters and survival signaling, EGCG has also been reported to modulate epigenetic mechanisms associated with drug resistance [6]. Epigenetic alterations—including aberrant DNA methylation, histone modifications, and dysregulation of microRNAs—are increasingly recognized as key contributors to chemoresistance [1], as they can silence tumor suppressor genes and promote CSC maintenance. Emerging evidence suggests that EGCG can modulate epigenetic regulatory mechanisms and restore the expression of tumor suppressor genes [3].

One such mechanism involves modulation of tumor-suppressive microRNAs associated with CSC regulation and drug resistance. In 5-fluorouracil-resistant cancer cells, EGCG significantly increased the expression of miR-34a, miR-145, and miR-200c, whereas treatment with 5-fluorouracil alone had little effect [6]. These microRNAs are well known to regulate pathways involved in stemness and epithelial–mesenchymal transition, suggesting that EGCG may attenuate CSC-associated programs that contribute to chemoresistance [6].

EGCG has also been shown to influence epigenetic regulators associated with drug resistance. Transcriptomic analyses revealed reduced expression of histone deacetylase 5 (HDAC5) following EGCG treatment in drug-resistant BEL7404/ADM cells [20]. More direct evidence of epigenetic regulation has been reported in cisplatin-resistant cancer cells, where EGCG inhibited both DNA methyltransferase (DNMT) and HDAC enzymatic activity, leading to decreased promoter methylation and reactivation of multiple tumor suppressor genes, including GAS1, TIMP4, ICAM1, and WISP2 [34]. These genes had previously been identified as epigenetically silenced during the development of cisplatin resistance. Notably, the epigenetic effects of EGCG were comparable to those observed with the demethylating agent 5-aza-2′-deoxycytidine (5-Aza-dC). Similarly, in paclitaxel-resistant ovarian cancer cells, co-treatment with EGCG and sulforaphane reduced DNMT1 protein expression, accompanied by suppression of hTERT expression [35].

2.5. Enhancement of DNA Damage Responses

EGCG has also been reported to induce or enhance drug-induced DNA damage in drug-resistant cancer cells. In small-cell lung carcinoma models, EGCG treatment induced significant DNA fragmentation, as detected by enzyme-linked immunosorbent assay and TUNEL assays [31].

Consistent with these findings, enhanced DNA damage signaling was observed in paclitaxel-resistant ovarian cancer models. In SKOV3 and paclitaxel-resistant SKOV3TR-ip2 cells, combined treatment with EGCG and sulforaphane markedly increased H2AX phosphorylation, a widely used marker of DNA damage [35].

In addition, sequential treatment with cisplatin followed by EGCG produced synergistic cytotoxicity in both cisplatin-sensitive and resistant ovarian cancer cells, accompanied by

increased intracellular platinum accumulation and platinum–DNA binding [33], suggesting that increased platinum–DNA binding contributes to the enhanced cytotoxic response.

2.6. Suppression of EMT, Cancer Stemness, and Invasive Phenotypes

EGCG has also been reported to attenuate invasive and stem cell-like phenotypes frequently associated with chemoresistance, extending its effects beyond the regulation of drug efflux and survival signaling [6,16]. Drug-resistant cancer cells often acquire EMT features, enhanced extracellular matrix (ECM) remodeling capacity, and enrichment of CSC populations, all of which contribute to tumor progression, metastasis, and therapeutic failure. EGCG appears to interfere with these processes by suppressing matrix-degrading enzymes, inhibiting EMT-associated invasion, and modulating CSC-related signaling pathways.

EGCG modulates matrix metalloproteinases (MMPs) involved in extracellular matrix (ECM) remodeling and tumor invasion. The doxorubicin-resistant breast cancer sublines MCF-7/DOX and MCF-7/DOX500 exhibited elevated MMP-2 and MMP-9 activities, whereas neither activity was detected in parental MCF-7 cells [36]. Despite markedly different P-glycoprotein levels, both resistant sublines showed concentration-dependent reductions in MMP-2 and MMP-9 activity after 24 h of exposure to 5–20 μM EGCG [36]. In tamoxifen-resistant MCF-7Tam cells, which displayed an EMT-like phenotype, EGCG reduced Matrigel invasion and lowered the protein levels of MMP-2, MMP-9, and extracellular matrix metalloproteinase inducer while increasing TIMP-1 and TIMP-2 expression. Gelatin zymography showed that the bands corresponding to MMP-2 and MMP-9 were undetectable after 24 h of exposure to either 50 or 100 μg/mL EGCG (approximately 109 and 218 μM, respectively) [16]. In drug-resistant BEL7404/ADM and BEL7402/5-FU cells, microarray analysis showed that exposure to 20 mg/L (43.6 μM) EGCG reduced MMP15 mRNA expression [20]. Although the two breast cancer studies assessed MMP-2 and MMP-9 activity after the same exposure duration in MCF-7-derived cells, the differences in acquired resistance phenotypes limit direct comparisons of EGCG sensitivity [16,36]. The study of BEL7404/ADM and BEL7402/5-FU cells extends these observations to a different MMP at the transcript level, further illustrating why the reported concentrations should be interpreted in relation to the resistance model and the endpoint measured.

In addition to regulating ECM remodeling, EGCG suppresses cancer stem cell-like properties associated with drug resistance. In colorectal cancer models, EGCG inhibited spheroid formation in both parental and drug-resistant cell lines, and co-treatment with 5-fluorouracil synergistically reduced spheroid numbers [6]. This effect was accompanied by downregulation of CSC markers including Oct4, Nanog, CD44, ALDH1, and CD133 [6]. Similarly, cisplatin-resistant lung cancer cells exhibited increased side-population fractions and elevated expression of stemness markers such as CD44, CD133, Sox2, Nanog, and Oct4, which were attenuated by EGCG treatment [37]. Mechanistically, EGCG upregulated miR-485, which directly targets CD44, thereby suppressing CSC-like properties [37]. In xenograft models, EGCG treatment also reduced CSC marker expression and the proliferation marker Ki-67 [37].

Consistent with these observations, EGCG has been reported to interfere with signaling networks that regulate CSC maintenance and self-renewal. EGCG suppressed Notch1 signaling, as evidenced by reduced levels of cleaved Notch1 and c-Myc, accompanied by downregulation of polycomb repressive complex components including Bmi1, Ezh2, and Suz12 [6].

Table 1 summarizes the preclinical studies discussed in Sections 2.1–2.6, including the models of acquired drug resistance and the reported effects of EGCG.

Table 1. Preclinical studies evaluating EGCG in acquired drug-resistant cancer models.

Cancer	Selecting Drug	Resistant Cells	Assessed Parameters	Outcome Measures	EGCG Treatment Conditions	Ref
Breast	DOX	MCF-7/DOX_{500}	↓MMP-2 ↓MMP-9	-	5–20 μM, 24 h	[36]
Breast	Lapatinib	SKLR SKTR SKTR	↑c-PARP ↓mTOR	↑Apoptosis ↓Proliferation ↓Tumor growth	60 μM, 2 or 5 d In vivo: 30 mg/kg, i.p., 3 days a week	[29]
Breast (reported) †	DOX	MCF-7/ADR	↑Caspase-7 ↑Caspase-9 ↑c-PARP ↓Bcl-2 ↓Survivin	↑Apoptosis ↑Cellular accumulation	2–4 μM/12 h	[23]
Breast	Tamoxifen	MCF-7Tam	↑TIMP-1 ↑TIMP-2 ↓EGFR ↓EMMPRIN ↓ERK1/2 ↓MMP-2 ↓MMP-9 ↓p-EGFR ↓p-ERK1/2	↓Cell invasion ↓Cell viability	10–100 μg/mL, 24 h	[16]
Breast	Tamoxifen	MCF-7Tam	↑Bax ↓Bcl-2 ↓Pgp	↑Apoptosis ↑Cellular uptake ↓Cell growth	100 μg/mL, 24 h	[14]
Breast	Trastuzumab	BT/Her^R	↑FOXO3a ↑p27 ↓ATP production ↓p-Akt	↓Cell number ↓Proliferation	40–160 μg/mL, 24 or 72 h	[28]
Cervical *	5-FU	BEL7402/5-FU	↓LRP ↓MDR1 ↓HSPA1L ↓USP5 ↓MMP-15	↑Drug sensitivity	7–20 μg/mL, 48 h	[20]
Cervical *	DOX	BEL7404/ADM	↑Cyclin G1 ↓HDAC5 ↓HSPA1B ↓LRP ↓MDR1 ↓MMP-15 ↓USP5	↑Drug sensitivity ↓Stress adaptation	7–20 μg/mL, 48 h	[20]
Cervical *	DOX	KB-A-1	-	↑Drug sensitivity ↓Cellular ROS	4–10 μg/mL, 24–72 h	[22]
Cervical *	DOX	KB-A-1	-	↑Cellular accumulation ↑Drug distribution in tumor tissue ↑Drug sensitivity ↓Tumor weight	20 μM, 48 h In vivo: 40 mg/kg, i.p. daily on days 1–9, with DOX on days 2, 4, 6, and 8	[18]
Cervical *	DOX	KB-A-1	↓Pgp ATPase activity	↑Cellular accumulation ↑Drug influx ↑Drug sensitivity ↓Drug efflux ↓Tumor weight	10 μg/mL, 72 h	[21]

Table 1. *Cont.*

Cancer	Selecting Drug	Resistant Cells	Assessed Parameters	Outcome Measures	EGCG Treatment Conditions	Ref
Colon	5-FU	5FUR	↑miR-145 ↑miR-200c ↑miR-34a ↓ALDH ↓Bmi1 ↓CD133 ↓CD44 ↓c-Myc ↓Ezh2 ↓Nanog ↓Notch1 ↓Oct4 ↓Suz12	↑Apoptosis ↑Drug sensitivity ↑G2 arrest ↓Spheroid-derived CSC formation ↓Tumor volume ↓Tumor weight	100 (25–400) μM In vivo: Cells pretreated with 100 μM EGCG for 48 h before implantation	[6]
Gastrointestinal	Imatinib	GIST-T1 IR	↑Caspase-3 ↑c-PARP ↓p-AKT, ↓p-ERK1/2 ↓p-KIT, ↓Survivin ↓XIAP	↑Cell death ↓Cell growth	10–80 μM, 4–72 h	[26]
Leukemia	DOX	CEM/ADR5000	-	↑Cellular accumulation ↑Drug sensitivity	12–20 μM, 48 h	[24]
Liver	Lenvatinib	Hep3BLR	↑miR-575 ↓HSP27 ↓EGFR ↓cCK8	↑Apoptosis ↓Proliferation	5–20 μg/mL, 24–72 h	[32]
Liver	Sorafenib	Hep3BSR	↑miR-575 ↓PON2 ↓EGFR ↓cCK8	↑Apoptosis ↓Proliferation	5–20 μg/mL, 24–72 h	[32]
Lung	Gefitinib	H1975 GR H1975 AR	↑Caspase-3 ↑c-PARP ↑p21 ↑p-AMPK ↓Bcl-2 ↓CDK2 ↓CDK6 ↓p-AKT ↓p-ERK1/2 ↓p-mTOR	↑Apoptosis ↑Cellular ROS ↑GO/G1 arrest ↑Mitochondria respiration ↓Cell viability ↓Colony formation ↓Glycolysis rate ↓Lactate secretion ↓Tumor size ↓Tumor volume ↓Tumor weight	15 μM (GR) or 50 μM (AR), 6–48 h In vivo: 50 mg/kg, i.p., 5 days on/2 days off for 21 days	[30]
Lung	Cisplatin	A549/CDDP	↑miR-485 ↓CD133 ↓CD44 ↓Ki-67 ↓Nanog ↓Oct4 ↓Sox2	↑Apoptosis ↓CSC-like properties ↓Proliferation ↓Tumor volume	10–40 μM, 24 h In vivo: 20 mg/kg, i.p., every 3 days	[37]

Table 1. *Cont.*

Cancer	Selecting Drug	Resistant Cells	Assessed Parameters	Outcome Measures	EGCG Treatment Conditions	Ref
Lung	Cisplatin	A549/DDP	↑GAS1 ↑ICAM1 ↑TIMP4 ↑WISP2 ↓DNMT ↓HDAC	↑Apoptosis ↑G1 arrest ↓Colony formation ↓Proliferation ↓Tumor size ↓Tumor volume	50 μM, 24 h In vivo: 10 mg/kg, i.p., on days 1–3 before cisplatin	[34]
Lung	Cisplatin	A549/Cis H460/Cis	↑IL-6 ↓AXL ↓TYRO3	↓Colony formation ↓Proliferation	80 μM, 24 h	[27]
Lung	Etoposide	H69VP	↑Caspase-3 ↑Caspase-9 ↓Telomerase	↑Apoptosis ↑Cell cytotoxicity ↑S arrest	70 μM, 24 or 36 h	[31]
Oral	Cisplatin	CAR	↑Atg12 ↑Atg5 ↑Atg7 ↑Bax ↑Beclin-1 ↑Caspase-3 ↑Caspase-9 ↑LC3B-II ↓Bcl-2 ↓MDR1 ↓p-Akt ↓Pgp ↓p-STAT3	↑Apoptosis ↑Autophagy ↓Cell viability	50 μM, 48 h	[15]
Ovarian	Paclitaxel	SKOV3TR-ip2	↑c-PARP ↑p-H2AX ↓Bcl-2 ↓DNMT1 ↓hTERT ↓Telomerase	↑Apoptosis ↑DNA damage ↑G2/M and S arrest ↓Cell viability ↓Colony formation	20 μM, 48 h	[35]
Reclassified/uncertain origin *	5-FU	SGC7901/FU MGC803/FU	↓MDR1 ↓Pgp ↓p-TFAP2A ↓VEGF	↓Colony formation ↓Proliferation ↓Tumor volume ↓Tumor weight	10–20 μM, 48–72 h In vivo: 25 mg/kg, twice weekly for 4 weeks	[19]

* Tissue annotations follow current Cellosaurus records: KB-A-1 belongs to a HeLa-derived lineage; SGC-7901, BEL-7402, and BEL-7404 are classified as HeLa derivatives; MGC-803 is considered a putative HeLa–gastric hybrid. Thus, the SGC7901/FU and MGC803/FU row is not classified as an authenticated gastric cancer model. STR authentication of the SGC7901/FU, MGC803/FU, BEL7402/5-FU, and BEL7404/ADM stocks was not reported in the cited studies. † MCF-7/ADR is retained as reported in [14], which describes selection from MCF-7 but provides no STR authentication results; its identity should not be inferred from the designation alone. Cellosaurus: https://www.cellosaurus.org/ (accessed 9 November 2026). ↑ indicates an increase, and ↓ indicates a decrease in the indicated parameter or outcome.

2.7. EGCG Derivatives and Nanoplatform Strategies to Overcome Pharmacological Limitations

Despite its diverse anti-resistance activities, the clinical application of EGCG remains limited by poor stability, rapid oxidation, and relatively low bioavailability. To address these limitations, recent studies have focused on EGCG derivatives and EGCG-based nanoplatforms designed to improve its pharmacological properties and efficacy in drug-resistant cancer models.

One major approach involves incorporating EGCG into nanocarrier systems to enable co-delivery with conventional chemotherapeutic agents. In MCF-7/ADR cells, PEI-DOX/EGCG and its folate-targeted formulation PEI-DOX/EGCG/FA suppressed P-gp

expression and enhanced intracellular doxorubicin accumulation [38]. The folate-modified nanoparticles further enhanced the inhibitory effect on cell migration [38]. These systems also mitigated doxorubicin-induced cardiotoxicity by attenuating oxidative stress, as evidenced by reduced levels of malondialdehyde, creatine kinase-MB, and lactate dehydrogenase together with restoration of superoxide dismutase activity. In xenograft models, both nanoparticle formulations suppressed tumor growth more effectively than free doxorubicin, whereas the folate-targeted system showed the greatest antitumor efficacy together with reduced cardiac doxorubicin accumulation and fibrosis [38]. These findings highlight the dual potential of EGCG-based nanoplatforms to overcome multidrug resistance while reducing doxorubicin-associated cardiotoxicity.

Similarly, an EGCG-loaded mesoporous silica–gold nanocluster formulation (EAuSSi) and its dual-drug counterpart co-encapsulating EGCG and the EGFR/VEGFR2 inhibitor ZD6474 (ZEAuSS) effectively overcame tamoxifen resistance by suppressing EGFR/VEGFR2/Akt signaling, resulting in enhanced apoptosis and cell-cycle arrest [39]. Enhanced therapeutic efficacy was associated with improved intracellular uptake and activation of mitochondrial apoptotic pathways, accompanied by downregulation of Bcl-2 and upregulation of Bax, Bak, Bim, and p53. In xenograft models, the dual-loaded nanoplatform produced the greatest tumor suppression, accompanied by reduced Ki-67 expression and increased TUNEL-positive cells [39].

In hematological malignancies, daunorubicin/EGCG nanocomplexes enhanced intracellular delivery and nuclear accumulation of daunorubicin, resulting in increased reactive oxygen species generation and activation of caspase-3 and caspase-7, thereby producing synergistic cytotoxicity accompanied by caspase-mediated apoptosis in multidrug-resistant leukemia cells [40].

EGCG-based platforms have also been extended to gene-targeting strategies. Nanoparticle-mediated delivery of siRNA targeting the resistance-associated long non-coding RNA TMEM44-AS1 reduced expression of the efflux transporters ABCC1 and ABCG2. This was accompanied by increased levels of cleaved caspase-3, Bax, p53, and AIFM2 together with reduced expression of Survivin and Bcl-2, resulting in enhanced chemosensitivity in resistant tumor models [41]. The chitosan–gelatin–EGCG nanoparticle (CGE) platform facilitated siRNA loading and lysosomal escape, leading to enhanced antitumor efficacy in 5-fluorouracil-resistant xenograft models [41].

In parallel, chemically modified EGCG derivatives have been developed to enhance etoposide intrinsic anticancer potency. The derivative G28 exhibited greater efficacy than native EGCG in suppressing cancer stem cell-like properties, achieving near-complete inhibition of mammosphere formation in parental MDA-MB-231 cells and their doxorubicin-resistant (231DXR) and paclitaxel-resistant (231PTR) derivatives [42].

The ethylated derivative Y6, developed to improve the stability and lipophilicity of native EGCG, reversed multidrug resistance in doxorubicin-resistant BEL-7404/DOX cells by downregulating ABCB1/P-gp expression and suppressing HIF-1α-mediated hypoxia signaling, thereby restoring apoptotic responsiveness [43]. In oxaliplatin-resistant SMMC-7721/OXA cells, Y6 further inhibited EMT-associated resistance in association with suppression of the HIF-1α/TWIST axis, accompanied by increased E-cadherin expression, reduced vimentin expression, and decreased migratory and invasive capacities [44].

Table 2 summarizes the preclinical studies discussed in Section 2.7, including the EGCG derivatives and nanoplatform-based delivery systems evaluated and their reported effects in models of acquired drug resistance.

Table 2. Preclinical studies evaluating EGCG derivatives and nanoplatform-based delivery systems in acquired drug-resistant cancer models.

Derivative/ Formulation	Cancer	Selecting Drug	Resistant Cells	Assessed Parameters	Outcome Measures	EGCG Treatment Conditions	Ref
PEI-DOX/ EGCG/FA	Breast (reported) †	DOX	MCF-7/ ADR	↑IL-10 ↑SOD ↑TNF-α ↑CRT ↑HMGB1 ↑IFN-γ ↓CK-MB ↓LDH ↓MDA ↓Pgp	↑ATP release ↑Cell cytotoxicity ↑Cellular uptake ↑Drug distribution in tumor tissue ↑Drug release (pH 5.5 > 7.4) ↑Drug retention ↓Cell migration ↓Cardiotoxicity ↓Drug distribution in heart tissue ↓Fibrosis ↓Tumor size ↓Tumor spheroid ↓Tumor volume	1–20 μg/mL DOX equivalent In vivo: 5 mg/kg DOX equivalent every 3 days (EGCG loading: 62.97% *w*/*w*)	[38]
EGCG-Derivate G28	Breast	DOX	231DXR	-	↓Cell viability ↓Mammosphere-formation capacity	(G28) 50 μM, 5 days	[42]
EGCG-Derivate G28	Breast	Paclitaxel	231PTR	-	↓Cell viability ↓Mammosphere-formation capacity	(G28) 50 μM, 5 days	[42]
EAuSSi ZEAuSS	Breast	Tamoxifen	MCF 7/ TAM	↑Bak ↑Bax ↑Bim ↑p53 ↓Bcl-2 ↓Ki-67 ↓p-Akt ↓p-EGFR ↓p-VEGFR2	↑Cellular uptake ↑Drug release (pH 5.2 > 7) ↑Sub-G1 arrest ↓Proliferation ↓Tumor mass ↓Tumor volume	ZEAuSSi for 48 h; IC_{50}, 20.18 μg/mL In vivo: ZEAuSSi i.v. twice weekly for 5 weeks (360 mg/kg)	[39]
EGCG-Derivate Y6	Cervical *	DOX	BEL-7404/ DOX	↓HIF-1α ↓MDR1 ↓Pgp	↑Apoptosis ↑Chemosensitivity	EGCG (10 μM) or Y6 (10 or 15 μM)	[43]
EGCG-Derivate Y6	Cervical *	Oxali-platin	SMMC-7721/OXA	↑E-cadherin ↑miR-338-3p ↓HIF-1α ↓TWIST ↓Vimentin	↑Chemosensitivity ↓Cell invasion ↓Cell migration ↓Cell survival ↓EMT progression	EGCG or Y6 (10 μM each, tested separately)	[44]
si-TMEM44-AS1	Gastric	5-FU	HGC-27/S MKN-45/S	↑AIFM2 ↑Bax ↑Caspase-3 ↑miR-2355-5p ↑p53 ↓Bcl-2 ↓BCRP ↓MRP1 ↓Survivin	↑Apoptosis ↓Proliferation ↓Tumor volume ↓Tumor weight	CGE/si-TMEM44-AS1 followed by 5-FU (5 μg/mL). In vivo: CGE/si-TMEM44-AS1 i.v., every 3 d, +5-FU (10 mg/kg, i.p.). EGCG conc./dose: NR	[41]

Table 2. *Cont.*

Derivative/ Formulation	Cancer	Selecting Drug	Resistant Cells	Assessed Parameters	Outcome Measures	EGCG Treatment Conditions	Ref
Dauno-MNC	Leukemia	Mitox-antrone	HL-60/ MX2	↑Caspase-3 ↑Caspase-7 ↑ROS level	↑Cellular uptake ↑Drug release (pH 5.5 > 7.4) ↑Drug retention ↓Cell viability	Dauno-MNC (0.05–1.6 μM DNR equivalent, 72 h); EGCG conc.: NR	[40]

* BEL-7404 and SMMC-7721 are classified as HeLa derivatives in Cellosaurus. STR authentication of BEL-7404/DOX and SMMC-7721/OXA was not reported in [33,34]. † MCF-7/ADR is retained as reported in [28]; cell provenance and STR authentication were not reported, so the stated breast origin could not be independently verified. Cellosaurus: https://www.cellosaurus.org/ (accessed 9 November 2026). The arrows ↑ and ↓ indicate an increase and a decrease, respectively, in the indicated parameter or outcome.

3. Clinical and Translational Relevance and Remaining Challenges of EGCG in Cancer

Given the extensive mechanistic evidence and recent advances in EGCG-based derivatives and delivery systems, an important question is whether these findings can be translated into clinically meaningful outcomes. Although direct clinical evidence in patients with established drug-resistant cancers remains limited, human pharmacokinetic studies confirm that orally administered EGCG is absorbed, with limited systemic exposure that varies according to dosing conditions [45].

Observational studies in Japan have associated higher green tea consumption with a lower risk of recurrence among patients with stage I-II breast cancer [46] and with later cancer onset in a population-based cohort [47]. A more recent meta-analysis reported inverse associations between green tea or EGCG intake and the risk of selected cancers [9]. These findings relate to cancer risk or recurrence and provide limited insight into therapeutic resensitization in patients with acquired drug resistance.

Trials in premalignant and high-risk populations have also evaluated green tea catechin preparations. Green tea extract supplementation was associated with fewer metachronous colorectal adenomas after polypectomy [7,8]. In men with high-grade prostatic intraepithelial neoplasia, an early trial reported fewer prostate cancer diagnoses with catechin supplementation [48], whereas a subsequent randomized trial in men with high-grade prostatic intraepithelial neoplasia and/or atypical small acinar proliferation found no statistically significant reduction in overall prostate cancer incidence [49]. In patients with high-risk oral premalignant lesions, clinical responses were more frequent at higher green tea extract doses, and reductions in stromal VEGF and cyclin D1 expression were observed among clinical responders [50].

In women with a history of hormone receptor-negative breast cancer, a phase Ib dose-escalation trial evaluated the tolerability of oral Polyphenon E and included exploratory biomarker analyses [51]. In a separate presurgical trial in patients with bladder cancer, Polyphenon E was associated with dose-dependent decreases in PCNA and clusterin expression [52]. In patients with asymptomatic, early-stage chronic lymphocytic leukemia, phase I and II studies of oral Polyphenon E reported decreases in absolute lymphocyte counts and/or lymphadenopathy [53,54]. Table 3 summarizes selected human trials of EGCG and EGCG-containing preparations, including the study populations, dosing regimens, endpoints, and outcomes.

Table 3. Selected human intervention trials cited in Section 3.

Design and Population	Preparation and Exposure	Endpoints	Main Outcomes	Ref
Randomized, open-label pilot trial. Post-polypectomy patients with a confirmed clean colon. 136 randomized, 125 assessed at follow-up.	GTE 1.5 g/day, providing 157.5 mg EGCG/day, for 12 months. Habitual green tea intake continued in both groups.	Metachronous colorectal adenomas at follow-up colonoscopy.	Adenomas in 9/60 (15%) with GTE vs. 20/65 (31%) without supplementation. RR 0.49 (95% CI 0.24–0.99), $p < 0.05$. No serious adverse events reported in the GTE group.	[7]
Randomized, open-label controlled trial with no-supplement control. Korean patients after complete adenoma removal. 176 randomized, 143 completed.	GTE 0.9 g/day, providing approximately 206 mg EGCG/day (reported as 0.2 g/day), for 12 months.	Metachronous colorectal adenomas at follow-up colonoscopy.	Adenomas in 17/72 (23.6%) with GTE vs. 30/71 (42.3%) in controls. RR 0.56 (95% CI 0.34–0.92). Fewer recurrent adenomas per patient with GTE ($p = 0.010$).	[8]
Double-blind, placebo-controlled proof-of-principle trial. Described as randomized, but the methods specify alternating allocation. 60 men with HGPIN.	Catechin preparation 600 mg/day in three capsules, containing approximately 311 mg EGCG/day, for 1 year.	Prostate cancer diagnosed on repeat biopsies.	Prostate cancer in 1/30 (3.3%) with catechins vs. 9/30 (30%) with placebo ($p < 0.01$). Preliminary evidence from a small trial with alternating allocation. No significant adverse effects reported.	[48]
Randomized, double-blind, placebo-controlled trial. 97 men with HGPIN and/or ASAP.	Polyphenon E providing 200 mg EGCG twice daily (400 mg/day), with food, for 1 year.	Primary endpoint was cumulative 1-year prostate cancer incidence.	Primary endpoint not met. Cancer in 5/49 (10.2%) vs. 9/48 (18.8%), $p = 0.25$. In the baseline HGPIN-only subgroup, prostate cancer plus ASAP was less frequent (3/26 vs. 10/25, $p = 0.024$), largely reflecting fewer ASAP diagnoses.	[49]
Phase II randomized, double-blind, placebo-controlled trial. High-risk oral premalignant lesions. 41 enrolled, 39 assessed for efficacy.	GTE 500, 750, or 1000 mg/m^2 per dose, three times daily after meals, for 12 weeks. These are GTE doses. Actual doses were rounded down to whole 350 mg capsules.	Primary endpoints were clinical and histologic lesion responses at 12 weeks. Secondary assessments included biomarkers and safety.	Clinical response was 50% with pooled GTE vs. 18.2% with placebo ($p = 0.09$). A dose–response trend was observed ($p = 0.03$). Histologic response was not significantly different ($p = 0.65$). Higher doses increased insomnia/nervousness.	[50]
Phase Ib randomized, double-blind, placebo-controlled dose-escalation trial. 40 women with a history of stage I–III hormone receptor-negative breast cancer.	Polyphenon E providing 400, 600, or 800 mg EGCG per dose, twice daily (800–1600 mg/day), with food, for 6 months.	Maximum tolerated dose and dose-limiting toxicity, with exploratory breast biomarkers.	MTD was 600 mg EGCG twice daily, with DLTs in 3/11 (27%) at that level. Grade III liver-function abnormality occurred at 800 mg twice daily. Breast Ki-67 and mammographic density did not change significantly compared with placebo.	[51]
Phase II randomized, double-blind, placebo-controlled presurgical trial. Bladder tumors awaiting resection or cystectomy. 31 randomized, 29 completed.	Polyphenon E providing 800 or 1200 mg EGCG/day, with food, for 14–28 days before surgery.	Primary endpoint was EGCG in nonmalignant bladder tissue. Secondary endpoints included tumor tissue EGCG, tissue biomarkers, and plasma/urine catechins.	Nonmalignant tissue EGCG did not differ significantly between pooled treatment groups and placebo ($p = 0.12$). Supplemental analyses across all three arms showed dose–response relationships in nonmalignant ($p = 0.046$) and tumor tissue ($p = 0.005$). PCNA and clusterin decreased with dose ($p = 0.016$ and 0.008).	[52]

Table 3. *Cont.*

Design and Population	Preparation and Exposure	Endpoints	Main Outcomes	Ref
Single-arm phase II evaluation. Previously untreated, asymptomatic Rai stage 0–II CLL. 42 evaluated, including six participants from phase I at the phase II dose.	Phase II regimen of Polyphenon E providing 1000 mg EGCG twice daily for 7 days, then 2000 mg twice daily (4000 mg/day), with a light meal/snack, for up to 6 months.	Tolerability and clinical activity, including ALC and lymph node measurements.	Sustained ≥20% ALC reduction in 13/42 (31%). ≥50% reduction in summed nodal area products in 20/29 (69%) with palpable nodes. Protocol-defined biologic response in 29/42 (69%). One partial remission was in a participant already reported in phase I. Grade 3 transaminitis, abdominal pain, and fatigue each occurred in one patient.	[54]
Single-arm phase I dose-escalation trial. 33 eligible patients with previously untreated, asymptomatic Rai stage 0–II CLL.	Polyphenon E providing 400–2000 mg EGCG per dose, twice daily (800–4000 mg/day), for up to 6 months.	Optimal dose, tolerability, trough plasma EGCG, and exploratory clinical activity.	MTD was not reached. One partial remission. Sustained ≥20% ALC reduction in 11/33 (33%). ≥50% reduction in summed nodal area products in 11/12 (92%) with palpable nodes. Transaminitis occurred in 33%, all grade 1.	[53]

Abbreviations. ALC, absolute lymphocyte count. ASAP, atypical small acinar proliferation. CI, confidence interval. CLL, chronic lymphocytic leukemia. DLT, dose-limiting toxicity. EGCG, epigallocatechin-3-gallate. GTE, green tea extract. HGPIN, high-grade prostatic intraepithelial neoplasia. MTD, maximum tolerated dose. RR, relative risk. Dose notes. All preparations were administered orally. EGCG amounts for Shimizu, Shin, and Bettuzzi were calculated from the reported tablet or capsule content. Shimizu participants continued habitual green tea consumption, so the stated EGCG amount represents the supplement alone. Polyphenon E doses are expressed as EGCG content. The two CLL reports include overlapping participants and should not be treated as independent cohorts. None of these studies directly tested reversal of clinically established acquired drug resistance. The protocol-defined biologic response in the CLL studies used lymphocyte and/or lymph node reductions and should not be interpreted as a standard complete or partial remission rate.

These findings document biological effects in specific clinical settings. The ability of EGCG to restore responsiveness to a therapy after resistance has emerged remains unproven. A key question for clinical translation is whether oral EGCG or an optimized formulation can achieve sufficient exposure within tumors to reproduce the effects observed in drug-resistant models. In healthy volunteers, a single oral dose of Polyphenon E containing 800 mg of EGCG yielded mean peak plasma concentrations of unconjugated EGCG of approximately 0.64 μM with food and 3.3 μM under fasting conditions [45]. The fasting peak was in the same range as the nominal 2 μM EGCG concentration used in the 48 h curcumin co-treatment experiment [23], but below the concentrations used in the 24 h MMP-2 and MMP-9 activity experiments [16,36]. This comparison illustrates the difference between a plasma peak after oral dosing and the concentration and duration of exposure used in cell culture. Whether comparable concentrations can be achieved and maintained within human tumors remains uncertain. In the presurgical bladder cancer trial, EGCG concentrations in nonmalignant bladder tissue did not differ significantly between the combined Polyphenon E groups and the placebo group, although supplemental analyses across all three study arms showed significant dose–response relationships in both nonmalignant and tumor tissue [52]. Differences among brewed green tea, standardized extracts, and purified EGCG further complicate comparisons across studies. Chemical instability, metabolism, dose-related toxicity, and potential interactions with anticancer agents also warrant consideration. In the Minnesota Green Tea Trial, daily supplementation with green tea extract containing

843 mg EGCG for one year was associated with more frequent ALT elevations than placebo (6.7% versus 0.7%) [55]. Thus, attempts to increase systemic exposure through higher supplement doses must also account for hepatic safety. EGCG derivatives and delivery systems may improve exposure, but their ability to restore drug responsiveness requires direct evaluation.

A search of ClinicalTrials.gov on 9 November 2026 identified registered EGCG-containing combination studies, including Polyphenon E plus erlotinib in head and neck chemoprevention (NCT01116336; completed) [56] and advanced non-small-cell lung cancer (NCT00707252; terminated) [57]. A breast cancer trial combining EGCG, quercetin, zinc, and metformin with chemotherapy had an unknown recruitment status (NCT05680662) [58]. No ongoing combination trial specifically designed to demonstrate reversal of acquired drug resistance was identified.

Trials aimed at reversing acquired resistance should enroll patients with documented resistance and evaluate an EGCG formulation in combination with the therapy to which resistance has emerged. Pharmacokinetic assessments should measure systemic and, where feasible, intratumoral exposure and examine how these exposures relate to changes in resistance-associated mechanisms, such as drug efflux, survival signaling, apoptotic responsiveness, or stem cell-like properties. Assessing whether the combination restores tumor responsiveness would help determine whether these pharmacodynamic changes translate into resensitization.

4. Conclusions

Evidence from established drug-resistant cancer models indicates that EGCG can resensitize resistant cells by modulating interconnected processes, including drug efflux, pro-survival signaling, apoptotic dysfunction, epigenetic regulation, DNA damage responses, and cancer stem cell-like and invasive phenotypes. This multi-targeted activity may explain its chemosensitizing effects across different cancer types and therapeutic agents. However, the contribution of individual mechanisms varies among models, and some molecular changes remain associative rather than direct determinants of resistance reversal.

EGCG derivatives and delivery systems may overcome the limited stability, bioavailability, and tumor exposure of native EGCG. By improving cellular uptake and delivery to tumor tissues [38,40], these approaches may enhance the modulation of resistance-associated pathways and provide a stronger pharmacological basis for EGCG-mediated chemosensitization. Further validation in clinically relevant resistant models, together with assessment of systemic and intratumoral exposure, will help determine the extent to which these advances can improve therapeutic responses.

The principal translational challenge is to determine whether EGCG can achieve sufficient exposure to reverse defined resistance mechanisms while maintaining an acceptable safety profile and compatibility with concurrently administered anticancer drugs. Future studies should combine optimized formulations with therapies to which resistance has developed and incorporate pharmacokinetic, pharmacodynamic, and resistance-associated biomarkers. Ultimately, trials in molecularly characterized drug-resistant cancers are needed to establish whether the multi-targeted activity of EGCG can produce a clinically meaningful restoration of therapeutic sensitivity.

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Abbreviations

The following abbreviations are used in this manuscript:

5-FU	5-fluorouracil
BCRP	breast cancer resistance protein
CGE	chitosan–gelatin–epigallocatechin-3-gallate
CSC	cancer stem cell
DNMT	DNA methyltransferase
DOX	doxorubicin
EAuSSi	EGCG-loaded mesoporous silica–gold nanoclusters
ECM	extracellular matrix
EGCG	epigallocatechin-3-gallate
EGFR	epidermal growth factor receptor
EMT	epithelial–mesenchymal transition
ERK	extracellular signal-regulated kinase
FA	folic acid
HDAC	histone deacetylase
HIF-1α	hypoxia-inducible factor 1 alpha
MAPK	mitogen-activated protein kinase
MDR	multidrug resistance
mTOR	mechanistic target of rapamycin
P-gp	P-glycoprotein
PEI	polyethyleneimine
RTK	receptor tyrosine kinase
siRNA	small interfering RNA
TUNEL	terminal deoxynucleotidyl transferase dUTP nick-end labeling
VEGF	vascular endothelial growth factor
ZEAuSS	ZD6474- and EGCG-loaded mesoporous silica–gold nanoclusters

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