Epigenetic Targets of Polyphenolic Nanoparticles in Cancer: Current Insights

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ABSTRACT

Epigenetic dysregulation such as aberrant DNA methylation, histone modifications, and non-coding RNA imbalance is now recognized as a central driver of tumour initiation, progression, and therapeutic resistance. Polyphenols, a diverse class of plant-derived metabolites, have demonstrated significant epigenetic remodelling activity; however, their therapeutic potential is hampered by poor solubility, rapid metabolism, and limited bioavailability. Nanoparticle-based delivery systems have emerged as a promising strategy to overcome these barriers, enabling targeted accumulation of polyphenols within tumour tissues and enhancing their mechanistic impact on epigenetic pathways. This review synthesizes recent advances in polyphenol-loaded nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles highlighting their ability to modulate DNMTs, HDACs, HATs, PRC2 components, and tumour-associated microRNAs and lncRNAs. We also compare *in vitro* and *in vivo* findings, discuss pharmacokinetic improvements, and identify key challenges including nanoparticle stability, immune interactions, protein corona formation, and off-target epigenetic effects. Overall, nano-enabled polyphenolic platforms represent a promising frontier for selective epigenetic cancer therapy, yet require rigorous evaluation and translational validation to move toward clinical application.

Keywords: Polyphenolic nanoparticles, Epigenetic modulation, DNA methylation inhibition, Histone deacetylase inhibition, Microrna regulation

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Introduction

One of the main causes of death globally, cancer poses a serious threat to public health. Traditional therapeutic modalities, such chemotherapy, radiation, and surgery, frequently have serious drawbacks, such as non-specific targeting of tumour areas, systemic toxicity, and drug resistance.[1] These problems impair patient outcomes and diminish therapeutic efficacy, underscoring the pressing need for novel and more potent cancer treatments. Natural substances, especially polyphenols, have garnered a lot of interest in this context as possible anticancer drugs. Widely found in fruits, vegetables, and medicinal plants, polyphenols have a variety of biological properties, such as anticancer, anti-inflammatory, and antioxidant actions.[2] Modification of cell proliferation, apoptosis induction, metastasis suppression, and control of key signalling pathways implicated in the advancement of cancer are some of their strategies. Even while polyphenols have therapeutic promise, their quick metabolism, systemic clearance, limited bioavailability, and poor solubility frequently prevent their clinical use.[3] Delivery techniques based on nanoparticles have been created to get around these obstacles. These nanocarriers maximize therapeutic efficacy while reducing off-target toxicity by increasing stability, improving bioavailability, and enabling targeted delivery to tumour tissues. It is known that epigenetic changes, such as DNA methylation, histone modification, and microRNA regulation, are important factors in the development and spread of cancer.[4] According to reports, polyphenols alter these epigenetic processes, providing a potential method for targeted cancer treatment. Researchers can accomplish targeted epigenetic modification by combining polyphenolic chemicals with delivery via nanoparticles, creating new opportunities for safer and more effective cancer therapies. With an emphasis on molecular insights, preclinical investigations, obstacles, and future research directions, this review attempts to present a thorough summary of the state of the art in the field of polyphenolic nanoparticles for epigenetic modification in cancer treatment.[5]

Importance of Cancer Therapy Challenges

Cancer continues to be a major cause of death globally, and traditional treatments are frequently constrained by problems including non-specific targeting, systemic toxicity, and drug resistance. To overcome these obstacles and enhance treatment results, new therapeutic approaches must be developed.[6]

Role of Polyphenols in Cancer Prevention and Therapy

Plant-based polyphenols are naturally occurring substances that have drawn interest due to possible anticancer effects. They have anti-inflammatory, anticancer, and antioxidant properties, among other biological actions. Polyphenols have the ability to alter a number of biological pathways, impacting processes including metastasis, apoptosis, and cell cycle progression.[7]

Advantages of Nano formulations for Targeted Delivery

Potential ways to improve polyphenol delivery and effectiveness in cancer treatment are provided by nanotechnology. The solubility, stability, and bioavailability of polyphenols can be enhanced via nanoparticle-based delivery methods, allowing for tailored distribution to tumour locations. This method improves treatment results while reducing systemic adverse effects.[8]

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Guarantor: Muskan Tomar

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Rationale for Epigenetic Modulation

The genesis and spread of cancer are significantly influenced by epigenetic changes, such as DNA methylation, histone modification, and non-coding RNA expression. A promising approach to cancer treatment is to target these epigenetic changes. It has been demonstrated that polyphenols affect epigenetic pathways, which may reverse abnormal gene expression linked to cancer.[9] Polyphenols modulate key epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA regulation, thereby influencing cancer initiation and progression (Figure 1).

Schematic representation of polyphenolic nanoparticles targeting epigenetic pathways in cancer. Polyphenols such as curcumin, EGCG, and resveratrol are delivered via nanocarriers to tumour cells, where they modulate DNA methylation, histone modification, and microRNA expression, ultimately inducing apoptosis, inhibiting proliferation, and suppressing tumour progression.

Review Methodology

This review adopts a transparent narrative/scoping review framework, designed to comprehensively capture and synthesize recent advances in polyphenolic nanoparticles for epigenetic regulation in cancer. Although not a systematic review, all steps were performed with methodological rigor to increase reliability, reduce bias, and ensure reproducibility of the evidence base. This review follows a narrative/scoping review approach, and reporting has been aligned with relevant PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines to enhance transparency and reproducibility. A detailed evidence summary of all included studies, including experimental models, epigenetic endpoints, assays, and quality assessment, is provided in Supplementary Table S1.

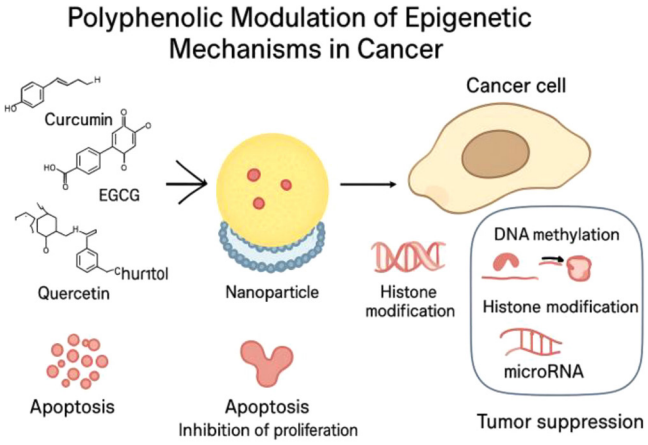

Fig 1 | Polyphenols modulating epigenetic pathways in cancer

Databases Searched

A structured literature search was carried out in the following databases:

- PubMed/MEDLINE
- Scopus
- Web of Science Core Collection
- ScienceDirect
- Google Scholar (manual screening for grey literature)

These databases were selected due to their broad coverage of biomedical, pharmaceutical, molecular biology, and nanotechnology research.

Search Strategy and Keywords

Search terms were designed using combinations of controlled vocabulary (MeSH terms) and free-text terms.

Primary Search Strings Used

"polyphenols" AND "nanoparticles" AND "cancer"

- "Polyphenolic nano formulation" AND "epigenetic modulation"
- "DNA methylation" OR "histone modification" AND "polyphenols"
- "Targeted delivery" AND "nanocarriers" AND "cancer therapy"
- "microRNA regulation" AND "polyphenolic nanoparticles"
- "EGCG/curcumin/resveratrol" AND "nanoparticles" AND "epigenetics."[10]

Filters Applied

- **Time range:** January 2010–December 2025
- **Language:** English
- **Document type:** Research articles, review papers, preclinical studies, *in vitro* and *in vivo* studies, and book chapters relevant to cancer nanotechnology.

The final literature search was completed on 15 December 2025.

Inclusion Criteria

Studies were included if they met the following criteria:

1. Discussed polyphenolic compounds (e.g., EGCG, curcumin, quercetin, resveratrol, gallic acid).
2. Described nanoparticle-based formulations (liposomes, polymeric NPs, SLNs, dendrimers, gold NPs, etc.).
3. Reported anticancer activity in cell lines or animal models.
4. Included epigenetic endpoints, such as:
   - DNA methylation
   - Histone acetylation/deacetylation
   - Chromatin remodelling
   - MicroRNA modulation

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5. Provided data on bioavailability, pharmacokinetics, or targeted delivery improvements.[11]

Exclusion Criteria

Studies were excluded if they:

- Did not involve polyphenols or nanoparticle delivery.
- Focused on diseases other than cancer.
- Lacked epigenetic or mechanistic data.
- Were conference abstracts without sufficient methodology/data.
- Were non-scientific sources (blogs, newspapers, promotional content).

Screening Process

A three-stage screening procedure was followed:

Step 1: Title Screening

- Irrelevant or duplicate titles were removed.

Step 2: Abstract Screening

- Abstracts were reviewed for relevance to polyphenols, nanocarriers, and cancer epigenetics.

Step 3: Full-Text Screening

- Eligible full articles were assessed for study design, type of polyphenol, nanocarrier used, epigenetic endpoints, and quality of evidence.

After screening, the final set of studies was included for qualitative synthesis.

Study selection and data extraction were performed independently by the author in two sequential rounds to minimize selection bias. In the first round, titles and abstracts were screened for relevance. In the second round, full texts were assessed against predefined inclusion and exclusion criteria. Any uncertainties were resolved by re-evaluation of the original articles and consensus-based judgement. The study selection process followed a structured screening strategy, summarized using a PRISMA-style flow diagram (Figure 2). Study selection and data extraction were performed by a single author using a two-stage screening process (title/abstract screening followed by full-text assessment). A total of 612 records were identified through database searching. After removal of 148 duplicates, 464 records were screened by title and abstract. Of these, 389 records were excluded. Seventy-five full-text articles were assessed for eligibility, and 42 studies were excluded. Finally, 33 studies were included in the qualitative synthesis.

Quality Appraisal

Although this is a narrative review, the scientific robustness of each included study was checked using criteria adapted from GRADE and ARRIVE guidelines:

- Clarity of nanoparticle synthesis method
- Physicochemical characterization reported (size, PDI, zeta potential, loading efficiency)
- Proper experimental controls included
- Validity of epigenetic assays (DNMT/HDAC activity, qRT-PCR for miRNA, bisulfite sequencing, chromatin assays)
- *In vivo* ethical compliance (for animal studies)
- Statistical analysis and reproducibility
- Evidence strength (*in vitro* vs. *in vivo vs*. clinical)
- Only studies with acceptable methodological rigor were included.[12]

Scope and Balance

To maintain scientific rigor and clarity, this review ensures appropriate scope and balanced interpretation of evidence:

1. **Inclusion of Less-Studied Polyphenols** – Compounds such as gallic acid, lignans, or rare stilbenes are discussed only when supported by strong mechanistic, molecular, or epigenetic data. No speculative claims or unsupported biological effects are included.
2. **Avoidance of Overgeneralization** – Anti-cancer or epigenetic effects are described within the context of specific studies, models, or formulations. Statements are restricted to documented outcomes rather than broad assumptions about polyphenols as a class.
3. **Clear Distinction Between Nanoparticle-Mediated and Free-Compound Effects** – Mechanistic outcomes such as DNMT/HDAC inhibition, promoter demethylation, miRNA modulation, or chromatin remodeling explicitly identify whether the effect was observed:
   - Only in free polyphenol form,
   - Only after nanoparticle delivery, or
   - Enhanced due to nano-encapsulation.
4. **Model-Specific Interpretation** – Epigenetic changes reported in in vitro assays, rodent models, or co-delivery systems are interpreted within the limitations of those systems, avoiding extensions to clinical settings unless supported by translational evidence.

A total of 612 records were identified, 148 duplicates were removed, 464 records were screened, 75 full-text articles were assessed for eligibility, and 33 studies were included in the final qualitative synthesis.

Reasons for Full-Text Exclusion

At the full-text screening stage, studies were excluded for the following reasons:

1. Absence of nanoparticle-based delivery systems,
2. Lack of epigenetic endpoints (DNA methylation, histone modification, or non-coding RNA analysis),
3. Studies focused on non-cancer disease models,
4. Insufficient methodological detail or absence of experimental validation, and
5. Conference abstracts or reports without accessible full texts.

Risk of Bias Assessment

Risk of bias was assessed qualitatively based on study design and reporting standards. For *in vivo* animal studies, key domains adapted from the SYRCLE risk-of-bias

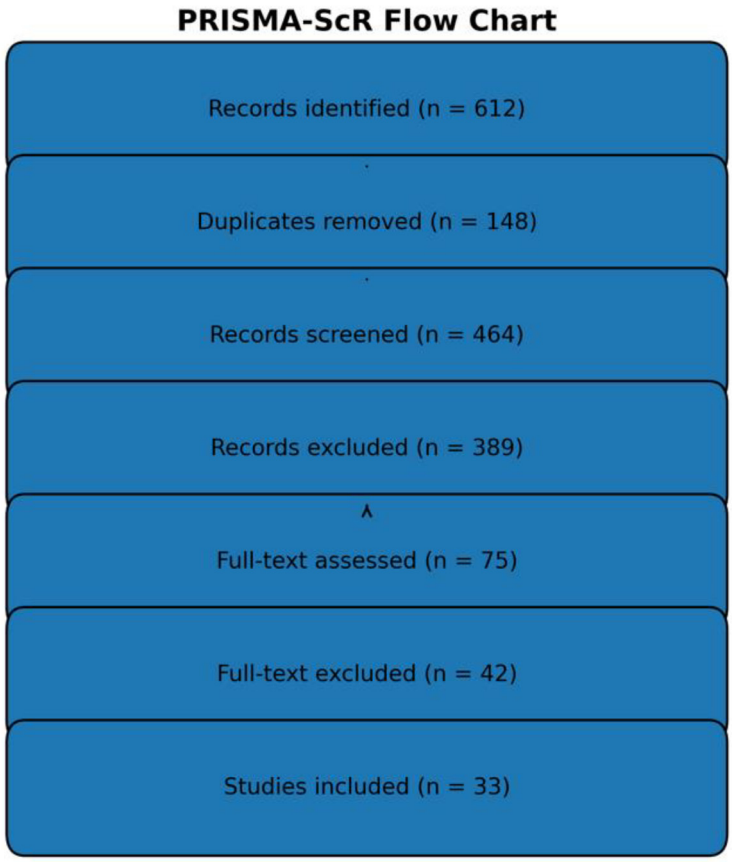

Fig 2 | PRISMA-style flow diagram illustrating study identification, screening, eligibility assessment, and inclusion

tool were considered, including randomization, blinding, outcome assessment, and completeness of data reporting. Most studies adequately described dosing and outcome measures, although randomization and blinding were inconsistently reported.

For in vitro studies, core quality criteria were evaluated, including use of appropriate controls, dose justification, reproducibility of assays, and clarity of epigenetic endpoints. While most studies demonstrated mechanistic validity, variability in exposure concentrations and limited replication were common limitations. Overall, the risk of bias was judged to be low to moderate across included studies.[13]

Structured Risk-of-Bias Summary

Risk of bias was assessed qualitatively based on study design and reporting standards. For in vivo animal studies, key domains adapted from the SYRCLE risk-of-bias tool were considered, including randomization, blinding, outcome assessment, and completeness of data reporting. For *in vitro* studies, quality criteria included use of appropriate controls, dose justification, reproducibility of assays, and clarity of epigenetic endpoints. Overall, the risk of bias across included studies was judged to be low to moderate. Risk-of-bias assessment was conducted using criteria adapted from the SYRCLE risk-of-bias tool for animal studies and general quality assessment principles for in vitro experiments Table 1.

Table 1 | Structured risk-of-bias assessment

Domain	Assessment
Selection bias	Low–moderate
Performance bias	Moderate
Detection bias	Low
Reporting bias	Low
Overall risk	Low–moderate

Polyphenols in Cancer Therapy

The anticancer potential of polyphenols, which are bioactive plant metabolites that include flavonoids, phenolic acids, stilbenes, and lignans, has been extensively researched. They impede the growth of cancer cells and induce apoptosis and cell cycle arrest, among other effects. Crucially, via altering DNA methylation, histone acetylation, and microRNA expression, polyphenols also control epigenetic processes, which reactivates tumour suppressor genes and inhibits carcinogenic pathways. The need for sophisticated delivery systems like nanoparticles to increase their effectiveness in cancer therapy is highlighted by the fact that, despite these encouraging effects, their therapeutic application is restricted because of their poor solubility, low bioavailability, rapid metabolism, and instability under physiological conditions.[14]

Classification & Sources of Polyphenols

Flavonoids, phenolic acids, stilbenes, and lignans are the main categories for the broad family of secondary metabolites found in plants known as polyphenols. Fruits, vegetables, drinks, nuts, seeds, and medicinal plants all contain these substances. Through a variety of routes, they have demonstrated encouraging anticancer actions. Onions, apples, and citrus fruits have quercetin, a flavonoid; grapes and red wine include resveratrol, a stilbene; turmeric has curcumin; various fruits and coffee contain gallic acid, a phenolic acid; and flaxseeds contain secoisolariciresinol, a lignan.[15] Major dietary polyphenols, their natural sources, and reported anticancer activities are summarized in Table 2.

Mechanisms of Anti-Cancer Action of Polyphenols

Palette of mechanisms by which polyphenols act against cancer Induction of apoptosis: Polyphenols influence mitochondrial pathways, activate caspases, and modify Bcl-2 family proteins in a way that promotes apoptosis. For instance, “DNMT1 and DNMT3a” expression is nearly eliminated by Qu therapy. Class I HDACs were likewise downregulated by therapy. Qu caused the pro-apoptotic genes DAPK1 and BCL2L11 to become demethylated. buildup of histones 3 and 4 that are acetylated, which raises APAF1 and BAX. Cell cycle arrest: Polyphenols modulate cyclins/CDKs, induce arrest at G1/S or G2/M phases. “Combinatorial resveratrol and pterostilbene induced apoptosis and cell cycle arrest in HCC1806 and MDA-MB-157 breast cancer cells,” according to the BMC Cancer research. Anti-proliferative effects & signalling pathway suppression: Inhibition of PI3K/AKT/mTOR, MAPK/ERK,

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Table 2 | Major polyphenols, their sources, and anticancer activities

S.no.	Polyphenols	Class	Natural Sources	Reported Anticancer Activities
1.	Quercetin	Flavonoid	Onions, apples, citrus fruits	Induces apoptosis; DNA methylation inhibition; HDAC inhibition[16]
2.	EGCG	Flavonoid	Green Tea	Anti-proliferative; modulates epigenetic enzymes[17]
3.	Resveratrol	Stilbene	Grapes, red wine	Regulates DNA methylation; histone acetylation; miRNA modulation
4.	Curcumin	Polyphenolic diarylheptanoid	Turmeric	Inhibits cell proliferation; reverses DNA methylation; modulates histone acetylation[18]
5.	Caffeic acid[19]	Phenolic acid	Coffee, fruits & vegetables	Induces apoptosis; antioxidant activity
6.	Secoisolariciresinol	Lignan	Flaxseeds	Estrogen receptor modulation; apoptosis induction

NF-κB etc. Particularly in cancer cells, quercetin inhibits PI3K/Akt/mTOR and MAPK/ERK signaling, which increases apoptosis and decreases proliferation. Epigenetic regulation: DNA methylation: Resveratrol and quercetin demethylate promoter regions of tumour suppressor or pro-apoptotic genes and inhibit DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B). Histone alterations include the inhibition of histone deacetylases (HDACs) by polyphenols and enhanced acetylation of histones H3 and H4. MicroRNA modulation: Modifying the expression of miRNAs implicated in metastasis, apoptosis, and proliferation; nevertheless, research on particular nanoparticle-delivered miRNA modulation is still ongoing in many circumstances.[20,21]

Challenges with Conventional Polyphenol Therapy

Low water stability and poor solubility in water (polyphenols breakdown). Rapid blood clearance and first-pass metabolism result in low bioavailability. quick excretion and metabolism (glucuronidation, sulfation). Oxidation and instability when pH changes Combinatorial resveratrol/pterostilbene therapies, for example, have epigenetic effects in cell culture; nevertheless, the authors point out that the dosages utilized frequently "far exceed physiologically achievable doses." Similarly, problems with quercetin's absorption *in vivo* hinder its promise epigenetic regulation *in vitro*.[22,23] Moreover, many in-vitro studies report epigenetic modulation at micromolar concentrations (typically 10–100 μM), which are substantially higher than plasma levels achievable in humans through oral or parenteral administration. These supra-physiological doses should be interpreted as proof-of-concept evidence rather than direct predictors of clinical efficacy.[24,25]

Nanoparticle-Based Delivery of Polyphenols

The pharmacokinetics and bioavailability of polyphenols, which are otherwise hampered by limited absorption, fast metabolism, and poor stability, are greatly enhanced by nanoparticle delivery methods. In a rat model, for example, EGCG loaded in solid lipid nanoparticles (SLN-EGCG) demonstrated sustained release, no acute or sub chronic toxicity, and much better bioavailability and protection against degradation when compared to free EGCG. Another study found that EGCG encapsulated in albumin nanoparticles had a longer half-life (15.6 h) and a plasma concentration that was about 1.5 times higher than that of free EGCG. Additionally, EGCG transport across intestinal epithelium was increased by folic acid (FA)-functionalized nanostructured lipid carriers, as seen by a 1.8-fold increase in apparent permeability (P_{app}), which suggests improved oral absorption. These nanoparticle platforms allow for improved cellular absorption and regulated release, which strengthens circulation time and tumour accumulation.[26,27]

Types of Nanocarriers

Nanotechnology-based carriers have emerged as effective systems to enhance solubility, stability, and delivery of polyphenols. Both hydrophilic and hydrophobic medications can be encapsulated in liposomes, which are phospholipid vesicles. When compared to free curcumin, curcumin-loaded liposomes demonstrated a considerable improvement in solubility, stability, and anticancer effectiveness. Nanoparticles of polymers (PLGA, chitosan): Provide regulated release and shield bioactive from metabolization. Quercetin-containing PLGA nanoparticles demonstrated significant cytotoxicity against breast cancer cells and improved bioavailability. Branched macromolecules having adjustable surface groups for targeted distribution are called dendrimers. PAMAM dendrimers coupled with resveratrol enhanced intracellular transport and solubility in breast cancer models.

Solid Lipid Nanoparticles (SLNs): Provide high drug stability and prolonged circulation. SLNs loaded with quercetin showed greater cytotoxicity in cancer cells and improved stability and sustained release.[28] The major types of nanocarriers used for polyphenol delivery, along with their key advantages and representative examples, are summarized in Table 3.

Targeted Delivery Strategies

Polyphenols can be delivered to specific locations by nanoparticles using both passive and active methods. The Enhanced Permeability and Retention (EPR) effect brought on by leaky vasculature and compromised lymphatic outflow causes nanoparticles to concentrate in tumour tissues during passive targeting. "The EPR effect, which permits nanoparticles to accumulate in tumour tissues due to leaky vasculature, is leveraged by passive targeting," according to the paper. Active targeting techniques are essential because tumour heterogeneity restricts passive absorption. Active targeting involves functionalizing nanoparticles with ligands

Table 3 | Nanocarrier types, advantages, and polyphenol examples[29–32]

S. No.	Nanocarrier Type	Advantages	Examples of Polyphenols Loading
1.	Liposomes	Improved solubility, stability, controlled release	Curcumin, Resveratrol
2.	Polymeric NPs	Controlled release, protection from metabolism	Quercetin, EGCG
3.	Dendrimers	High surface functionality, targeted delivery	Resveratrol, Gallic acid
4.	Solid Lipid NPs	High stability, sustained release	Quercetin, Curcumin

that bind selectively to tumour cell overexpressed receptors, such as FA, antibodies, or peptides.[33] In folate receptor-positive cancer cells, for instance, folate-conjugated nanoparticles showed "significantly enhanced selective cellular uptake and cytotoxic effects." Nanoparticle-based delivery systems employ both passive and active targeting mechanisms to enhance tumour-specific accumulation of polyphenols (Figure 3).

Pharmacokinetics & Bioavailability Enhancement

General Pharmacokinetic Improvement Trends

Nanoparticle encapsulation consistently improves the pharmacokinetic behavior of polyphenols by enhancing chemical stability, intestinal absorption, systemic exposure, and circulation time. Across preclinical studies, nano-enabled polyphenols show reproducible increases in bioavailability relative to free compounds, although the magnitude varies with carrier composition, surface modification, and route of administration.

Typical improvement ranges reported in rodent models include:

- **Albumin/protein nanoparticles:** ~1.3–2.5-fold increase in AUC
- **Solid lipid nanoparticles (SLN)/nanostructured lipid carriers (NLC):** ~1.5–5-fold increase in AUC
- **Polymeric nanoparticles (e.g., PLGA, chitosan):** ~1.5–4-fold enhancement in systemic exposure
- **Liposomes:** ~1.5–3-fold increase in apparent bioavailability
- **Targeted nanocarriers:** ~1.5-fold to >10-fold higher tumour accumulation compared with free polyphenols

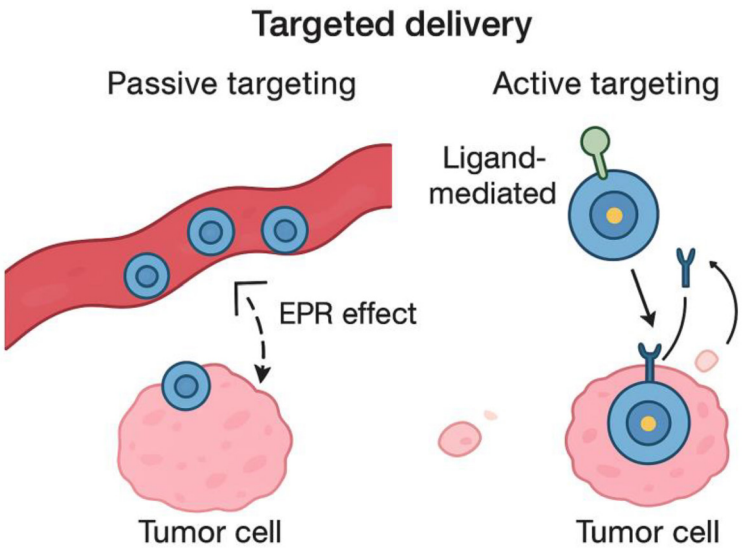

Fig 3 | Targeted delivery strategies
(Targeted delivery strategies for polyphenolic nanoparticles in cancer therapy. This schematic illustrates passive targeting via the EPR effect and active targeting through ligand-functionalized nanocarriers (e.g., folate or peptide conjugation). These strategies enhance tumour accumulation, cellular uptake, and therapeutic efficacy of nano-encapsulated polyphenols.)

These values represent generalized ranges derived from multiple preclinical studies and should not be interpreted as formulation-independent constants.

Study-Specific Pharmacokinetic Examples

Where quantitative pharmacokinetic parameters are available, they are reported with explicit specification of species, dose, route of administration, formulation, and units. In one representative study, albumin-encapsulated epigallocatechin-3-gallate (EGCG) administered orally to rats at a dose of 50–100 mg/kg resulted in an approximately 1.4–1.6-fold increase in plasma Cmax (μg/mL) and $AUC_{0-\infty}$ (μg·h/mL) compared with free EGCG. This formulation also prolonged the terminal half-life ($T_{1/2}$ ≈ 14–16 h), indicating reduced clearance and sustained systemic exposure. Similarly, EGCG-loaded solid lipid nanoparticles (SLN-EGCG) administered orally in rats demonstrated a 1.5–5-fold increase in $AUC_{0-\infty}$ (μg·h/mL) relative to free EGCG, depending on lipid composition and administered dose. These systems additionally provided protection against gastrointestinal degradation and enabled sustained release.

Polymeric nanoparticle systems, such as PLGA-based formulations, typically yield ~1.5–4-fold increases in systemic exposure (AUC) in rodent models following oral or intravenous administration, while liposomal polyphenol formulations generally produce ~1.5–3-fold improvements in bioavailability.

Tumour accumulation data are primarily derived from rodent xenograft models following intravenous or oral administration and demonstrate increased intratumoral exposure compared with free polyphenols; however, these findings remain species- and model-dependent.

Dose Exposure Relationships and Translational Considerations

Dose–exposure relationships for nano-polyphenols are generally linear at low to moderate doses but may become nonlinear at higher doses due to saturation of metabolic enzymes or transport pathways. Importantly, rodents often exhibit higher systemic exposure per mg/kg dose than humans, limiting direct interspecies extrapolation.

For epigenetic modulation, the therapeutic window appears narrower than that required for overt cytotoxicity. Preclinical evidence suggests that partial inhibition of DNMTs or HDACs sufficient to restore tumour-suppressor gene expression can occur at lower exposure levels, whereas excessive systemic exposure may increase the risk of off-target epigenetic alterations in normal tissues.[34]

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Therefore, translation of nano-polyphenolic formulations to human use will require careful dose optimization, allometric scaling, and physiologically based pharmacokinetic (PBPK) modeling, followed by early-phase clinical studies incorporating formulation-specific pharmacokinetic and pharmacodynamic endpoints.

All quantitative pharmacokinetic claims in this section are reported with explicit specification of species, route of administration, dose, formulation, and units to minimize overgeneralization and improve translational interpretability. The comparative differences between free polyphenols and nano-enabled polyphenols are summarized in Box 1 (adapted from Refs. 8, 11, and 22).

Polyphenolic Nanoparticles for Epigenetic Modulation

Nanoparticle-delivered polyphenols have demonstrated significant potential in modifying epigenetic markers in cancer models. For instance, when EGCG-capped gold nanoparticles (EGCG-AuNPs) were applied to hepatocellular carcinoma cells, the expression of caspase-3 increased, oncogenic c-Myc was downregulated, and tumour suppressor microRNAs let-7a and miR-34a were significantly upregulated. This indicated increased apoptotic activity in comparison to free EGCG. Another study demonstrated that curcumin treatment in lung cancer cells (A549) reversed hypermethylation in regulatory regions of tumour suppressor genes (such as MEG3) and increased the expression of miR-26a while decreasing the expression of DNA methyltransferase enzymes DNMT3B. This finding established a connection between miRNA regulation and changes in DNA methylation.[35] Furthermore, curcumin was shown to downregulate DNMT3b mRNA levels and demethylate the RARβ promoter in A549 and H460 lung cancer cells, restoring RARβ gene expression. Together, these findings imply that polyphenols delivered via nanoparticles may enable more effective epigenetic modification, resulting in cell cycle arrest, death, and tumour growth reduction. A comparative summary of representative polyphenolic nano formulations, their cancer models, epigenetic targets, dosing context, and level of evidence is presented in Table 4.

Direct epigenetic targeting was considered supported only when orthogonal validation methods (e.g., DNMT/HDAC activity assays, bisulfite sequencing, or ChIP-based analyses) were reported.

Short critical synthesis – what this mapping shows (key takeaways)

1. Consistent pattern: For all four polyphenols, nano-encapsulation improves cellular uptake, systemic exposure, and potency, and in several reported cases enhances epigenetic modifications (↓DNMT/HDAC, promoter demethylation, changes in histone marks, miRNA modulation) compared to free compound.
2. Evidence type & weight: Most strong, mechanistic epigenetic evidence comes from *in vitro* studies (cell lines) and selected *in vivo* rodent/xenograft studies that report both tumour response and limited epigenetic readouts. Clinical evidence of epigenetic modulation by nano-polyphenols in humans is presently absent or very limited.
3. Heterogeneity & dose issues: Reported treatment concentrations vary widely (low-μM to tens of μM *in vitro*; mg/kg *in vivo*). Many *in vitro* concentrations exceed physiologically achievable plasma concentrations, raising translational uncertainties. Careful PK/PD bridging studies are needed.
4. Mechanistic ambiguity: Polyphenols are pleiotropic — observed epigenetic effects may reflect direct enzyme inhibition (DNMT/HDAC), indirect changes through redox/stress pathways, or downstream responses to other signaling changes. Distinguishing direct epigenetic targeting from secondary effects requires orthogonal assays (e.g., bisulfite sequencing, ChIP-seq, DNMT enzyme assays), which are not uniformly performed.
5. Conflicting contexts (example — resveratrol): Resveratrol's SIRT1 modulation shows context-dependent results: in some settings SIRT1 activation promotes

Box 1 | Free polyphenols versus nano-enabled polyphenols: mechanistic and translational differences

Aspect	Free Polyphenols	Nano-Enabled Polyphenols
Stability	Poor chemical stability; rapid degradation	Improved stability and protection from degradation
Solubility	Low aqueous solubility	Enhanced apparent solubility
Bioavailability	Low due to rapid metabolism and clearance	Increased systemic exposure and prolonged circulation
Cellular uptake	Limited Passive Diffusion	Enhanced uptake via endocytosis
Tumour accumulation	Minimal and non-specific	Increased accumulation via EPR effect and active targeting.
Epigenetic impact	Requires high (often supra-physiological) concentrations	Comparable epigenetic modulation at lower effective exposure
Translational potential	Limited clinical applicability	Improved translational feasibility

Table 4 | Polyphenolic nano formulations and epigenetic effects in cancer[36,37]

Polyphenol	Nanocarrier Type	Functionalization	Cancer Model	Epigenetic Targets	Dose/Route	Evidence	Key-Outcomes
Curcumin	PLGA NPs, liposomes	PEG, folate	Lung, glioblastoma	↓DNMTs, ↓HDACs, ↑H3/H4 acetylation	μM (*in vitro*); mg/kg oral	*In vitro* + *in vivo*	Gene reactivation, apoptosis
EGCG	SLNs, albumin NPs, AuNPs	Protein capping, FA	Liver, breast	↓DNMT1, ↑miR-34a	μM; oral/IV	*In vitro* + *in vivo*	Improved PK, apoptosis
Quercetin	PLGA NPs, liposomes	PEG-ylation	Breast, colorectal	↓DNMTs, ↓HDACs	10–100 μM; oral	*In vitro*	Cytotoxicity ↑
Resveratrol	Polymeric NPs, dendrimers	PEG	Breast, colon	DNMT inhibition, SIRT1	μM; oral	*In vitro* (+ limited *in vivo*)	Anti-proliferative

tumour cell survival, in others it enhances apoptosis. Thus, epigenetic directionality (activation vs repression) can be tumour-type dependent.

6. **Translational gaps and safety:** Important translational gaps remain — protein corona effects, immune sequestration (MPS), long-term epigenetic off-targeting, large-scale GMP manufacturing, and chronic toxicity — all of which need addressing before clinical trials with epigenetic endpoints proceed.

Mechanistic Interpretation

Direct Versus Indirect Epigenetic Effects: Direct epigenetic targeting refers to mechanisms in which polyphenols or polyphenolic nanoparticles directly inhibit or modulate epigenetic enzymes, such as DNA methyltransferases (DNMTs) or HDACs. Evidence for direct targeting requires orthogonal validation, including DNMT or HDAC enzymatic activity assays, locus-specific DNA methylation analysis (e.g., bisulfite sequencing), or chromatin immunoprecipitation–based approaches (ChIP or ChIP-seq) demonstrating changes in histone marks at defined gene promoters.

In contrast, indirect or downstream epigenetic effects arise secondary to broader cellular responses, such as oxidative stress modulation, inflammatory signaling, kinase pathway inhibition (e.g., PI3K/AKT or MAPK), mitochondrial stress, or apoptosis induction. In such cases, altered expression of DNMTs, HDACs, or non-coding RNAs may represent downstream consequences rather than direct enzymatic inhibition. Therefore, changes in epigenetic markers without orthogonal validation should be interpreted cautiously.

DNA Methylation & Histone Modification

In a variety of cancer models, polyphenolic nanoparticles have shown potent effects on histone modification and DNA methylation. For instance, curcumin nano formulations increase histone acetylation and reactivate repressed genes by downregulating DNMT3A and DNMT3B, reducing hypermethylation of tumour-suppressor promoters (such as p16INK4a and RARβ), and inhibiting HDAC activity. Curcumin nanoparticles were demonstrated to downregulate DNMT3A, SUZ12, and the long non-coding RNA HOTAIR, which is implicated in epigenetic silencing, in glioblastoma, suggesting that both chromatin regulators and DNA methylation are modulated. Likewise, EGCG delivered via nanoparticles or conjugated systems suppresses DNMT1 and upregulates histone acetylation marks, restoring expression of genes such as p16, p21, and TIMP-3 in cancer cell.[38] In several of these studies, epigenetic modulation was inferred from changes in DNMT/HDAC expression or global histone acetylation, without direct enzyme activity assays or locus-specific chromatin validation; thus, these effects likely reflect indirect downstream mechanisms. In several of these studies, epigenetic modulation was inferred primarily from changes in DNMT or HDAC expression levels or global histone acetylation, without direct enzyme activity assays or locus-specific chromatin validation; therefore, these effects are best interpreted as indirect or associative.

MicroRNA-Based Modulation Context-Dependent Roles

Polyphenolic nanoparticles modulate microRNA (miRNA) expression profiles involved in cancer progression, apoptosis, and stress responses. However, the biological roles and directionality of several miRNAs are highly context-dependent and vary according to cancer type, cellular microenvironment, and experimental conditions.

EGCG-based nanoformulations have been reported to modulate multiple miRNAs, including members of the let-7 family, miR-34a, miR-15, and miR-210. Notably, miR-210 is a hypoxia-responsive miRNA with context-dependent oncogenic or tumor-suppressive functions, depending on tumor oxygenation status and cancer type. Similarly, the miR-15/16 family is frequently downregulated in certain malignancies (e.g., chronic lymphocytic leukemia) but exhibits variable roles across solid tumors.

In hepatocellular carcinoma models, EGCG-capped gold nanoparticles (EGCG-AuNPs) downregulated oncogenic c-Myc and increased caspase-3 expression, accompanied by upregulation of let-7a and miR-34a, which are widely recognized tumor-suppressive miRNAs in this context. These findings suggest enhanced apoptotic signaling following nano-delivery.

Importantly, in several studies, miRNA modulation was inferred from expression profiling alone, without functional validation of direct epigenetic enzyme targeting. Therefore, observed miRNA changes are best interpreted as downstream consequences of altered cellular signaling and stress responses rather than direct modulation of epigenetic machinery.

Preclinical Evidence

Numerous *in vivo* and *in vitro* investigations confirm that polyphenolic NPs can modulate epigenetics. Curcumin-loaded liposomes restored gene expression in A549 lung cancer cells by reducing DNMT activity and reversing hypermethylation *in vitro*. In lung cancer, EGCG inhibited DNMT1/HDACs and restored gene expression; however, in most studies this conclusion was based on expression-level changes rather than direct DNMT/HDAC enzymatic activity measurements. In animal models, EGCG by nano-delivery decreased tumour development while reactivating methylation-silenced genes. Curcumin nanoparticles decreased tumour volume and altered DNMT3A/SUZ12/HOTAIR in glioblastoma models, supporting both anticancer and epigenetic effects *in vivo*.[40]

Translational Challenges

There are challenges in bringing polyphenolic NPs to the clinic, despite promising preclinical results. One major concern is the stability of nanoformulations in physiological settings; aggregation, early drug

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release, or deterioration in circulation might reduce their effectiveness. Manufacturing is difficult in terms of scalability and repeatability, especially for complicated ligand-modified or multifunctional NPs. Given the paucity of long-term toxicity and safety evidence for nanomedicines, regulatory approval is still up in the air. Unintentional changes in gene expression or off-target epigenetic modifications are equally dangerous. All of these difficulties highlight the necessity of thorough toxicity assessment, standardization, and optimization prior to clinical translation. For epigenetic modulation, the therapeutic window is particularly critical, as partial inhibition of DNMTs or HDACs may be sufficient to restore tumour-suppressor gene expression, whereas excessive systemic exposure could lead to off-target chromatin remodeling in normal tissues. Preclinical studies suggest that effective epigenetic modulation often occurs at exposure levels lower than those required for cytotoxicity; however, these thresholds remain poorly defined and highly formulation-dependent.[41] Pleiotropy and Mechanistic Attribution (Limitation). A key limitation in interpreting the epigenetic activity of polyphenolic nanoparticles is the inherently pleiotropic nature of polyphenols. Compounds such as curcumin, EGCG, quercetin, and resveratrol simultaneously modulate multiple cellular processes, including redox balance, inflammatory signaling, kinase cascades (e.g., PI3K/AKT, MAPK), mitochondrial stress, and apoptosis. Consequently, observed changes in DNA methylation, histone modifications, or non-coding RNA expression may arise indirectly as downstream consequences of altered cellular signaling or stress responses rather than from direct inhibition of epigenetic enzymes. Many studies infer epigenetic targeting based on changes in DNMT/HDAC expression or global histone acetylation without confirming direct enzyme engagement or locus-specific chromatin remodeling. To establish causality, future studies should incorporate orthogonal validation approaches, including DNMT and HDAC enzyme activity assays, locus-specific DNA methylation analysis by bisulfite sequencing, and chromatin immunoprecipitation followed by sequencing (ChIP-seq) to confirm direct effects on histone marks at defined gene promoters. Integration of these methods with transcriptomic and proteomic analyses will be essential to distinguish primary epigenetic mechanisms from secondary pleiotropic effects and to improve mechanistic rigor and translational relevance.

Strengthened Translational Challenges

Despite significant preclinical promise, the clinical translation of polyphenolic nanoparticles faces several mechanistic, manufacturing, and regulatory barriers. A major challenge is the heterogeneity of the EPR effect, which varies widely between tumour types and even among patients. Poorly vascularized or fibrotic tumours show minimal EPR, drastically reducing nanoparticle accumulation. Furthermore, once nanoparticles enter circulation, they rapidly adsorb serum proteins, forming a protein corona that alters surface charge, ligand orientation, biodistribution, and targeting efficiency. This corona can mask active ligands (e.g., folate, peptides) and redirect nanoparticles toward macrophages, reducing tumour specificity.[42] Immune interactions also pose barriers to translation. Nanoparticles are readily recognized by the mononuclear phagocyte system (MPS), leading to hepatic and splenic sequestration. Some nano formulations activate complement pathways or trigger cytokine release, raising concerns regarding immunotoxicity. From an epigenetic standpoint, polyphenolic nanoparticles carry the risk of off-target epigenetic modulation, such as DNMT/HDAC inhibition in healthy tissues, which may unintentionally alter methylation patterns, chromatin states, or microRNA networks, potentially affecting genomic stability over long-term use. At the manufacturing level, scalability and CMC (Chemistry, Manufacturing, and Controls) are major bottlenecks. Many polyphenol nano formulations (e.g., ligand-functionalized, stimuli-responsive, hybrid systems) show batch-to-batch variability in size, surface charge, loading efficiency, and release profile. Achieving GMP-compliant, reproducible large-scale production remains difficult. Regulatory pathways are also evolving; both FDA and EMA currently evaluate nanomedicines under expanded frameworks requiring extensive physicochemical characterization, biodistribution profiling, genotoxicity testing, and long-term toxicology data. Long-term safety remains another gap. Polyphenolic nanoparticles may accumulate in RES organs, induce oxidative stress, alter mitochondrial function, or lead to chronic inflammation with repeated dosing. Limited chronic toxicity studies exist for most formulations, especially those intended to modulate epigenetic pathways. Overall, addressing these translational challenges through improved nanoparticle design, corona-resistant coatings (PEG, zwitterions), immune-evasive strategies, scalable manufacturing, and robust regulatory evaluation will be essential for successful clinical application. Importantly, pharmacokinetic parameters derived from rodent models cannot be directly extrapolated to humans due to interspecies differences in absorption, metabolism, distribution, and clearance. Rodents often exhibit higher exposure per mg/kg dose compared with humans, and nanoparticle biodistribution patterns may differ substantially. Therefore, human dose prediction will require appropriate allometric scaling, physiologically based pharmacokinetic (PBPK) modeling, and early-phase clinical PK studies.[43,44] Overall, although polyphenolic nanoparticles consistently modulate epigenetic readouts in preclinical cancer models, only a subset of studies provides orthogonal validation sufficient to distinguish direct epigenetic enzyme targeting from indirect downstream effects. Future investigations should integrate enzyme activity assays and locus-specific chromatin analyses to establish mechanistic causality and improve translational robustness.

Clinical Translation and Ongoing Trials

Clinical evaluation of polyphenolic nanoformulations is still in its early stages. Although several nano-curcumin

and nano-EGCG formulations have advanced to Phase I or II trials for cancer and inflammatory conditions, none of these trials have yet incorporated epigenetic endpoints such as DNA methylation, histone marks, or microRNA modulation. Several nano-curcumin and nano-EGCG formulations have entered early-phase clinical evaluation for cancer and inflammatory conditions; however, these trials have primarily focused on safety, tolerability, and pharmacokinetics rather than mechanistic epigenetic outcomes. These trials have demonstrated safety and improved pharmacokinetics, but efficacy outcomes remain modest.[45] No clinically approved polyphenolic nanoparticle currently exists, and no active trial specifically evaluates the epigenetic effects of nano-polyphenols in human subjects. This highlights a major translational gap and an opportunity for future studies integrating mechanistic epigenetic readouts into early-phase clinical trial design. It is important to distinguish the intrinsic epigenetic activity of free polyphenols from the enhancements achieved through nano-encapsulation. While free compounds such as curcumin, EGCG, and resveratrol exhibit DNMT and HDAC inhibitory effects *in vitro*, nanoparticle-based delivery primarily improves their cellular uptake, stability, bioavailability, and tumour accumulation. Thus, nano formulations amplify the magnitude and consistency of epigenetic modulation rather than introducing entirely new molecular mechanisms. Representative examples include nano-curcumin formulations evaluated in Phase I/II clinical studies for pancreatic cancer (e.g., NCT01486421; oral curcumin nanoparticle formulation) and colorectal cancer, as well as EGCG-based formulations assessed in metabolic and inflammatory disorders. These studies reported acceptable safety profiles and modest improvements in systemic exposure; however, none incorporated epigenetic biomarkers such as DNA methylation, histone modifications, or microRNA profiling as clinical endpoints. To date, no published human clinical studies evaluating polyphenolic Nano formulations have reported direct epigenetic readouts, such as DNA methylation changes, histone modification profiling, or microRNA modulation.[46] The current clinical translation status of polyphenolic nanoformulations, including formulation type, indication, trial phase, route of administration, and key pharmacokinetic and safety outcomes, is summarized in Table 5.

Importantly, none of the listed clinical studies have evaluated epigenetic endpoints such as DNA methylation, histone modifications, or non-coding RNA regulation in human subjects. To date, epigenetic effects of polyphenolic nanoformulations remain supported exclusively by preclinical evidence.

Clinical Translation: Evidence from Human Studies

To date, the clinical evaluation of polyphenolic nanoformulations remains limited to early-phase studies primarily focused on safety, tolerability, and pharmacokinetics. Importantly, no published or registered clinical trial has yet incorporated epigenetic endpoints, such as DNA methylation profiling, histone modification analysis, or microRNA modulation, in human subjects.

Oral nano-curcumin formulations have advanced furthest clinically. A Phase I/II study in pancreatic cancer patients (NCT01486421) demonstrated acceptable safety and tolerability at high oral doses, along with modest improvements in systemic exposure compared with free curcumin. Similarly, a Phase II trial evaluating nano-curcumin as an adjuvant therapy in metastatic colorectal cancer (NCT02017353) reported a favorable safety profile but limited clinical efficacy. In both studies, epigenetic biomarkers were not assessed.

Encapsulated or nano-formulated EGCG has been evaluated in early Phase I clinical studies for metabolic and inflammatory conditions (NCT00951834), showing improved oral bioavailability and no serious adverse events. However, these trials focused exclusively on pharmacokinetics and safety, without investigation of DNMT/HDAC activity, histone marks, or non-coding RNA changes.

Early clinical exploration of nano-resveratrol formulations (NCT01370889) similarly demonstrated improved stability and acceptable tolerability, although substantial inter-individual pharmacokinetic variability was observed. Again, no epigenetic endpoints were included.

Collectively, these studies confirm that nano-encapsulation can enhance the pharmacokinetic profile and safety of polyphenols in humans; however, direct clinical evidence linking nano-polyphenol exposure to epigenetic reprogramming is currently absent. This represents a critical translational gap and highlights the need for future early-phase oncology trials

Table 5 | Clinical translation status of polyphenolic nano formulations in humans

Formulation	Indication/Population	Phase	Route	Key PK/Safety Outcomes	NCT ID
Nano-curcumin	Pancreatic cancer	I /II	Oral	Improved oral bioavailability compared with free curcumin; acceptable safety and tolerability at high doses; no dose-limiting toxicity or serious adverse events reported.	NCT01486421
Nano-curcumin	Metastatic colorectal cancer	II	Oral	Favorable safety profile with improved systemic exposure; no severe treatment-related adverse events; pharmacokinetic improvement relative to conventional curcumin formulations.	NCT02017353
Nano-EGCG	Metabolic/inflammatory disorders	I	Oral	Enhanced oral bioavailability and systemic exposure; good tolerability; no serious adverse events observed during treatment.	NCT00951834
Nano-resveratrol	Healthy volunteers/ cancer prevention	I	Oral	Improved formulation stability and systemic exposure; acceptable safety; high inter-individual pharmacokinetic variability reported; no major safety concerns.	NCT01370889

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to integrate epigenetic pharmacodynamic biomarkers alongside conventional PK and safety assessments.[47,48]

Future Perspectives and Research Gaps

Although polyphenolic nanoparticles show great promise for clinical translation, a number of research gaps need to be filled before their full therapeutic potential may be realized. Clinical Translation Potential: Although preclinical results are promising, issues with formulation stability, repeatability, and long-term safety still exist. For polyphenolic NPs to proceed to clinical trials, these problems must be resolved by standardizing production procedures and doing thorough toxicity profiling. Combination therapy with immunotherapy or chemotherapy: Polyphenolic nanoparticles can work in concert with current therapies to improve their effectiveness and get past drug resistance. Co-administration of immune checkpoint inhibitors or chemotherapeutics, for instance, may enhance apoptosis, sensitize tumour cells, and alter the tumour microenvironment, providing a multifaceted treatment approach. Personalized Medicine Approach: A one-size-fits-all strategy might not be the best option due to individual differences in tumour epigenetics and miRNA profiles. Precision epigenetic treatment may be made possible by customizing polyphenolic NP formulations according to patient-specific molecular signatures to optimize effectiveness and reduce off-target effects. In order to connect preclinical success with clinical application, it will be crucial to integrate translational research, multi-omics analysis, and improved nanoparticle engineering. Future clinical trials evaluating polyphenolic nanoformulations should integrate well-defined epigenetic endpoints, including DNA methylation profiling, histone modification analysis, and microRNA expression signatures, alongside conventional safety and efficacy outcomes. Incorporating such mechanistic biomarkers will be critical to establish causal links between nano-polyphenol exposure and epigenetic reprogramming in human cancers.[47]

Conclusion

Due to its capacity to alter epigenetic processes such as DNA methylation, histone changes, and microRNA control, polyphenolic nanoparticles provide a promising new avenue for cancer treatment. Preclinical research has shown that NP-based administration improves polyphenols' bioavailability, specificity, and therapeutic effectiveness, resulting in tumour suppressor gene reactivation, apoptosis induction, and suppression of proliferation and metastasis. Future research should concentrate on overcoming these limitations through advanced nanoparticle engineering, combinatorial therapies, and personalized medicine approaches tailored to patient-specific molecular profiles. Despite these encouraging results, a number of obstacles impede clinical translation, including nanoparticle stability, reproducibility, large-scale manufacturing, long-term safety, and potential off-target epigenetic effects. Overall, polyphenolic NPs offer a versatile and potent platform for epigenetic cancer therapy. With rigorous optimization, standardized protocols, and careful clinical evaluation, these nanomedicines could pave the way for precision-targeted epigenetic interventions in oncology. Despite encouraging preclinical findings, the current evidence supporting polyphenolic nanoparticles as epigenetic cancer therapeutics remains largely limited to *in-vitro* and animal studies. Therefore, these results should be interpreted cautiously and not directly extrapolated to clinical outcomes. Rigorous translational studies addressing pharmacokinetics, long-term safety, and off-target epigenetic effects are essential before clinical application.

List of Abbreviations

AUC: Area Under the Curve
AuNPs: Gold Nanoparticles
BAX: Bcl-2–Associated X Protein
BCL2L11: BCL2-liKe 11 (BIM)
Cmax: Maximum Plasma Concentration
CMC: Chemistry, Manufacturing, and Controls
ChIP-seq: Chromatin Immunoprecipitation Sequencing
DNMT: DNA Methyltransferase
DNMT1: DNA Methyltransferase 1
DNMT3A: DNA Methyltransferase 3 Alpha
DNMT3B: DNA Methyltransferase 3 Beta
EPR: Enhanced Permeability and Retention
EGCG: Epigallocatechin-3-Gallate
EMA: European Medicines Agency
FA: Folic Acid
FDA: Food and Drug Administration
GBM: Glioblastoma Multiforme
GMP: Good Manufacturing Practice
HAT: Histone Acetyltransferase
HDAC: Histone Deacetylase
HOTAIR: HOX Transcript Antisense Intergenic RNA
H3: Histone 3
H4: Histone 4
IP: Intraperitoneal
IV: Intravenous
lncRNA– Long Non-Coding RNA
MAPK: Mitogen-Activated Protein Kinase
miRNA: MicroRNA
MPS: Mononuclear Phagocyte System
mTOR: Mechanistic Target of Rapamycin
NLC: Nanostructured Lipid Carrier
NPs: Nanoparticles
PBPK: Physiologically Based Pharmacokinetic
PDI: Polydispersity Index
PEG: Polyethylene Glycol
PK: Pharmacokinetics
PLGA: Poly(lactic-co-glycolic acid)
PRC2: Polycomb Repressive Complex 2
RARβ: Retinoic Acid Receptor Beta
RES: Reticuloendothelial System
ROS: Reactive Oxygen Species
RT-PCR / qRT-PCR: Quantitative Real-Time Polymerase Chain Reaction
SLN: Solid Lipid Nanoparticle
SIRT1: Sirtuin 1
T½: Terminal Half-Life
TIMP: Tissue Inhibitor of Metalloproteinases

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Supplementary

Supplementary Table S1 | Summary of preclinical epigenetic evidence for polyphenolic nano formulations

Polyphenol	Nano Formulation	Model	Dose/Route	Epigenetic endpoint (assay)	Key Outcome	Quality
Curcumin	PLGA NPs	A549 cells	10–50 μM	DNMT3B; H3/H4 acetylation (qRT-PCR, HDAC assay)	DNMT downregulation; histone acetylation ↑	Moderate
Curcumin	Nano-curcumin	A549 xenograft (mouse)	50 mg/kg, oral	DNMTs (qRT-PCR)	Tumor growth ↓; promoter demethylation	Moderate
EGEC	AuNPs	HepG2 cells	20 μM	miR-34a, let-7a (qRT-PCR)	Tumor-suppressive miRNAs ↑	Low
EGEC	SLNs	Rat xenograft	50 mg/kg, oral	DNMT1 (qRT-PCR)	Bioavailability ↑; DNMT1 ↓	Moderate
Quercetin	PLGA NPs	MCF-7 cells	25–100 μM	DNMTs/HDACs (WB, qRT-PCR)	Epigenetic enzyme expression ↓	Low
Resveratrol	Polymeric NPs	Colon Cancer	10–50 μM	DNMTs; SIRT1 (qRT-PCR)	Anti-proliferative; indirect epigenetic effects	Low

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