The AAPS Journal (2026) 28:105
https://doi.org/10.1208/s12248-026-01258-3

REVIEW ARTICLE

Nanotechnology-enhanced Natural Products for Cancer Chemoprevention: Molecular Mechanisms and Clinical Translation

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Received: 9 February 2026 / Accepted: 6 May 2026

Abstract

Cancer remains a major global health challenge. Natural compounds, such as curcumin, resveratrol, genistein, thymoquinone, and paclitaxel, show chemopreventive activity by modulating signaling pathways, including PI3K/Akt, NF-κB, and p53. These agents also promote apoptosis, autophagy, and DNA repair. However, their clinical use is restricted by poor solubility, instability, and low bioavailability. Nanotechnology offers solutions by improving stability, enhancing pharmacokinetics, and enabling targeted delivery. Liposomes, polymeric nanoparticles, dendrimers, and albumin-bound systems amplify the anticancer effects of natural compounds. Preclinical studies confirm improved efficacy, while early clinical trials reveal both promise and barriers. The key translational challenges include immune clearance, large-scale reproducibility, and regulatory approval. This review highlights the synergy between nanotechnology and natural compounds in cancer chemoprevention and outlines opportunities for future research.

Keywords cancer chemoprevention · curcumin and resveratrol · nanomaterials · nanotechnology · targeted delivery

List of Abbreviations

AKBA	6-Acetyl-11-keto-β-boswellic acid
Akt	Protein Kinase B
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
COX-2	Cyclooxygenase-2
DDBJ	DNA Data Bank of Japan
EGCG	Epigallocatechin gallate
EMT	Epithelial-mesenchymal transition
HCC	Hepatocellular carcinoma
HPLC	High-Performance liquid chromatography
NCI	National Cancer Institute
NIH	National institutes of health
NSCLC	Non-small cell lung cancer
PCL-PEG-PCL	Polycaprolactone-polyethylene glycol-polycaprolactone
PVA	Polyvinyl alcohol
ROS	Reactive oxygen species
TNF-α	Tumor necrosis factor-alpha

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Introduction

Cancer remains the second leading cause of death and illness worldwide, following heart disease (1). Historical records of cancer date back about 3,000 years, and its incidence has steadily increased, particularly since the twentieth century

Published online: 13 May 2026

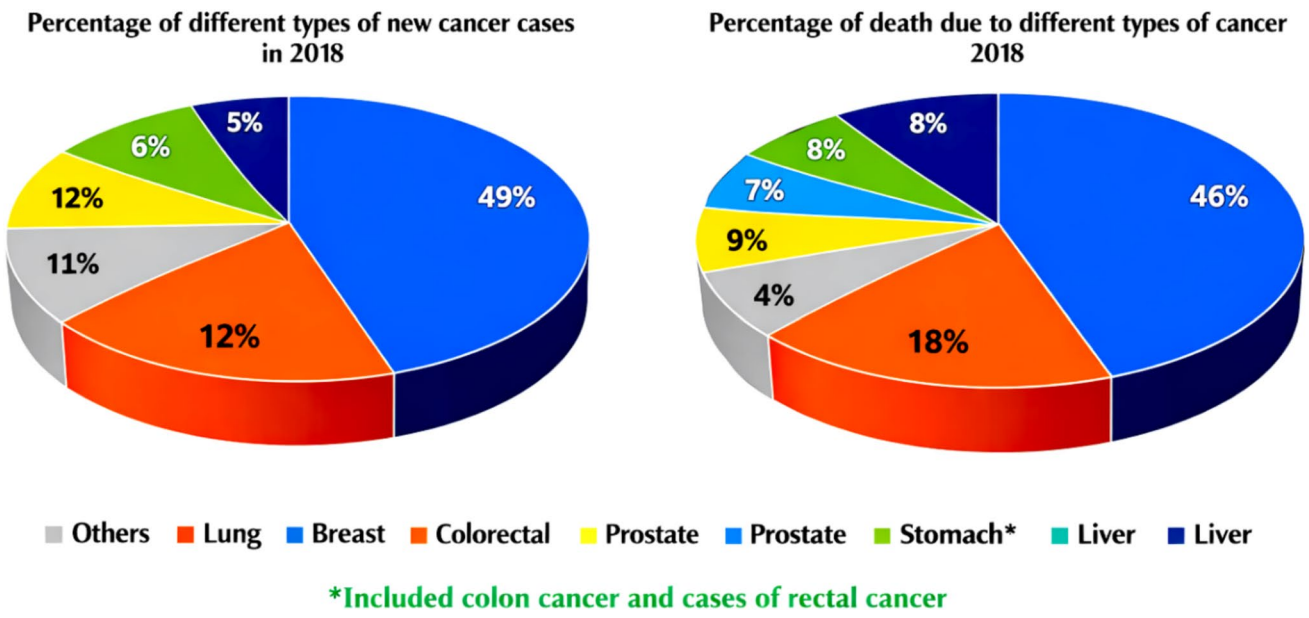

Fig. 1 Pie chart showing the distribution of cancer cases and deaths by type (%)

(2). Cancer is defined by uncontrolled cell proliferation that leads to tumor formation and metastasis, the spread of malignant cells to distant organs (3). The National Cancer Institute identifies breast, lung, colorectal, and prostate cancers as the most common types, with lung cancer responsible for 18.4% of cancer-related deaths. In India, about 54% of cancer-related deaths are attributed to lung, breast, colorectal, prostate, liver, and stomach cancers (4). Figure 1 shows the distribution of new cancer cases and deaths, with lung and breast cancers highlighted as especially lethal, particularly among women (5).

The global cancer burden is projected to rise substantially in the coming decades. By 2040, new cancer cases are expected to approach 30 million annually, accompanied by more than 15 million cancer-related deaths (4). This increase is attributed to demographic ageing, sedentary lifestyles, dietary patterns, environmental pollution, and heightened exposure to carcinogens (6). Although advances in diagnosis and treatment have improved outcomes for certain cancers, mortality remains high, particularly in low- and middle-income countries where access to healthcare is limited. Conventional treatments such as chemotherapy, radiotherapy, and surgery, while **central** to cancer management, are frequently associated with significant toxicity, high costs, and limited efficacy in advanced disease (6, 7). These challenges underscore the pressing need for preventive strategies capable of reducing cancer incidence prior to malignant transformation.

Cancer chemoprevention involves the use of natural or synthetic agents to inhibit, delay, or reverse carcinogenesis (8). A broad range of naturally derived compounds, including curcumin, epigallocatechin gallate (EGCG), luteolin, genistein, resveratrol, quercetin, sulforaphane, and thymoquinone, have demonstrated the ability to modulate molecular pathways associated with inflammation, oxidative stress, apoptosis, and cell proliferation (9–13). Such multi-target activity is particularly attractive for chemoprevention, where long-term, low-dose intervention aims to suppress early carcinogenic events rather than induce tumor cell death.

However, the clinical translation of many chemopreventive natural products has been constrained by poor aqueous solubility, rapid metabolism, short systemic half-life, and limited target engagement at physiologically relevant preventive doses (14, 15). These pharmacokinetic barriers represent a major translational bottleneck in cancer chemoprevention. Nanotechnology offers a range of strategies to address these challenges by improving solubility, enhancing stability, prolonging circulation time, and enabling more controlled tissue distribution of bioactive compounds (16, 17).

Nanocarrier-based formulations of natural products, including curcumin-loaded polymeric nanoparticles, puerarin nanosuspensions, and plumbagin-loaded metallic nanoparticles, have demonstrated improved pharmacokinetics, bioavailability, and tissue targeting in preclinical models (18–21). Importantly, such nano-enabled delivery systems offer the potential to sustain pathway modulation at doses compatible with long-term preventive use. This review integrates key mechanisms of carcinogenesis with chemopreventive pathways and nano-enabled delivery strategies, outlining how natural compounds and advanced nanoformulations strengthen the translational potential of cancer chemoprevention. By explicitly distinguishing chemopreventive

mechanisms from therapeutic cytotoxicity and emphasizing dose relevance, delivery challenges, and long-term applicability, this review addresses a critical gap in the recent literature on nano-enabled phytochemicals.

Materials and Methods

A structured literature search was conducted to examine cancer chemoprevention using natural products and their integration with nanotechnology. Peer-reviewed articles published in English between January 2010 and August 2025 were retrieved from PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Search terms included combinations of natural products, chemoprevention, nanotechnology, molecular mechanisms, DNA damage, signaling pathways, and cancer, using Boolean operators where appropriate.

Original research articles reporting mechanistic insights, nanoformulation strategies, or translational relevance in cancer prevention or therapy were considered. Studies unrelated to cancer chemoprevention, non-English publications, duplicate records, and articles lacking accessible abstracts or full texts were excluded. Review articles and meta-analyses were not included in the primary dataset but were consulted to contextualize mechanistic and translational themes.

The initial search identified 204 records. Following title and abstract screening, 74 articles were retained for qualitative synthesis. Data were extracted on compound origin, chemical class, molecular mechanisms, cancer type, delivery strategy, and translational context. The selected literature provides a PRISMA-informed overview of nano-enabled natural products in cancer chemoprevention without applying a formal systematic review or quantitative meta-analysis. Methodological limitations include reliance on preclinical evidence, heterogeneity in experimental design, and potential publication bias.

Mechanisms of Cancer Development

Cancer development involves genetic, epigenetic, and environmental factors that disrupt normal regulatory mechanisms controlling cell growth, differentiation, and apoptosis (3, 23). Mutations in oncogenes and tumor suppressor genes play a central role in this disruption, leading to uncontrolled cell proliferation and impaired immune surveillance (24). Figure 2 illustrates the general mechanism of tumor development, showing the transition from a normal cell to a cancerous one and highlighting the roles of oncogenes and tumor suppressor genes in cancer progression. Multiple signaling pathways interact during early carcinogenesis, and these alterations occur in a coordinated manner rather than in isolation.

The tumor suppressor protein p53 maintains genomic stability. Under normal conditions, p53 is present at low levels, but it becomes stabilized and activated in response to cellular stress, DNA damage, hypoxia, or oncogene activation. Activated p53 triggers DNA repair, cell cycle arrest, senescence, or apoptosis (25). The pro-apoptotic gene Bax, a p53 target, promotes programmed cell death in damaged cells. Inhibition of p53 by MDM2 or MDMX proteins allows abnormal cells to survive and proliferate, contributing to tumor progression (26, 27). Loss of p53 function also amplifies downstream oncogenic signaling, illustrating how early molecular defects propagate across multiple pathways during tumor initiation.

The PI3K/AKT/mTOR signaling pathway, frequently activated in cancer, promotes cell survival, proliferation, and metabolic adaptation while suppressing apoptosis (28). This pathway increases MDM2 protein expression, further inhibiting p53 and accelerating tumor progression (25). The tumor suppressor PTEN negatively regulates this pathway by dephosphorylating PIP3, which reduces AKT activation and restores apoptotic signaling (29, 30). Oncogenes such as Myc, E2F, and Raf drive cell cycle progression and tumorigenesis, while the JAK/STAT signaling pathway regulates genes involved in proliferation, differentiation, and immune evasion (26, 31). These pathways form an interconnected regulatory network, and their dysregulation is a hallmark of early malignant transformation.

Natural products modulate these pathways. Curcumin activates p53, Bax, and caspase-3 while inhibiting NF-κB and COX-2. Resveratrol targets the PI3K/AKT and p53 pathways to suppress tumor growth (9, 32). Thymoquinone induces DNA damage and apoptosis through telomere shortening and oxidative stress, while epigallocatechin gallate (EGCG) inhibits the PI3K/AKT/mTOR pathway to reduce tumor cell survival and proliferation (30, 33). Luteolin targets the JAK/STAT pathway to inhibit cancer cell growth and immune evasion. Genistein modulates tumor suppressor gene expression and inhibits angiogenesis (11, 29).

Quercetin induces apoptosis by activating caspase-3 and inhibiting NF-κB. Sulforaphane enhances detoxification enzyme expression and inhibits histone deacetylases (34, 35). Paclitaxel stabilizes microtubules, causing cell cycle arrest and apoptosis, and demonstrates the diverse mechanisms by which natural products exert anticancer effects (36). Most of these mechanisms reflect chemopreventive actions, including enhancement of DNA repair, reduction of oxidative stress, and restoration of tumor-suppressive signaling. Agents such as paclitaxel act primarily through DNA damage induction and microtubule stabilization, which are therapeutic rather than preventive mechanisms.

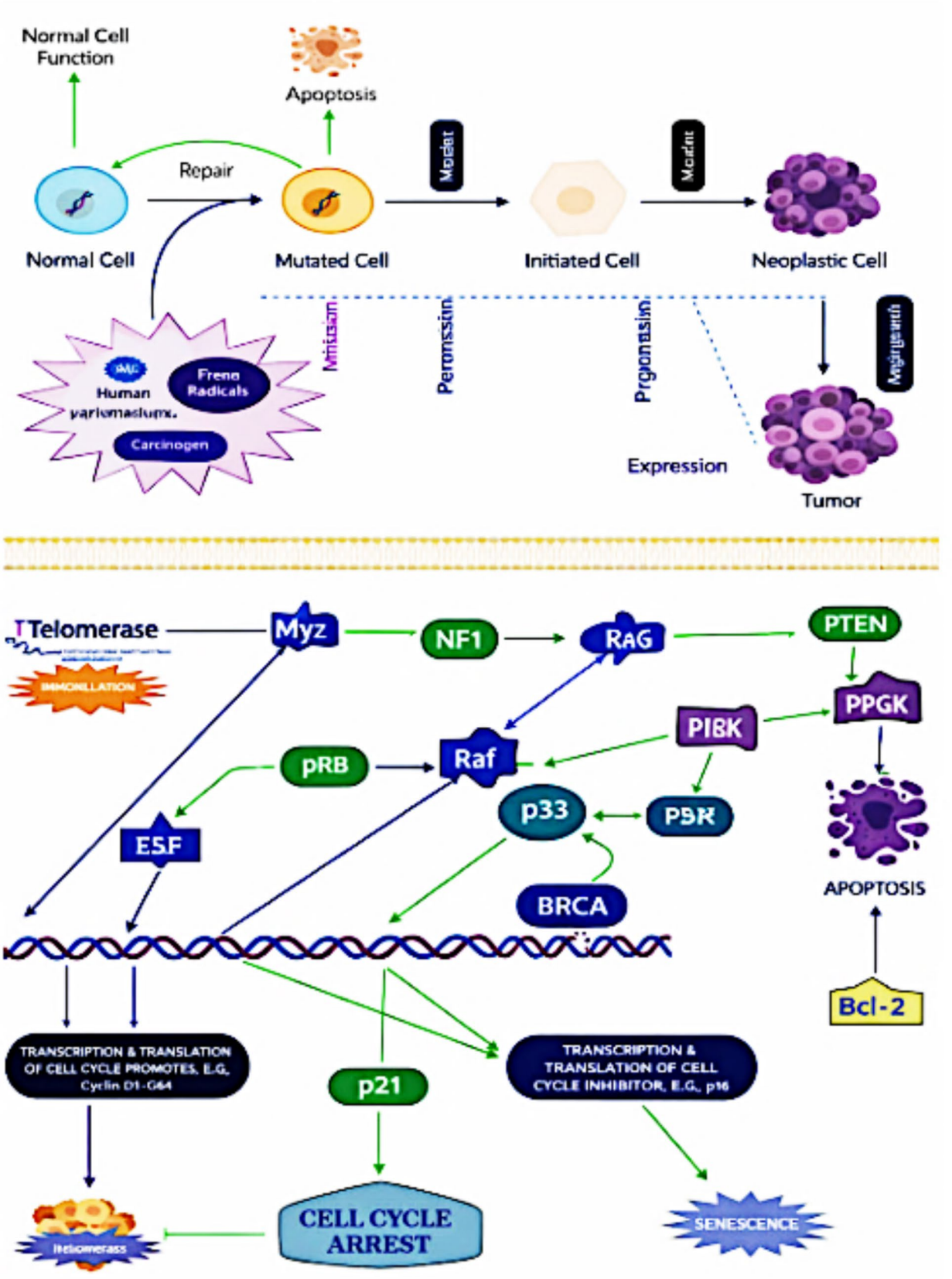

Fig. 2 Generalized mechanism of tumor generation from a normal cell

Clinical application of these natural products is limited by poor solubility, low bioavailability, and rapid metabolism, which reduce their efficacy (14, 15). Nanotechnology-based delivery systems address these issues. Curcumin-loaded PCL-PEG-PCL nanoparticles improve pharmacokinetics and anticancer activity *in vivo*. Paclitaxel in mesoporous silica nanoparticles enhances tumor targeting and cytotoxicity (18, 22). Puerarin nanosuspensions increase selectivity, and silver nanoparticle-caged plumbagin improves efficacy. Liposome-based systems enhance tumor-specific delivery of hydrophobic drugs (20, 21, 37, 38). The integration of nanotechnology with natural products offers a promising approach to cancer chemoprevention by overcoming limitations of traditional delivery methods. Nano-enabled delivery increases local concentrations of bioactive compounds at early lesion sites, improves intracellular uptake, and enables sustained modulation of pathways such as PI3K/AKT/mTOR, NF-κB, p53, and JAK/STAT at physiologically achievable doses.

Although natural products modulate key oncogenic and tumor-suppressive pathways, their preventive potential is often constrained by limited absorption, short systemic persistence, and insufficient target engagement. Nanotechnology-based delivery systems address these mechanistic limitations by improving pharmacokinetics, enhancing tissue-specific accumulation, and enabling sustained intracellular availability of bioactive compounds (16, 39, 40). By increasing local concentrations of curcumin, resveratrol, EGCG, sulforaphane, and other agents at sites of early carcinogenic change, nanocarriers strengthen pathway modulation across PI3K/AKT/mTOR, NF-κB, p53, and JAK/STAT signaling (9, 10, 30, 41). Improved stability and controlled release also enhance activation of apoptosis-related genes, suppression of inflammatory mediators, and restoration of tumor-suppressive functions (33, 36, 42). Nano-enabled enhancements provide a mechanistic rationale for integrating nanotechnology with natural compounds to achieve more effective and biologically relevant chemopreventive outcomes.

Cancer Chemoprevention

Cancer chemoprevention involves dietary components and natural agents that inhibit the transformation of normal cells into malignant ones (2). Herbs, spices, and plant-based products have long been used in disease prevention (1). Wattenberg classified chemopreventive agents into two categories: blocking agents and suppressing agents (8). The blocking agents prevent carcinogens from binding to DNA, proteins, or RNA. Suppressing agents inhibit the progression of initiated cells into malignant forms. Examples of suppressing agents include β-carotene, curcumin, genistein, and resveratrol (1). These categories remain relevant, particularly for early carcinogenic events where low-toxicity agents can modulate multiple pathways.

Phytochemicals with chemopreventive properties interfere with the multistep process of carcinogenesis. These compounds act during the initiation and promotion stages and can slow or halt the progression of precancerous cells into malignant tumors (43). Figure 3 depicts how natural agents intervene in carcinogenesis, blocking initiation, promotion, and progression to prevent or reverse tumor development (43). These effects occur at physiologically achievable concentrations, typically lower than those used in therapeutic models, highlighting the distinction between preventive and cytotoxic mechanisms.

Curcumin, a turmeric-derived polyphenol, modulates NF-κB, COX-2, and PI3K/AKT pathways, reducing inflammation, oxidative stress, and tumor growth (9, 44). Resveratrol, found in grapes and red wine, activates p53 and SIRT1 to induce apoptosis and suppress tumor progression (10). Epigallocatechin gallate (EGCG), a green tea polyphenol, inhibits the PI3K/AKT/mTOR pathway, reducing cancer cell survival (30). Luteolin, a flavonoid in vegetables and fruits, targets the JAK/STAT pathway, suppressing cancer cell growth and immune evasion (26). These mechanisms reflect classical chemopreventive actions, including enhancement of DNA repair, reduction of inflammation, and restoration of tumor-suppressive signaling, rather than induction of high-dose cytotoxicity.

Genistein, a soy isoflavone, modulates tumor suppressor genes and inhibits angiogenesis (29). Quercetin, abundant in apples and onions, induces apoptosis by activating caspase-3 and inhibiting NF-κB (34). Sulforaphane, from cruciferous vegetables, enhances detoxification enzymes and inhibits histone deacetylases (35). Thymoquinone, from black seed oil, induces DNA damage and apoptosis through telomere shortening and oxidative stress (33). Paclitaxel, from the Pacific yew tree, stabilizes microtubules, causing cell cycle arrest and apoptosis (36). Paclitaxel is primarily a therapeutic agent rather than a chemopreventive compound; its inclusion reflects mechanistic diversity rather than preventive relevance. Recent reviews confirm that these compounds act through complementary mechanisms, including apoptosis induction, anti-inflammatory activity, angiogenesis inhibition, detoxification, and microtubule stabilization (41, 45, 46).

An effective chemopreventive agent should meet several criteria, including low toxicity and efficacy at low doses. Despite their potential, many natural chemopreventive agents face limitations such as poor bioavailability, rapid metabolism, and lack of specificity (14, 15). Nanotechnology offers solutions. Nanomaterials, liposomes, polymeric nanoparticles, and albumin-bound carriers improve delivery, stability, solubility, and tumor-specific targeting (16, 39).

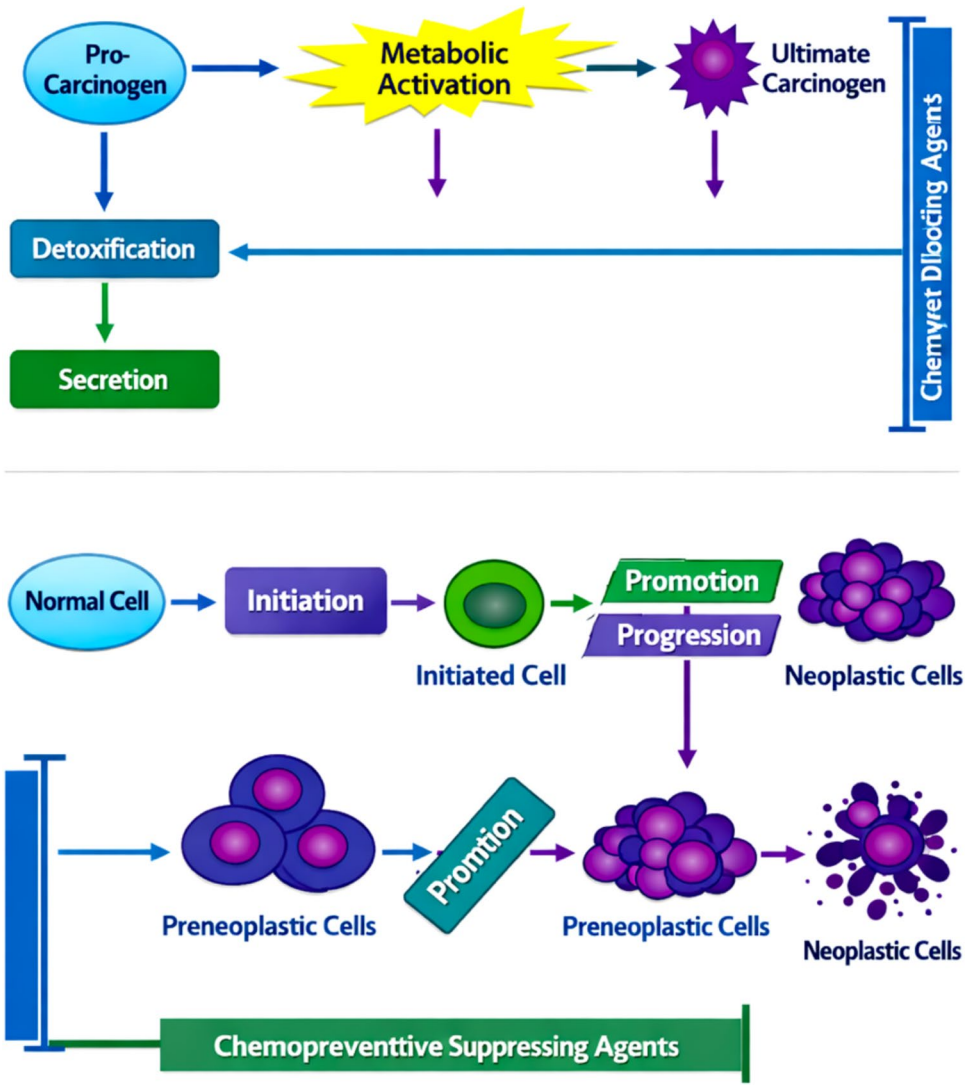

Fig. 3 Chemoprevention by different types of chemopreventive agents

The integration of nanotechnology with natural products represents a strategy for cancer prevention that may lead to safer, more effective interventions. Nano-enabled delivery is particularly relevant for chemoprevention because it enhances local tissue exposure at early lesion sites, improves intracellular uptake at low doses, and enables sustained modulation of preventive pathways such as NF-κB, PI3K/AKT/mTOR, and p53.

Prevention is Better Than Cure

Disease prevention is especially important for conditions that are incurable or difficult to treat, such as cancer. The high cost, severe side effects, and complexity of conventional therapies highlight the need for preventive strategies. Cancer often affects multiple organs and may cause secondary complications, which further emphasize the value of early intervention (6, 7). Cancer chemoprevention refers to the use of natural or synthetic agents to inhibit, delay, or reverse carcinogenesis (8). The multistep nature of cancer, which may take years to progress from initiation to malignancy, provides a critical window for preventive intervention. Dietary and lifestyle factors strongly influence cancer risk. Epidemiological studies show that diets rich in vegetables, fruits, whole grains, and fiber, combined with regular physical activity, reduce the risk of several cancer types (4).

Natural compounds such as curcumin, EGCG, luteolin, genistein, resveratrol, paclitaxel, quercetin, sulforaphane, and thymoquinone have been extensively studied for their chemopreventive potential. These agents exhibit anti-inflammatory, antioxidant, and pro-apoptotic properties, and they modulate key signaling pathways involved in cancer development (9, 10, 12, 26). Some have advanced to clinical trials, demonstrating translational relevance (50–52). Despite this promise, many natural chemopreventive agents face limitations of poor solubility, low bioavailability, and non-specific

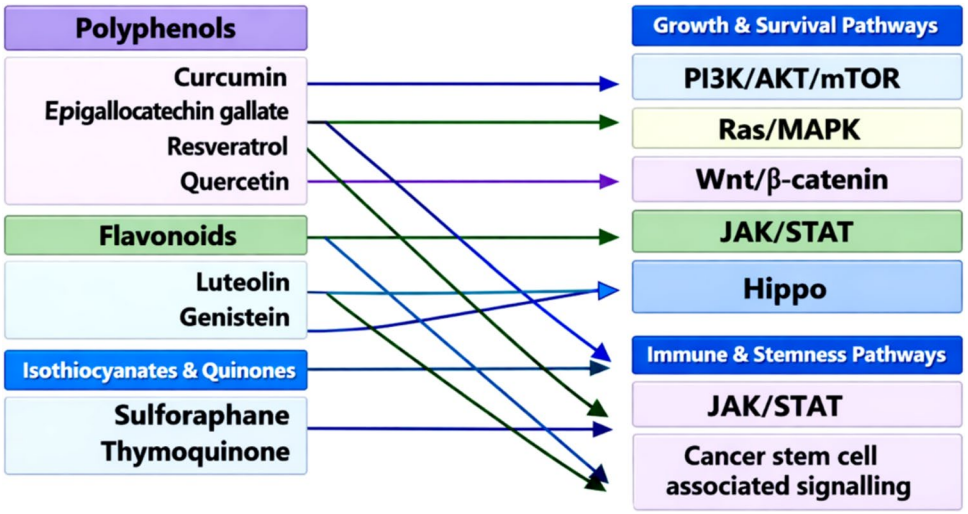

Fig. 4 Inhibitory effects of selected compounds on major cancer-related signaling pathways

distribution (14). These limitations hinder clinical effectiveness. Nanotechnology-based delivery systems address these issues. Liposomes, polymeric nanoparticles, and albumin-bound systems improve pharmacokinetic and pharmacodynamic profiles (16, 39). The integration of nanotechnology with natural products represents a strategy for cancer prevention that may reduce cancer incidence and improve public health outcomes (42, 48, 49). Nano-enabled systems are relevant for chemoprevention because they enhance local tissue exposure at early lesion sites, improve intracellular uptake at low doses, and sustain pathway modulation over longer periods than free compounds.

Chemoprevention and Natural Products: Signaling Pathways in Various Cancers

The discovery of oncogenes such as MYC, RAS, BRAF, and KIT, along with tumor suppressors TP53, BRCA1, and PTEN, has transformed understanding of cancer biology (3). Dysregulation of intracellular signaling pathways is a hallmark of cancer, driving uncontrolled proliferation, resistance to apoptosis, angiogenesis, and metastasis (23). Figure 4 illustrates the inhibitory effects of natural compounds, including curcumin, EGCG, luteolin, genistein, resveratrol, paclitaxel, quercetin, sulforaphane, and thymoquinone, on major cancer-related signaling pathways such as PI3K/AKT/mTOR, Ras/MAPK, Wnt/β-catenin, JAK/STAT, NF-κB, Hedgehog, Hippo, and cancer stem cell-associated signaling (9, 10, 30, 41, 45). Figure 4 also shows the nanoparticle-mediated delivery steps involving mechanistic pathways with nano-enabled chemoprevention.

The PI3K/AKT/mTOR pathway, frequently altered in breast, prostate, and thyroid cancers, regulates cell growth, proliferation, and survival. Mutations in PI3K, AKT, or PTEN often drive its activation (28). Natural compounds such as curcumin and resveratrol inhibit this pathway, offering chemopreventive benefits (28). Genistein also inhibits this pathway, suggesting a preventive role (29). The Ras/MAPK pathway, critical for cell proliferation and differentiation, is commonly mutated in melanoma, colorectal, and thyroid cancers (24). Genistein inhibits this pathway, supporting its potential in prevention (29). Natural products can suppress two of the most frequently dysregulated growth pathways in cancer.

The Wnt/β-catenin pathway, essential for cell proliferation and stem cell maintenance, is often dysregulated in colon, liver, and breast cancers. Sulforaphane and quercetin inhibit this pathway (34, 35). The JAK/STAT pathway, which is involved in cell growth, survival, and immune response, is frequently dysregulated in leukemia, breast cancer, and head and neck cancers (26). Curcumin and genistein inhibit this pathway. These compounds converge on Wnt and JAK/STAT signaling, reducing proliferation and immune evasion (9, 29).

The NF-κB pathway regulates inflammation, immune response, and cell survival, and its activation promotes tumor proliferation, angiogenesis, and resistance to apoptosis. The Hedgehog pathway, critical for embryonic development and stem cell maintenance, is dysregulated in breast, gastric, and pancreatic cancers (53). Sulforaphane inhibits this pathway, showing promise in cancer prevention (35). The Hippo pathway, which regulates organ size, proliferation, and apoptosis, is frequently altered in breast, colorectal, and liver cancers (31). Curcumin and resveratrol modulate this pathway (9, 10). Natural products act on NF-κB, Hedgehog, and Hippo signaling to reduce tumor growth and survival (42, 49). These effects represent chemopreventive mechanisms that operate at low, non-cytotoxic concentrations, distinguishing them from therapeutic agents that rely on high-dose cytotoxicity.

Cancer stem cells (CSCs), identified in acute myeloid leukemia, breast, colon, and liver cancers, drive tumor growth,

recurrence, and therapy resistance (54). The key CSC pathways include Notch, Wnt, and PI3K/AKT. Curcumin and resveratrol target CSCs by modulating these pathways (9, 10). An elevated HDAC7 and HDAC1 maintain CSC traits in breast cancer, while inducible nitric oxide synthase (iNOS) promotes Notch signaling in liver CSCs, accelerating tumor development (55). Carboxypeptidase A4 (CPA4) regulates inflammation and fibrosis in liver cancer and is linked to poor prognosis (21). The lower CD44 mRNA levels in hepatic metastases correlate with better survival in colorectal cancer, while co-expression of CD44 and CD133 marks aggressive disease (26). Natural compounds may suppress CSC-driven tumor progression by targeting epigenetic regulators and stem cell signaling. Nano-enabled formulations further enhance these effects by improving CSC-targeted delivery and sustaining intracellular concentrations in stem-like tumor niches.

The MAPK and PI3K pathways are key drivers in thyroid tumor development (24). The PI3K pathway also regulates growth, proliferation, and angiogenesis in breast cancer, with clinical trials increasingly favoring PI3K inhibitors (30). Oral cancer develops through dysregulation of PI3K/AKT/mTOR, Ras/MAPK, Wnt, NF-κB, and Hippo pathways, with genetic alterations in TP53, PTEN, and others contributing to progression (11). The NF-κB pathway, normally inhibited by I-κB, regulates genes such as Bcl2, VEGF, and IL-6, promoting proliferation and chemoresistance (55). The Wnt pathway is crucial in breast, lung, and oral cancers, with its activation linked to poor prognosis (53). Hypoxia in oral cancer upregulates Notch target genes HEY1 and HES1, promoting proliferation (11). The MAPK pathway, through ERK1/2, JNK, ERK5, and p38 branches, regulates apoptosis, proliferation, and metastasis (24). The Hippo pathway, disrupted in breast, colorectal, and liver cancers, controls tumor growth via MST and LATS kinases (31). The Hedgehog pathway is activated through canonical and non-canonical mechanisms, which drive breast and gastric cancers (56, 57).

EGCG demonstrates multi-target effects across PI3K/AKT, EMT suppression, and inflammatory signaling, supporting its role as a chemopreventive scaffold (49). Sulforaphane modulates Nrf2 at the epigenetic level via DNA methyltransferase regulation in intestinal models, strengthening its detoxification and antioxidant rationale (40, 42). Herbal anticancer products show convergent mechanisms, including apoptosis, autophagy, ferroptosis, and pathway modulation across curcumin, resveratrol, EGCG, and ginsenosides (45). Natural compounds act through multi-level regulatory effects across signaling, epigenetics, and cell-death programs. This multi-target behavior aligns with nano-enabled chemoprevention, where improved delivery enhances coordinated modulation of these interconnected pathways.

Natural Compounds and DNA Damage Relation in Various Cancers

Cancer is characterized by genomic instability, driven by persistent DNA damage and impaired repair mechanisms. The DNA damage response (DDR) preserves genomic integrity by detecting and repairing lesions caused by oxidative stress, radiation, or carcinogens (58). Natural compounds modulate DDR pathways by either enhancing DNA repair in normal cells or inducing lethal damage in cancer cells, offering therapeutic potential for chemoprevention (9, 17). Chemopreventive agents typically act by reducing oxidative stress and enhancing repair fidelity at low, non-cytotoxic doses, whereas therapeutic agents induce high levels of DNA damage to trigger apoptosis.

Natural compounds regulate DNA damage and repair through diverse mechanisms across multiple cancer types. These bioactive agents influence apoptosis, oxidative stress, and DNA repair, making them promising candidates for cancer prevention (41, 45). Table I summarizes the major classes of natural compounds, their representative molecules, mechanisms of action, and the cancer types they target. Nano-enabled formulations enhance DNA-modulatory effects by improving stability, intracellular uptake, and sustained exposure at early lesion sites.

Natural compounds influence DNA damage and repair through multiple mechanisms, ranging from apoptosis induction and oxidative stress modulation to telomere shortening and immune activation. Their ability to selectively enhance DNA repair in normal cells while inducing lethal damage in cancer cells positions them as powerful chemopreventive agents (47, 48). Nano-enabled delivery strengthens dual actions by improving pharmacokinetics, enhancing tissue-specific accumulation, and sustaining intracellular availability of DNA-modulatory phytochemicals at preventive doses.

Polyphenols, abundant in fruits, vegetables, and tea, are renowned for their antioxidant and anticancer properties. They can induce DNA damage in cancer cells to promote apoptosis or enhance DNA repair in healthy cells (1). Curcumin, derived from *Curcuma longa*, selectively targets cancer cells by promoting apoptosis and inhibiting NF-κB, while enhancing DNA repair (9). Resveratrol induces DNA damage and modulates p53 to trigger apoptosis in prostate, colorectal, and breast cancers, with low doses promoting non-mutagenic DNA repair (10). Epigallocatechin gallate (EGCG), a green tea polyphenol, enhances DNA repair, reduces oxidative stress, and induces apoptosis in breast, prostate, and lung cancers (30, 63). Polyphenols demonstrate dual roles in protecting normal cells while sensitizing malignant cells (42, 49). Nano-formulations further strengthen preventive effects by increasing bioavailability and enabling consistent modulation of DDR pathways.

Table I Summary of Natural Compound Classes and Their Effects on DNA Damage and Repair Mechanisms in Various Cancers

Compound Class	Representative Compounds	Mechanism of Actions	Cancer Types Affected	Reference
Polyphenols	Curcumin	Apoptosis, DNA repair enhancement, NF-κB inhibition	Breast, colorectal, pancreatic	(9)
Polyphenols	Resveratrol	DNA damage, p53 modulation, apoptosis	Prostate, colorectal, breast	(10)
Polyphenols	Epigallocatechin gallate (EGCG)	Antioxidant, DNA repair enhancement, apoptosis	Breast, prostate, lung	(30)
Flavonoids	Luteolin	Apoptosis, G2/M cell cycle arrest, pathway inhibition	Breast, colorectal, liver	(11, 12)
Flavonoids	Genistein	DNA damage, apoptosis, angiogenesis inhibition	Breast, prostate, ovarian	(29)
Flavonoids	Quercetin	Antioxidant, DNA damage repair, apoptosis	Lung, colorectal, liver	(34)
Flavonoids	Trifolirhizin	Anti-inflammatory, apoptosis, DNA damage	Ovarian, lung, oral, leukemia	(59)
Terpenoids	Paclitaxel	Microtubule stabilization, apoptosis, DNA damage	Breast, ovarian, lung	(22, 36)
Terpenoids	Ginsenoside RK1	Apoptosis, ferroptosis	Hepatocellular carcinoma	(60)
Alkaloids	Matrine	EMT inhibition, invasion suppression	Hepatocellular carcinoma	(61)
Isothiocyanates	Sulforaphane	Antioxidant, DNA repair enhancement, apoptosis	Prostate, colorectal, breast	(35)
Polysaccharides	*Cordyceps sinensis* polysaccharides	Immune activation, apoptosis	Various cancers	(62)
Quinones	Thymoquinone	DNA damage, apoptosis, telomere shortening	Glioblastoma, leukemia	(33)

Flavonoids provide anticancer and antioxidant benefits through DNA damage modulation. Luteolin induces apoptosis, arrests cells at G2/M, and inhibits oncogenic signaling, showing efficacy in breast, colorectal, and liver cancers (11). Genistein, a soybean isoflavone, causes DNA damage, promotes apoptosis, and inhibits angiogenesis in breast, prostate, and ovarian cancers (12, 29). Quercetin enhances DNA repair and induces apoptosis in lung, colorectal, and liver cancers (34). Trifolirhizin, from *Sophora flavescens*, exerts anti-inflammatory effects, promotes apoptosis, and causes DNA damage in ovarian, lung, oral, and leukemia cells (59). Nano-enabled delivery of flavonoids enhances stability and intracellular retention, improving DNA-modulatory capacity at preventive doses.

Terpenoids trigger cell death through multiple mechanisms. Paclitaxel, from the Pacific yew, stabilizes microtubules, induces apoptosis, and causes DNA damage in breast, ovarian, and lung cancers (22, 36). However, paclitaxel represents a therapeutic rather than a chemopreventive mechanism, and its inclusion reflects mechanistic diversity rather than preventive relevance. Ginsenoside RK1, a ginseng component, induces apoptosis and ferroptosis in hepatocellular carcinoma (60). Nano-delivery systems enhance terpenoid activity by improving solubility and enabling targeted accumulation in dysplastic tissues.

Alkaloids such as matrine suppress invasion and migration in hepatocellular carcinoma by inhibiting epithelial-mesenchymal transition (EMT) (61). By targeting EMT and DNA damage pathways, alkaloids provide a complementary chemopreventive strategy. Isothiocyanates, such as sulforaphane from cruciferous vegetables, act as antioxidants, enhance DNA repair, and induce apoptosis in prostate, colorectal, and breast cancers (35).

Polysaccharides from *Cordyceps sinensis* activate immune responses and induce apoptosis across multiple cancers. Their immunomodulatory effects complement DNA repair modulation, broadening chemopreventive potential (62). Quinones, such as thymoquinone from *Nigella sativa*, induce DNA damage, apoptosis, and telomere shortening in glioblastoma and leukemia cells. By targeting telomere stability, quinones add another layer of genomic stress to malignant cells (33). Nano-encapsulation of quinones reduces off-target toxicity and enhances selective DNA damage in premalignant tissues.

Natural compounds influence DNA damage and repair through multiple mechanisms, ranging from apoptosis induction and oxidative stress modulation to telomere shortening and immune activation. Their ability to selectively enhance DNA repair in normal cells while inducing lethal damage in cancer cells positions them as powerful chemopreventive agents (47, 48). Nano-enabled delivery strengthens dual actions by improving pharmacokinetics, enhancing tissue-specific accumulation, and sustaining intracellular availability of DNA-modulatory phytochemicals at preventive doses.

Mechanism of Chemoprevention By Natural Products

Cancer development is a multistep process involving initiation, promotion, and progression, each characterized by distinct molecular and cellular alterations. Initiation is typically irreversible and results from genotoxic insults, such as carcinogen exposure, leading to DNA mutations (3). Natural products exert chemopreventive effects by interfering with these stages through two primary mechanisms: (i) blocking carcinogens from reaching or interacting with cellular targets, and (ii) suppressing the transformation of initiated cells into malignant phenotypes (8). These mechanisms involve modulation of xenobiotic metabolism, regulation of cell cycle checkpoints, enhancement of DNA repair, and induction of apoptosis. Based on current evidence, the chemopreventive actions of natural products can be broadly categorized into four functional domains: (i) induction of cellular defense mechanisms, (ii) reduction of inflammation, (iii) inhibition of metastasis, and (iv) promotion of apoptosis (8, 41, 45). These actions occur at low, physiologically relevant concentrations and reflect preventive rather than therapeutic mechanisms.

Induction of Cellular Defense Mechanisms

Reactive oxygen species (ROS), particularly hydroxyl radicals, are among the most damaging byproducts of oxidative stress. These species directly damage DNA, proteins, and lipids, contributing to mutagenesis and carcinogenesis. Lifestyle factors, such as poor diet and environmental exposure, can exacerbate ROS production (64). Natural compounds such as curcumin, quercetin, and resveratrol enhance endogenous antioxidant defenses by upregulating enzymes, including superoxide dismutase, catalase, and glutathione peroxidase (65). Antioxidant Activity Maintains Redox Homeostasis and Prevents Oxidative DNA Damage.

Curcumin neutralizes ROS and upregulates antioxidant enzymes, protecting cells from oxidative stress (9). Quercetin scavenges free radicals and enhances antioxidant enzyme activity, reducing oxidative damage in cancer cells (34). Resveratrol activates the Nrf2 pathway, leading to the upregulation of antioxidant genes and protecting cells from ROS-induced damage (10). These compounds strengthen cellular defense systems and reduce the mutagenic burden that drives carcinogenesis (42, 49). Figure 5 shows the inflammation pathway and counteraction by natural products. Nano-enabled formulations enhance antioxidant and cytoprotective effects by improving solubility, stability, and sustained intracellular availability at preventive doses.

Reduction of Inflammation

Chronic inflammation is a well-established risk factor for cancer, contributing to approximately 20% of all cases (4). The NF-κB signaling pathway plays a central role in regulating inflammatory responses and is frequently activated in tumor microenvironments (55). Activation of NF-κB by pro-inflammatory cytokines such as TNF-α leads to transcription of genes involved in proliferation, angiogenesis, and survival (66). Natural products, including curcumin, genistein, luteolin, and resveratrol, inhibit NF-κB activation by blocking IκB kinase (IKK) activity and preventing IκB degradation. This inhibition reduces expression of inflammatory mediators such as COX-2, IL-6, and TNF-α, thereby attenuating inflammation-driven tumorigenesis (44).

Curcumin suppresses NF-κB signaling by inhibiting IKK activity, lowering pro-inflammatory cytokine expression (9). Genistein modulates NF-κB, downregulating COX-2 and IL-6 in cancer cells (29). Luteolin inhibits NF-κB activation, reducing inflammation and tumor progression (11). Resveratrol blocks NF-κB signaling, decreasing production of inflammatory mediators (10). These compounds counteract chronic inflammation, a key driver of cancer initiation and promotion (46, 48). Nano-delivery systems enhance anti-inflammatory effects by increasing tissue penetration, improving bioavailability, and facilitating consistent suppression of NF-κB signaling at early lesion sites.

Inhibition of Metastasis

Metastasis is a leading cause of cancer-related mortality and involves the dissemination of cancer cells from the primary tumor to distant organs. This process is facilitated by epithelial-mesenchymal transition (EMT), during which epithelial cells lose adhesion and acquire migratory properties (23). Downregulation of E-cadherin and activation of transcription factors such as Snail and Twist are key events in EMT (67). Natural compounds, including curcumin, genistein, paclitaxel, resveratrol, and thymoquinone, inhibit EMT by restoring E-cadherin expression and suppressing mesenchymal markers. These effects reduce cell migration and invasion, thereby limiting metastatic potential (54). Anti-metastatic actions occur at low, non-cytotoxic concentrations consistent with chemopreventive activity, distinguishing them from therapeutic EMT-targeting strategies.

Curcumin inhibits EMT by upregulating E-cadherin and downregulating Snail and Twist, reducing cancer cell migration (9). Genistein suppresses EMT by modulating the PI3K/AKT pathway, inhibiting invasion (29). Paclitaxel stabilizes microtubules, preventing EMT and reducing metastasis (36). However, paclitaxel represents a therapeutic rather than a chemopreventive mechanism, and its inclusion reflects mechanistic diversity rather than

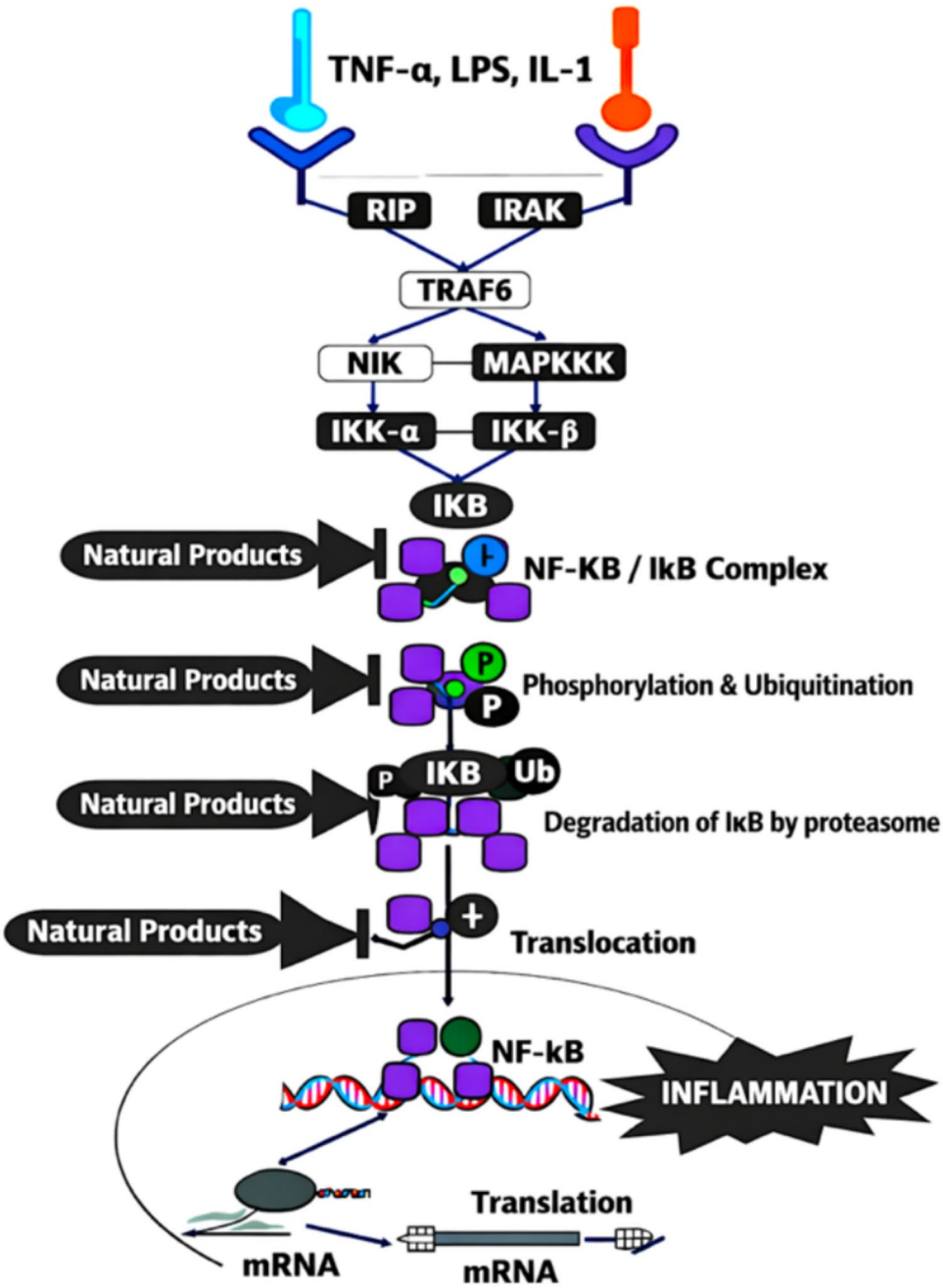

Fig. 5 The inflammation pathway and counterattack by natural products

preventive relevance. Resveratrol downregulates mesenchymal markers and restores E-cadherin expression (10). Thymoquinone modulates the Wnt/β-catenin pathway, limiting cancer cell migration (33). Natural products can interfere with EMT signaling to suppress metastatic spread (41, 48). Nano-enabled formulations enhance anti-metastatic effects by improving tissue penetration, stabilizing bioactive compounds, and sustaining pathway modulation in early metastatic niches.

Promotion of Apoptosis

Apoptosis, or programmed cell death, is a critical mechanism for eliminating damaged or abnormal cells. Loss of apoptotic control is a hallmark of cancer and is often associated with mutations in the p53 tumor suppressor gene (3). Restoration of apoptosis in cancer cells is a key strategy in chemoprevention. In preventive contexts, these effects occur at lower doses that restore physiological

Table II List of Selected Compounds Isolated From Plants in Cancer Chemoprevention

Compound	Plant Source	Chemical Class	IC_{50} Value (Cancer Cell Line)	Primary Cancer Targets	Reference
Curcumin	*Curcuma longa*	Curcuminoid	40.32 μM (MCF-7), 18.39 μM (HT-29), 18.25 μM (BxPC-3)	Breast, colorectal, pancreatic	(9)
EGCG	*Camellia sinensis*	Flavonoid	37.7 μM (MCF-7), 27.12 μM (A549)	Breast, prostate, lung	(30)
Genistein	*Glycine max*	Isoflavone	10 μM (MCF-7), 25 μM (LNCaP)	Prostate, breast, ovarian	(29)
Luteolin	*Brucea javanica*	Flavonoid	48 μM (MCF-7), 27.12 μM (A549)	Breast, lung, colorectal	(11)
Paclitaxel	*Taxus brevifolia*	Diterpenoid alkaloid	0.22 μM (MCF-7), 0.00319 μM (SKOV-3)	Breast, ovarian, lung	(36, 70)
Quercetin	*Allium cepa*	Flavonoid	90 μM (HCC LM3), 5.25 μM (A549)	Liver, breast, lung	(34)
Resveratrol	*Vitis vinifera*	Stilbene	50 μM (HT-29), 50 μM (MCF-7)	Colorectal, breast, prostate	(10)
Sulforaphane	*Brassica oleracea*	Isothiocyanate	15 μM (LNCaP), 15 μM (MCF-7)	Prostate, breast, colorectal	(35)
Thymoquinone	*Nigella sativa*	Monoterpene	75 μM (U87MG)	Glioblastoma, leukemia	(33)

apoptotic signaling rather than inducing high-dose cytotoxicity.

Natural products such as curcumin, epigallocatechin gallate (EGCG), luteolin, genistein, resveratrol, paclitaxel, quercetin, sulforaphane, and thymoquinone activate both intrinsic and extrinsic apoptotic pathways. These compounds modulate pro-apoptotic proteins (e.g., Bax, caspases) and inhibit anti-apoptotic proteins (e.g., Bcl-2), leading to mitochondrial dysfunction and cell death (68). Multi-pathway effects highlight the systems-level nature of chemopreventive apoptosis modulation.

Curcumin activates the intrinsic apoptotic pathway by upregulating Bax and downregulating Bcl-2, leading to mitochondrial dysfunction and caspase-3 activation (9). EGCG induces apoptosis by activating caspases and modulating the PI3K/AKT pathway, upregulating p53 and Bax while downregulating Bcl-2 (30). Luteolin promotes apoptosis by upregulating pro-apoptotic proteins, inhibiting anti-apoptotic proteins, and activating caspase-3 and caspase-9 (11). Genistein induces apoptosis by activating caspase-3 and modulating NF-κB, increasing Bax and decreasing Bcl-2 (29).

Resveratrol activates both intrinsic and extrinsic apoptotic pathways, upregulating p53 and Bax while downregulating Bcl-2 (10). Paclitaxel stabilizes microtubules, triggering apoptosis through caspase-3 activation and mitochondrial dysfunction (36). Paclitaxel's apoptotic effects reflect therapeutic rather than chemopreventive activity. Quercetin induces apoptosis by activating caspases and modulating PI3K/AKT, upregulating Bax and downregulating Bcl-2 (34). Sulforaphane promotes apoptosis by modulating the Nrf2 pathway, activating caspases, and inducing p53-mediated mitochondrial dysfunction (35). Thymoquinone induces apoptosis by activating caspase-3 and modulating the p53 pathway, upregulating Bax and downregulating Bcl-2 (33).

Natural products modulate apoptosis through both intrinsic and extrinsic pathways, converging on caspase activation and mitochondrial dysfunction. Recent reviews consolidate these mechanisms, including pathway crosstalk, caspase orchestration, and mitochondrial control, across diverse scaffolds (46). Nano-enabled delivery systems potentiate apoptotic effects by enhancing intracellular accumulation, improving pharmacokinetics, and enabling sustained activation of pro-apoptotic pathways at preventive doses.

Natural Products in Chemoprevention

Research on natural products with anticancer properties has been ongoing for decades, gaining momentum after the discovery of paclitaxel from *Taxus brevifolia*. Since then, numerous natural agents, ranging from crude extracts to purified phytochemicals, have demonstrated chemopreventive and chemotherapeutic potential (9, 69). Food-derived phytochemicals have attracted attention because of their low toxicity and broad biological activity. Bridging the gap between preclinical promise and clinical application requires evaluation of pharmacological properties, delivery strategies, and clinical progress of key natural compounds (17, 39). Table II summarizes selected natural products with demonstrated chemopreventive activity, highlighting potency (IC_{50} values) and primary cancer targets. These examples illustrate the wide potency range among natural compounds and underscore the importance of distinguishing chemopreventive low-dose mechanisms from high-dose therapeutic cytotoxicity.

Curcumin, isolated from the roots of *Curcuma longa*, is a curcuminoid with an $\mathbf{IC_{50}}$ of 40.32 μM in MCF-7 breast cancer cells, demonstrating activity against colorectal, pancreatic, and breast cancers (9). Epigallocatechin gallate (EGCG), derived from the leaves of *Camellia sinensis*, is a flavonoid with an $\mathbf{IC_{50}}$ of 37.7 μM in MCF-7 breast cancer cells, showing efficacy against breast, prostate, and lung cancers (30). Genistein, obtained from *Glycine max* seeds, is an isoflavone with an $\mathbf{IC_{50}}$ of 25 μM in LNCaP prostate cancer cells, indicating its role in prostate, breast, and

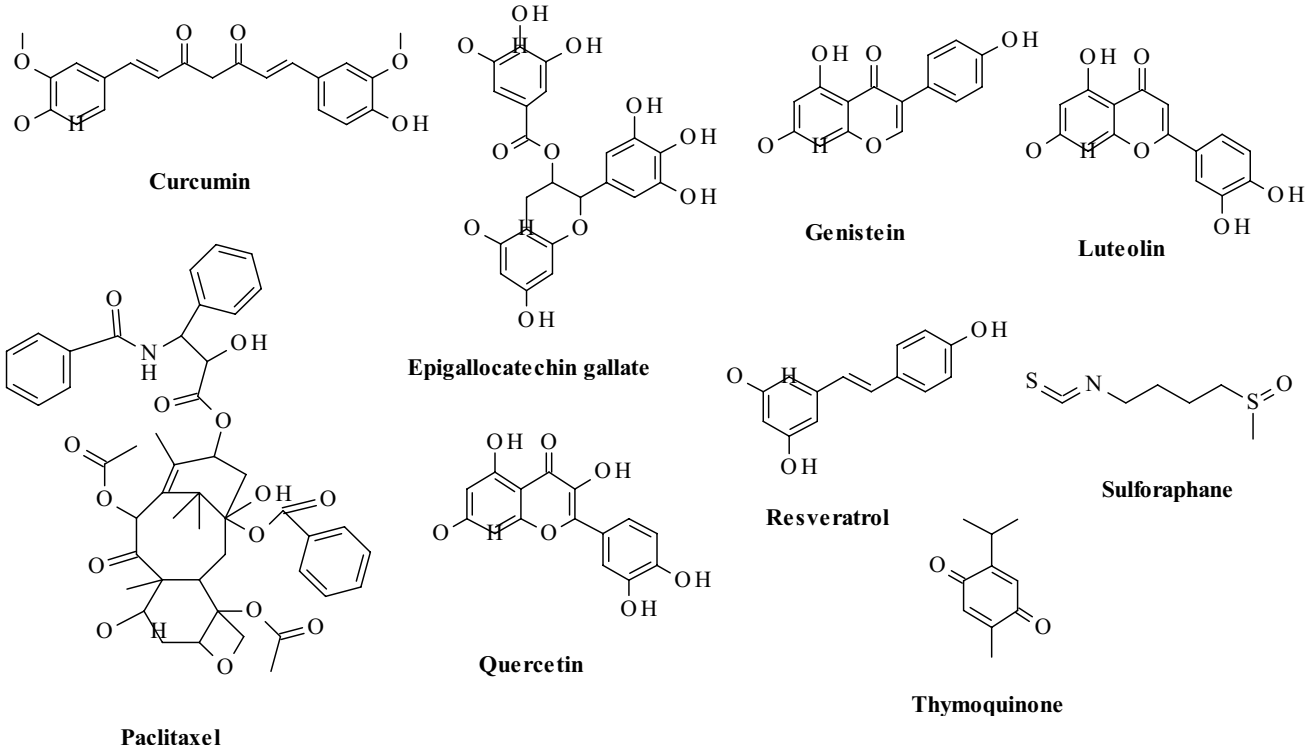

Fig. 6 The chemical structures of curcumin, epigallocatechin gallate, luteolin, genistein, resveratrol, paclitaxel, quercetin, sulforaphane, and thymoquinone in cancer chemoprevention

ovarian cancer prevention (29). Luteolin, isolated from *Brucea javanica*, is a flavonoid with an $\mathbf{IC_{50}}$ of 48 µM in MCF-7 breast cancer cells, suggesting potential in colorectal, breast, and lung cancers (11).

Paclitaxel, extracted from the bark of *Taxus brevifolia*, is a diterpenoid alkaloid with the highest potency, exhibiting an $\mathbf{IC_{50}}$ of 0.00319 µM in SKOV-3 ovarian cancer cells. Its exceptional cytotoxicity underpins clinical success in breast, ovarian, and lung cancers (36). Paclitaxel represents a therapeutic rather than a chemopreventive mechanism; its inclusion reflects mechanistic diversity rather than preventive relevance. Quercetin, derived from *Allium cepa* (onions), is a flavonoid with an $\mathbf{IC_{50}}$ of 90 µM in HCC LM3 liver cancer cells, indicating potential in liver, breast, and lung cancers (34).

Resveratrol, obtained from *Vitis vinifera* fruits, is a stilbene with an $\mathbf{IC_{50}}$ of 50 µM in MCF-7 breast cancer cells, demonstrating efficacy against colorectal, breast, and prostate cancers (10). Sulforaphane, isolated from *Brassica oleracea* (broccoli), is an isothiocyanate with an $\mathbf{IC_{50}}$ of 15 µM in LNCaP prostate cancer cells, highlighting activity against prostate, breast, and colorectal cancers (35). Thymoquinone, derived from *Nigella sativa* seeds, is a monoterpene with an $\mathbf{IC_{50}}$ of 75 µM in U87MG glioblastoma cells, indicating potential in glioblastoma and leukemia (33). The $\mathbf{IC_{50}}$ value represents the concentration required to inhibit 50% of cancer cell viability, serving as an indicator of cytotoxic strength.

These findings highlight variability in anticancer efficacy among natural compounds and emphasize the importance of delivery systems, such as nanoparticle formulations, in enhancing therapeutic outcomes (17). Structural diversity underpins the ability to target multiple pathways, but clinical translation depends on overcoming pharmacokinetic limitations. Nano-enabled delivery systems address these limitations by improving solubility, enhancing bioavailability, enabling controlled release, and increasing tissue-specific accumulation, thereby strengthening both chemopreventive and therapeutic potential. Figure 6 outlines the chemical structures of curcumin, EGCG, luteolin, genistein, resveratrol, paclitaxel, quercetin, sulforaphane, and thymoquinone, providing a visual reference for structural diversity.

Nanotechnology, Natural Products, and Chemoprevention

Drug delivery plays a decisive role in the effectiveness of therapeutic and preventive strategies, particularly in oncology. Conventional delivery systems often suffer from poor solubility, rapid metabolism, and non-specific distribution, which limit the clinical utility of many promising natural compounds (39, 43). Nanotechnology addresses these

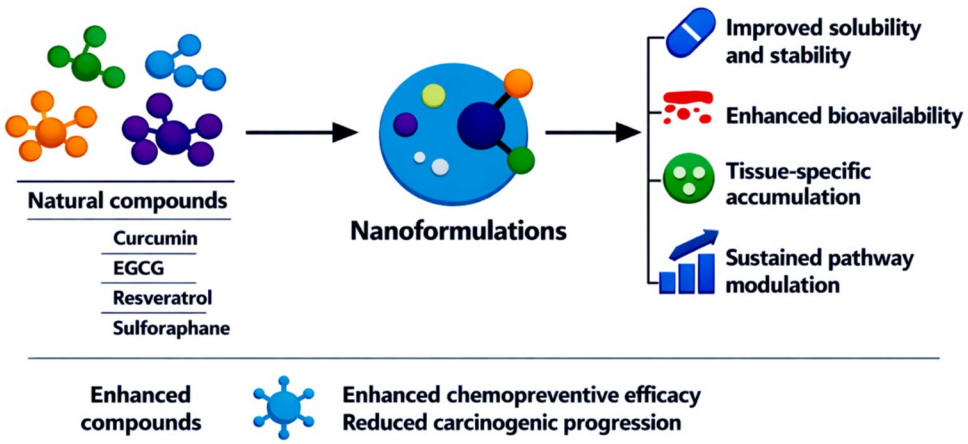

Fig. 7 Schematic representation of the mechanisms through which nanoformulations enhance the chemopreventive efficacy of natural compounds

limitations by enabling precise and efficient delivery of bioactive agents, improving therapeutic outcomes while reducing systemic toxicity (39, 43).

In cancer chemoprevention, nanoscale carriers enhance pharmacokinetics, stability, and bioavailability, thereby supporting the development of clinically viable formulations of natural products (17). This interdisciplinary approach draws on materials science, molecular biology, and pharmacology to engineer carriers capable of overcoming biological barriers and delivering phytochemicals directly to cancer cells (17). Nano-enabled formulations are mapped to physicochemical limitations (solubility, stability, targeting) and translational bottlenecks (41). Herbal-based nanoparticles are developed to improve payload solubility and tumor accumulation while preserving safety (48). Nano-enabled strategies are relevant for chemoprevention, where sustained low-dose exposure and improved tissue retention are essential for long-term efficacy.

Mechanistic Advantages of Nanotechnology in Chemoprevention

Nanotechnology enhances the performance of natural compounds through multiple, interrelated mechanisms. By improving delivery efficiency, nanoparticles minimize systemic toxicity and reduce adverse side effects, a critical advantage for long-term chemopreventive use (39, 43). They also improve pharmacological properties by extending half-life, increasing solubility, and stabilizing compounds against premature degradation, which collectively enhance tumor accumulation and therapeutic efficacy (39). Importantly, nanoparticles can overcome biological barriers, including the blood–brain barrier, enabling delivery of phytochemicals to tissues that are otherwise inaccessible (17). These improvements allow natural compounds to maintain preventive pathway modulation at physiologically relevant concentrations, rather than relying on high-dose cytotoxicity.

Targeted delivery further refines this approach by directing compounds specifically to tumor cells, thereby reducing off-target accumulation in vital organs such as the liver, spleen, and kidneys (18). Beyond delivery, nanotechnology supports enhanced diagnostics and imaging, allowing improved tumor site monitoring and evaluation of chemopreventive efficacy (22). Coupling natural compounds with imaging agents enables real-time *in vivo* assessment of drug distribution and activity (22). Nanocarriers also help overcome drug resistance by bypassing efflux pumps and directing agents to tumor sites (20).

Advances in synthetic vaccine development illustrate how nanotechnology can deliver tumor-associated antigens and adjuvants, offering novel strategies for cancer prevention (17). These mechanistic advantages demonstrate how nanotechnology transforms natural compounds from promising molecules into clinically viable chemopreventive agents. Figure 7 provides a schematic overview of how nanoformulations enhance chemopreventive efficacy by improving solubility, stability, bioavailability, tissue-specific accumulation, and sustained modulation of key signaling pathways. Nano-enabled advantages support effective low-dose, long-term preventive use and strengthen pathway engagement across early carcinogenic stages (17, 39, 41, 43).

Types of Nanoparticles Used in Natural Product Delivery

Several nanoparticle platforms have been developed to optimize the delivery of phytochemicals, each offering distinct advantages. Liposomes are biocompatible vesicles capable of encapsulating both hydrophilic and hydrophobic drugs, improving solubility and enabling targeted delivery (39). Polymeric nanoparticles, such as those based on PLGA and PCL-PEG, provide controlled release and enhanced stability, prolonging systemic circulation (18). Dendrimers, with their branched polymeric architecture, offer high drug-loading capacity and surface functionality, allowing precise delivery of natural compounds (17).

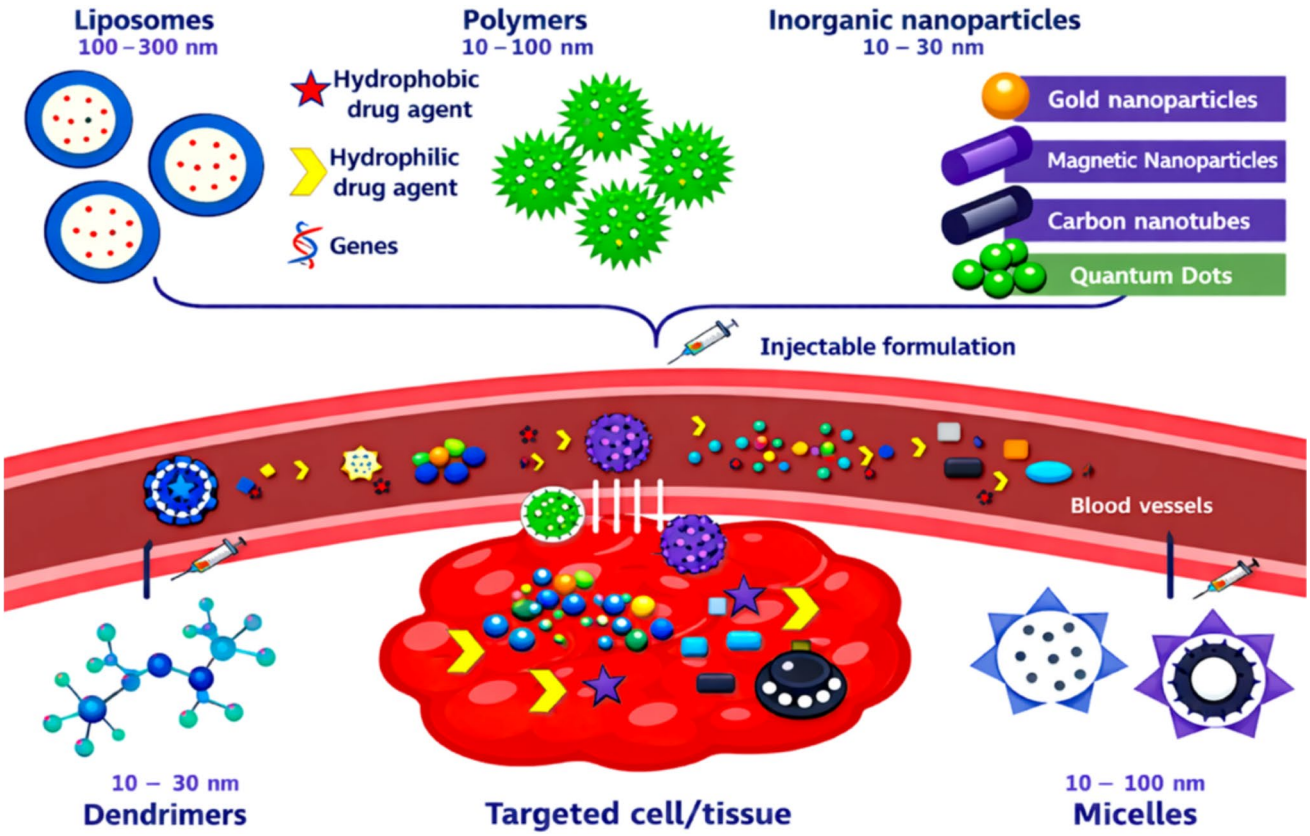

Fig. 8 Various types of nanoparticles and their mode of delivery systems

Magnetic nanoparticles enable site-specific delivery through external magnetic fields and can be applied in hyperthermia-based therapies (20). Inorganic nanoparticles, including silica and calcium phosphate systems, provide pH-sensitive release, optimizing drug delivery within tumor microenvironments (22). These platforms expand the chemopreventive potential of natural products by improving delivery efficiency, stability, and therapeutic precision. Delivery systems are valuable for chemoprevention, where sustained low-dose exposure and improved tissue retention are essential for long-term pathway modulation. Figure 8 schematically represents nanoparticle types and their modes of delivery in cancer therapy.

Integration of Nanotechnology With Natural Products: Case Studies

The integration of nanotechnology with natural compounds has yielded several promising nanoformulations. Curcumin, for example, suffers from poor bioavailability, but encapsulation in PCL-PEG-PCL nanoparticles significantly improves mean residence time and reduces clearance, enhancing tumor targeting and reducing off-target effects (9, 18). These improvements support chemopreventive use by enabling sustained low-dose exposure and consistent pathway engagement. Paclitaxel, when formulated as mesoporous silica nanoparticles, demonstrates improved tumor targeting and cytotoxicity in breast cancer models, while simultaneously reducing systemic toxicity (22, 36). Paclitaxel reflects therapeutic rather than chemopreventive activity; its inclusion illustrates broader mechanistic relevance of nano-enabled delivery.

Thymoquinone, delivered via liposomes or polymeric nanoparticles, shows enhanced bioavailability and apoptosis induction in glioblastoma models (33, 71). Resveratrol, encapsulated in PLGA nanoparticles, exhibits increased cytotoxicity against cancer cells by elevating intracellular reactive oxygen species and improving cellular uptake (10, 43). Genistein, when delivered through liposomal formulations, demonstrates improved stability and uptake in prostate cancer cells, enhancing anticancer efficacy (12, 29).

Nanovaccine platforms have emerged as a frontier in chemoprevention, enabling precise delivery of tumor-associated antigens and adjuvants. These systems enhance immune activation and offer theranostic capabilities for treatment and real-time monitoring to support personalized cancer prevention strategies (72). Case studies illustrate how nanotechnology rescues compounds with poor pharmacokinetics

and expands therapeutic scope. In chemopreventive contexts, nano-enabled enhancements allow natural compounds to maintain biological activity at physiologically relevant concentrations, strengthening early-stage pathway modulation and long-term preventive efficacy.

Translational Challenges and Considerations

Despite encouraging preclinical results, several challenges hinder the clinical translation of nanoformulated natural products. Nanoparticles often aggregate in biological environments, altering size and surface properties, which reduces biodistribution and therapeutic efficacy (39, 43). Immune system clearance further limits circulation time, and although PEGylation strategies can reduce recognition, they do not fully overcome this barrier (17, 18). These limitations are relevant for chemopreventive applications, where long-term, low-dose exposure requires stable and predictable nanoparticle behavior *in vivo*. Patient variability adds complexity, as differences in physiology can lead to inconsistent therapeutic outcomes, highlighting the need for personalized approaches (20, 22).

Large-scale manufacturing remains technically challenging and costly, with batch-to-batch variability and scalability issues hindering commercial production (17, 71). Regulatory delays also persist, as the absence of standardized evaluation protocols and long-term safety data slows approval processes (17, 39, 43). Such variability affects both preventive and therapeutic contexts, emphasizing the importance of adaptable nanoformulation strategies. Addressing translational barriers requires coordinated efforts among researchers, clinicians, and regulatory bodies to ensure reproducibility, safety, and clinical applicability. Overcoming these challenges is necessary for the promise of nanoformulated natural products to be realized in cancer chemoprevention. Continued progress in nanoparticle design, safety assessment, and scalable production will support the advancement of nanoformulated natural compounds toward preventive clinical applications.

Molecular Mechanisms

Cancer chemoprevention using nanotechnology-enhanced natural products leverages intricate molecular mechanisms to inhibit carcinogenesis at multiple stages, including initiation, promotion, and progression (8, 9). Compounds such as curcumin, EGCG, luteolin, genistein, resveratrol, paclitaxel, quercetin, sulforaphane, and thymoquinone target key signaling pathways, modulate gene expression, and regulate cellular processes to prevent tumor development (9, 10). Nanotechnology amplifies these effects by improving delivery precision, increasing bioavailability, and enabling targeted molecular interactions (39, 43). Nano-enabled enhancements support sustained low-dose pathway modulation, which is essential for chemopreventive rather than therapeutic activity.

Modulation of Oncogenic Signaling Pathways

Dysregulation of signaling pathways is a hallmark of cancer, driving uncontrolled proliferation, survival, and metastasis. The PI3K/AKT/mTOR pathway, frequently activated in breast, prostate, and thyroid cancers, promotes cell growth and suppresses apoptosis. Curcumin and resveratrol, delivered via polymeric nanoparticles, inhibit this pathway by suppressing AKT phosphorylation and mTOR activation, thereby restoring apoptotic signaling (9, 10, 43). Nano-enabled effects allow preventive modulation of PI3K/AKT/mTOR signaling at physiologically relevant concentrations. The Ras/MAPK pathway, critical in melanoma and colorectal cancers, is targeted by genistein-loaded liposomes, which downregulate ERK1/2 activity and halt cell cycle progression (12, 29).

The Wnt/β-catenin pathway, often dysregulated in colon and liver cancers, is inhibited by sulforaphane and quercetin in albumin-bound nanoparticles, reducing β-catenin nuclear translocation and oncogenic gene expression (34, 35). The JAK/STAT pathway, implicated in leukemia and breast cancers, is suppressed by luteolin and genistein nanoformulations, blocking STAT3 activation and cytokine-driven proliferation (11, 29).

Similarly, the NF-κB pathway, a central regulator of inflammation and survival, is inhibited by curcumin and resveratrol in liposomal systems, preventing IκB degradation and reducing COX-2 and IL-6 expression (9, 10). The Hedgehog and Hippo pathways, which regulate stem cell maintenance and organ size, are modulated by sulforaphane and curcumin nanoparticles, inhibiting Gli and YAP1/TAZ activity, respectively (9, 35). Nanoformulated natural products converge on multiple oncogenic pathways, enabling coordinated, multi-target chemopreventive activity across early carcinogenic stages.

Induction of Apoptosis and Cell Cycle Arrest

Apoptosis and cell cycle regulation are essential for eliminating damaged cells and preventing tumor formation. Nanoformulated natural compounds activate both intrinsic and extrinsic apoptotic pathways (9, 68). Curcumin encapsulated in PCL-PEG-PCL nanoparticles upregulates Bax and caspase-3 while downregulating Bcl-2, triggering mitochondrial dysfunction in breast and colorectal cancer cells. EGCG in polymeric nanoparticles enhances p53 expression and caspase-9 activation, promoting apoptosis in prostate and lung. Nano-enabled enhancements support sustained

apoptotic signaling at concentrations consistent with chemopreventive rather than high-dose therapeutic activity.

Paclitaxel, delivered via magnetic mesoporous silica nanoparticles, stabilizes microtubules and induces G2/M arrest with caspase-mediated apoptosis in ovarian and breast cancers (22, 36). Paclitaxel reflects therapeutic cytotoxicity; its inclusion illustrates mechanistic breadth rather than chemopreventive relevance. Thymoquinone in liposomal formulations induces DNA damage and telomere shortening, activating p53-dependent apoptosis in glioblastoma (33, 71). Quercetin and luteolin nanoformulations arrest the cell cycle at G2/M by upregulating p21 and inhibiting cyclin D1, preventing proliferation in liver and colon cancers (11, 34). These compound-specific findings are consistent with recent reviews, which emphasize the shared apoptotic signatures of natural products across multiple chemical classes (46). In chemopreventive contexts, nano-enabled apoptotic and cell-cycle effects contribute to early removal of damaged cells and suppression of malignant transformation.

Regulation of Oxidative Stress and DNA Repair

Oxidative stress and genomic instability contribute to carcinogenesis by inducing DNA damage and mutations. Nanoformulated natural compounds counteract these effects by enhancing antioxidant defenses and DNA repair mechanisms (9, 64). Resveratrol and sulforaphane in PLGA nanoparticles activate the Nrf2 pathway, upregulating superoxide dismutase, catalase, and glutathione peroxidase, thereby neutralizing reactive oxygen species in prostate and colorectal cancers ($\mathbf{IC_{50}}$ = 50 µM MCF-7 for resveratrol, 15 µM LNCaP for sulforaphane) (10, 35). Nano-enabled antioxidant responses help maintain redox balance at concentrations compatible with long-term chemopreventive use.

Curcumin nanoparticles enhance base excision repair and non-homologous end joining, protecting healthy cells from arsenic-induced damage while inducing lethal DNA damage in cancer cells ($\mathbf{IC_{50}}$ = 18.25 µM BxPC-3) (9, 19). EGCG in liposomal systems reduces oxidative stress by modulating PI3K/AKT and NF-κB, enhancing DNA repair in normal cells while promoting apoptosis in breast cancer cells ($\mathbf{IC_{50}}$ = 37.7 µM MCF-7) (30, 43). Genistein nanoformulations stabilize p53 and PTEN, inhibiting ROS-driven mutations and preventing tumor initiation in ovarian cancers ($\mathbf{IC_{50}}$ = 10 µM MCF-7) (12, 29). These findings highlight the dual role of nanoformulated natural products in protecting normal cells while selectively inducing genomic stress in malignant cells. This duality is central to chemoprevention, enabling preservation of genomic integrity in healthy tissues while suppressing early malignant transformation. While IC_{50} values are commonly reported for natural compounds in *in vitro* studies, they primarily reflect cytotoxicity rather than chemopreventive potency. These values should be interpreted with caution, as they do not directly translate to preventive efficacy *in vivo* (41, 45, 46). The comparative IC_{50} data are shown in Table II.

Inhibition of Inflammation and Metastasis

Chronic inflammation and metastasis are major drivers of cancer progression. Nanoformulated natural compounds suppress inflammatory pathways and inhibit epithelial-mesenchymal transition (EMT). Curcumin and luteolin in polymeric nanoparticles inhibit NF-κB and COX-2, reducing TNF-α and IL-6 levels and attenuating inflammation-driven tumorigenesis in pancreatic and lung cancers (9, 11). Anti-inflammatory effects support chemopreventive activity by limiting early microenvironmental changes that facilitate malignant transformation.

Resveratrol and thymoquinone in liposomal systems block EMT by upregulating E-cadherin and downregulating Snail and Twist, thereby inhibiting migration in glioblastoma and breast cancers (10, 33). Paclitaxel nanoparticles target the Wnt/β-catenin pathway, reducing mesenchymal markers and preventing metastasis in ovarian cancers (22, 36). Paclitaxel represents therapeutic cytotoxicity rather than chemopreventive activity; its inclusion reflects mechanistic breadth. Genistein in albumin-bound systems modulates the PTEN/AKT pathway, suppressing invasion in prostate cancers (12, 29). Nanoformulated natural products suppress inflammation and disrupt metastatic signaling, reducing the risk of tumor spread. In chemopreventive contexts, nano-enabled effects help maintain tissue homeostasis and prevent early dissemination events that contribute to malignant progression.

Clinical Translation

The clinical translation of nanotechnology-enhanced natural products for cancer chemoprevention holds potential to address the global cancer burden. By overcoming limitations of natural compounds, such as poor bioavailability, rapid metabolism, and non-specific distribution, scalable nanoformulation strategies enable safer, more effective, and accessible preventive interventions (39, 43, 72). Nanoformulations align with principles of precision oncology, allowing tailored interventions that minimize off-target effects, as demonstrated by targeted delivery systems for phytochemicals (17, 73). Recent reviews emphasize that while clinical progress remains limited, integration of nanomedicine with natural products is advancing, supported by innovations in biomimetic carriers, stimuli-responsive systems, and AI-assisted formulation design (41, 74). These developments strengthen the translational foundation for chemopreventive

Table III Key Clinical Trials of Nanoformulated Natural Products: Phase, Endpoints, Nano-platform Type, and Outcomes

Compound	Nano-platform (Trial ID)	Phase	Endpoints	Outcomes	References
Paclitaxel	Albumin-bound nanoparticle (NCT00887136)	II/III	Efficacy, safety	Improved targeting, reduced toxicity	[51, 52]
Curcumin	Liposome/Polymer (NCT02944578)	I/II	Bioavailability, safety	Prolonged circulation, enhanced bioavailability	[9, 19]
EGCG	Liposome (NCT01360320)	I	Stability, uptake	Enhanced uptake, improved stability	[30, 43]
Genistein	Polymeric nanoparticle (NCT00244933)	I/II	Pharmacokinetics, safety	Enhanced pharmacokinetics profile	[29]
Sulforaphane	Polymeric nanoparticle (NCT01228084)	I	Efficacy, safety	Entering clinical evaluation	[35, 70, 73]

applications, where long-term safety and consistent biological activity are essential.

Progress in Clinical Trials

Several nanotechnology-enhanced natural products have advanced to clinical evaluation, underscoring translational potential. Paclitaxel, formulated as albumin-bound nanoparticles (nab-paclitaxel), has been approved for breast, lung, and pancreatic cancers, demonstrating improved tumor targeting and reduced toxicity compared to conventional formulations, with $\mathbf{IC_{50}}$ values of 0.22 µM (MCF-7) and 0.00319 µM (SKOV-3) (22, 36). Clinical work continues albumin-bound paclitaxel beyond breast and pancreas, including sarcoma interest and ovarian neoadjuvant combinations with carboplatin, emphasizing platform flexibility (51, 52). Paclitaxel represents therapeutic cytotoxicity rather than chemopreventive activity; its success illustrates how nano-enabled delivery platforms can achieve regulatory approval and clinical adoption.

Curcumin, encapsulated in liposomal and polymeric nanoparticles, has entered phase I/II trials for colorectal and pancreatic cancers, showing enhanced bioavailability and prolonged circulation, with $\mathbf{IC_{50}}$ values of 18.39 µM (HT-29) and 18.25 µM (BxPC-3) (9, 19). Resveratrol in PLGA nanoparticles is under early-phase investigation for glioblastoma, with preliminary data reporting increased apoptosis and reduced systemic toxicity (10, 43).

EGCG in liposomal formulations is being evaluated for breast and prostate cancer prevention, with phase I studies showing improved stability and uptake (30, 43). Genistein and quercetin, delivered via polymeric nanoparticles, are in early-phase trials for prostate and liver cancers, respectively, with preliminary data indicating enhanced pharmacokinetic profiles (29, 34). These trials highlight the feasibility of nanoformulated natural products in clinical settings, supported by favorable safety profiles and biological activity (17). The success of nab-paclitaxel underscores the importance of scalable nanoformulations, paving the way for other compounds such as sulforaphane ($IC_{50} = 15$ µM LNCaP) to enter clinical evaluation (35, 70, 73).

Recent analyses emphasize that although only a limited number of phytochemical nanoformulations have progressed to human trials, the clinical pipeline is steadily widening. Among the most advanced candidates are sulforaphane, curcumin, and EGCG, which exemplify how nanotechnology can translate dietary compounds into viable chemopreventive interventions (41). Emerging clinical data indicate that nano-enabled phytochemicals are beginning to bridge the gap between preclinical promise and preventive clinical application. Table III maps key clinical trials, including phase, endpoints, nano-platform type, and outcomes for each compound.

Challenges in Clinical Translation

Despite encouraging preclinical results, several barriers hinder the clinical translation of nanoformulated natural products. Nanoparticle aggregation in biological environments reduces efficacy, necessitating advanced surface modifications (39, 43). Immune clearance by the reticuloendothelial system limits circulation time, requiring stealth coatings such as PEGylation (17). Variability in patient responses, driven by genetic and physiological differences, complicates therapeutic outcomes and highlights the need for personalized approaches (19). Large-scale manufacturing remains technically complex and costly, with batch-to-batch variability limiting reproducibility (39, 43). Regulatory delays, due to the absence of standardized evaluation protocols and long-term safety data, further impede progress (17). These regulatory constraints are particularly stringent for chemopreventive applications, where long-duration exposure demands higher safety assurance than short-term therapeutic use.

A major barrier for chemopreventive nanoformulations is the lack of long-duration safety studies, as most nanocarriers have been evaluated in short-term therapeutic models rather than chronic preventive settings. Regulatory agencies

increasingly require extended biodistribution, immunogenicity, and toxicokinetic assessments for long-term use, yet such datasets remain limited for phytochemical nanoformulations (70, 73). Scalability also restricts translation, as many nanoformulations rely on laboratory-scale synthesis methods that are difficult to reproduce under GMP conditions, particularly for polymeric and biomimetic systems (41, 74**).** These challenges are compounded by the need to balance efficacy, safety, and affordability in low-resource settings, where cancer incidence is rising most rapidly (43, 74). Together, these barriers illustrate the gap between preclinical promise and real-world preventive deployment, underscoring the need for harmonized regulatory, manufacturing, and safety frameworks tailored to chemopreventive nanoformulations. The comparative IC_{50} data are shown in Table II.

Strategies for Overcoming Translational Barriers

Several strategies are being developed to address these challenges. Multifunctional nanoparticles capable of co-delivery, imaging, and tumor-specific responsiveness have demonstrated improved therapeutic precision. pH-responsive nanoparticles, for example, enhance drug release at tumor sites, as shown in curcumin and paclitaxel formulations. pH-responsive nanoparticles have enhanced drug release at tumor sites, as shown in curcumin and paclitaxel formulations, with $\mathbf{IC_{50}}$ values of 18.39 µM (HT-29) and 18.25 µM (BxPC-3) for curcumin (9, 19), and 0.22 µM (MCF-7) and 0.00319 µM (SKOV-3) for paclitaxel (22, 36). Responsive systems are valuable for chemoprevention, where controlled, low-dose release can sustain long-term pathway modulation without inducing toxicity.

Precision medicine approaches, supported by molecular diagnostics and theranostic technologies, are enabling patient-specific nanoformulations. Biomarker-driven trials are currently evaluating sulforaphane and thymoquinone, with $\mathbf{IC_{50}}$ values of 15 µM (LNCaP) for sulforaphane (35) and 75 µM (U87MG) for thymoquinone (33). Biomarker-guided strategies align with chemopreventive goals, allowing early intervention in high-risk populations. Standardized safety protocols and long-term toxicity studies are essential to ensure biocompatibility. Preclinical models have provided supporting data for luteolin and genistein, with $\mathbf{IC_{50}}$ values of 48 µM (MCF-7) for luteolin (11) and 25 µM (LNCaP) for genistein (29).

Advances in scalable manufacturing, including microfluidics and continuous-flow synthesis, show potential to reduce production costs and improve reproducibility (17, 39). Interdisciplinary collaboration among researchers, clinicians, and regulatory agencies is also critical. Ongoing initiatives involving resveratrol and EGCG are contributing to this effort, with $\mathbf{IC_{50}}$ values of 50 µM (MCF-7) for resveratrol (10) and 37.7 µM (MCF-7) and 27.12 µM (A549) for EGCG (30). The use of microfluidics has also demonstrated promise in producing uniform nanoparticles for thymoquinone, potentially reducing manufacturing costs in glioblastoma applications (33).

Recent reports highlight microfluidics as a promising approach for producing uniform nanoparticles, including thymoquinone formulations for glioblastoma, with reduced costs and improved reproducibility (41). These $\mathbf{IC_{50}}$ values are provided for comparative purposes and should be interpreted with caution, as they primarily reflect cytotoxicity *in vitro* and do not directly translate to chemopreventive efficacy *in vivo*. The comparative $\mathbf{IC_{50}}$ data are shown in Table II. Long-duration safety evaluation is critical for preventive applications, where exposure extends far beyond typical therapeutic windows. Technological and collaborative advances strengthen the translational pathway for chemopreventive nanoformulations, supporting progression toward real-world preventive use.

Future Outlook and Global Impact

The future of clinical translation for nanotechnology-enhanced natural products lies in integrating advanced technologies with global collaboration. Machine learning and computational modeling can predict nanoparticle behavior and optimize formulations, as seen in studies with quercetin and sulforaphane (34, 35). Theranostic nanoparticles, combining diagnostics and therapy, enable real-time monitoring of treatment efficacy, with applications in paclitaxel and curcumin trials (9, 19, 22, 36).

Public–private partnerships can accelerate translation by funding large-scale trials and manufacturing, as demonstrated with (33, 36). Cost-effective nanoformulations offer a practical approach to reducing disparities in access to treatment, particularly in low- and middle-income countries. Bioactive compounds such as thymoquinone and genistein represent promising examples of such formulations (29, 33). These developments highlight how nano-enabled phytochemicals can be adapted for preventive use in diverse healthcare systems, including settings with limited resources.

Regulatory harmonization across regions can streamline approval processes, facilitating global adoption (39, 43). By leveraging these strategies, nanotechnology-enhanced natural products can transform cancer chemoprevention, reduce incidence, and improve outcomes worldwide (17). Clinical translation of these nanoformulations is a multidisciplinary effort with the potential to advance preventive oncology (72, 73). Realization of their full impact depends on innovation, validation, and equitable access across diverse healthcare settings.

Global initiatives, including cancer control programs led by international health organizations, have the capacity

to incorporate cost-effective and scalable nanoformulation strategies such as sulforaphane (IC_{50} = 15 μM LNCaP) to address cancer disparities in underserved populations (35, 73). Such integration would position nanoformulated natural products as accessible, population-level chemopreventive tools capable of contributing to global cancer reduction efforts.

Discussion

The increasing global burden of cancer has created a demand for safer and more affordable therapeutic alternatives. Conventional treatments, such as chemotherapy and radiotherapy, while effective, are often associated with severe side effects and high costs, limiting long-term use and accessibility, especially in low-resource settings (9, 17). Nanotechnology-enhanced natural products have emerged as promising candidates for cancer chemoprevention due to their favorable safety, affordability, and broad biological activity. Among the most studied compounds are curcumin, EGCG, luteolin, genistein, resveratrol, paclitaxel, quercetin, sulforaphane, and thymoquinone, representing diverse chemical classes with demonstrated chemopreventive effects (9, 30). Multitarget activity and favorable safety profiles make them suitable for long-term preventive use.

Natural compounds act through multiple mechanisms to exert anticancer effects. Apoptosis induction plays a central role in eliminating abnormal cells and preventing tumor progression, as seen with curcumin and paclitaxel (9, 36). Additional mechanisms include anti-inflammatory activity, cell cycle regulation, and modulation of oxidative stress and oncogenic signaling pathways, such as NF-κB and PI3K/AKT (10, 19). Despite biological potency, many compounds exhibit poor bioavailability, rapid metabolism, and limited systemic distribution.

These limitations have led to the application of nanotechnology to improve pharmacokinetic profiles. The ability of natural compounds to target multiple pathways simultaneously, such as NF-κB and PI3K/AKT, offers a synergistic advantage over single-target therapies, as demonstrated by resveratrol in glioblastoma (10, 43). In chemopreventive contexts, multi-pathway modulation supports early intervention and sustained suppression of carcinogenic processes.

Nanotechnology provides a platform to address the delivery challenges of natural compounds. Nanoformulations, such as liposomes, polymeric nanoparticles, and pH-responsive systems, enhance solubility, stability, and targeted delivery (39, 43). Paclitaxel encapsulated in poly β-amino ester nanoparticles has shown increased cytotoxicity in breast cancer cells (22, 36). Resveratrol loaded into PLGA nanoparticles has demonstrated enhanced intracellular reactive oxygen species generation and apoptosis in glioma cells (10, 43). Curcumin delivered via PCL-PEG-PCL nanoparticles has exhibited prolonged circulation and reduced clearance (9, 19).

These examples demonstrate the potential of nanotechnology-enhanced natural products to improve the therapeutic performance of phytochemicals. The application of theranostic nanoparticles in nanovaccine platforms, which combine imaging and therapeutic functions, has shown promise in enhancing clinical outcomes (72). Preclinical studies involving EGCG have further supported this approach (17, 30). In chemopreventive contexts, multi-pathway modulation supports early intervention and sustained suppression of carcinogenic processes.

Several nanoformulated natural compounds have progressed to clinical trials. However, challenges remain in translating preclinical success into clinical application. Regulatory complexity, immune clearance, and the absence of long-term safety data are significant barriers. The scalability of nanoparticle production and the lack of standardized evaluation protocols further complicate clinical adoption (17, 39).

Interdisciplinary collaboration among researchers, clinicians, pharmacologists, and regulatory authorities is necessary to develop reproducible and safe nanoformulations suitable for clinical use (43). Patient-centered trial designs, incorporating real-world evidence, could accelerate validation of nanoformulations like quercetin (IC_{50} = 5.25 μM A549), addressing variability in clinical responses (34). Such approaches are important for chemopreventive agents, where long-term safety, adherence, and population-level applicability must be rigorously evaluated. This IC_{50} value is provided for comparative purposes and should be interpreted with caution, as it primarily reflects cytotoxicity *in vitro* and does not directly translate to chemopreventive efficacy *in vivo*. The comparative IC_{50} data are shown in Table II.

Challenges and Future Directions

Future research in cancer chemoprevention should prioritise multifunctional nanoparticle systems capable of co-delivery, real-time imaging, and tumour-specific responsiveness (39, 41). Precision-medicine-guided approaches are increasingly recognised as essential for tailoring nanoformulations to individual risk profiles, enabling more effective and safer preventive interventions (75). In this context, standardised safety protocols and long-term toxicological evaluations are critical to assess the biocompatibility of repeated or chronic nanoparticle exposure (76). Particular emphasis should be placed on biodegradable nanocarriers, such as those developed for sulforaphane delivery, which offer predictable degradation and reduced accumulation, thereby minimising long-term toxicity risks (35, 39). These design

considerations are especially important for chemopreventive applications, where sustained low-dose exposure is required over extended periods rather than short-term therapeutic administration (41).

Multi-omics approaches provide a framework for defining response heterogeneity, identifying molecular signatures linked to preventive benefit or adverse effects, and optimising intervention strategies across complex biological systems (77, 78). In particular, epigenetic modulation has emerged as a key mechanistic layer underlying long-term cancer risk reduction, reinforcing the relevance of epigenomic endpoints in chemoprevention research (79).

Clinical translation remains a major bottleneck despite promising preclinical evidence (39, 41, 43). Longitudinal clinical trials are required to establish dose relevance, safety, and preventive efficacy of nanoformulated natural products in populations at elevated cancer risk (43, 75). Coordinated frameworks involving oncologists, pharmacologists, toxicologists, and regulatory agencies are required to support trial design and regulatory alignment for prevention-specific nanomedicines (75, 78). International collaborative consortia and shared trial infrastructures may facilitate protocol standardisation and accelerate global adoption of validated chemopreventive nanotechnologies (51, 52, 70).

Looking ahead, computational modelling and artificial-intelligence-guided optimisation are increasingly relevant for predicting targets, ADME properties, and safety profiles, supporting rational formulation development and reducing experimental inefficiency (80). Whole-body exposome modelling provides a complementary systems framework for integrating environmental, lifestyle, and biological inputs into population-level risk stratification and preventive planning (81). These computational approaches can support scalable chemopreventive strategies when combined with delivery innovation and systems-level biological interpretation (39, 80, 81).

Conclusion

This review explores the emerging role of nanotechnology-enhanced natural products in cancer chemoprevention, integrating molecular mechanisms, delivery strategies, and translational considerations that underpin their potential for long-term preventive use. Nanotechnology-enhanced natural products provide an effective and patient-friendly alternative. Preclinical and emerging clinical studies highlight the chemopreventive potential of phytochemicals like curcumin, paclitaxel, and resveratrol, particularly when delivered through advanced nanocarriers. These systems enhance drug solubility, prolong circulation, and enable targeted delivery to tumor tissues, maximizing therapeutic efficacy while minimizing side effects. In chemopreventive contexts, these nano-enabled advantages support sustained, low-dose biological activity suitable for long-term use.

Future efforts should focus on exploring underutilized natural compounds and optimizing their scalable nanoformulation strategies through rigorous pharmacological and toxicological studies. The development of multifunctional, patient-specific delivery systems, guided by precision medicine, will be crucial for translating laboratory success into clinical applications. Nanotechnology-enhanced natural products research represents a versatile and multidisciplinary frontier with the potential to revolutionize cancer prevention and treatment. Through sustained innovation, collaboration, and clinical validation, this approach can lead to safe, cost-effective, and accessible therapies that improve outcomes globally. As regulatory frameworks, manufacturing technologies, and predictive design tools continue to advance, nanoformulated phytochemicals are increasingly positioned to contribute meaningfully to population-level cancer prevention.

Acknowledgements We are thankful to the DBT-NER project (Sanction Order: BT/PR25123/NER/95/1027/2017) for their support and the Bioinformatics Centre, Assam University, Silchar, for the software support through DBT-Bioinformatics Infrastructure Facility, and e-journal access facility through DBT e-Library Consortium (DeLCON). Lutfun Nahar gratefully acknowledges the salary support from the European Regional Development Fund (Project ENOCH #CZ.02.1.01/0.0/0.0/16_019/0000868) and the Czech Science Foundation (Project #23-05474S).

Authors Contributions All authors contributed equally to the data collection and compilation of information. **Rajat Nath:** Writing—original draft. **Sibashish Kityania**: Writing: original draft. **Deepa Nath:** Writing—original draft. **Jayanta Kumar Patra**: Writing-original draft. **Emran Habibi**: Writing—original draft, drawing structures, and software. **Satyajit D. Sarker**: Conceptualization, Writing—review & final editing, drawing structures, and software. **Anupam Das Talukdar**: Conceptualization, Methodology, Writing—review & final editing. **Lutfun Nahar**: Conceptualization, Methodology, Writing- original review & final editing. All authors reviewed the final version.

Funding No funding was received for this publication.

Data Availability No data was used for the research described in the article.

Declarations

Ethics This manuscript does not include human or animal research.

Conflict of interest There is no conflict of interest.

Competing interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review article.

A.I. Statement AI technology was used to assist in drafting one preliminary figure concept. All final figures included in the manuscript were prepared and finalized by the authors.

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