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Review Paper

Natural Chemopreventive Agents in Cancer Prevention and Supportive Therapy: Mechanisms, Clinical Evidence, and Future Perspectives

Esther Jose, Reeshma R., Dr. Musthaq Ahmed*

Microbiology, Virology, Immunology, Fergana Medical Institute of Public Health, Uzbekistan.

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ABSTRACT

Cancer ranks among the foremost causes of global mortality, underpinned by intricate interactions among genetic predispositions, environmental carcinogens, and modifiable lifestyle determinants. Conventional therapeutic modalities — encompassing surgical resection, cytotoxic chemotherapy, ionising radiation, and molecularly targeted agents — have substantially improved outcomes in selected patient populations; however, dose-limiting toxicities, therapeutic resistance, and high recurrence rates continue to constrain their clinical utility. Over recent decades, phytochemicals derived from dietary spices and culinary herbs have emerged as biologically active entities with demonstrable chemopreventive and adjunctive anticancer properties. This review critically synthesises the mechanisms, preclinical evidence, and clinical trial data pertaining to eight well-characterised natural agents — curcumin (*Curcuma longa*), eugenol (*Syzygium aromaticum*), cinnamaldehyde (*Cinnamomum* spp.), gingerol (*Zingiber officinale*), crocin (*Crocus sativus*), allicin (*Allium sativum*), d-limonene (citrus peel), and piperine (*Piper nigrum*). These compounds exert their anticancer effects through multiple non-redundant pathways, including suppression of the NF- κ B and PI3K/Akt/mTOR signalling axes, induction of mitochondria-mediated apoptosis, cell cycle arrest, anti-angiogenesis via VEGF downregulation, and modulation of epigenetic marks. Persistent translational barriers — principally inadequate oral bioavailability, absence of standardised therapeutic dosing, and a paucity of large-scale randomised controlled trials — continue to limit clinical implementation. Emerging nanotechnology-based delivery platforms and artificial intelligence-assisted phytochemical screening represent promising avenues toward overcoming these obstacles. This review concludes that natural chemopreventive agents, when rigorously evaluated and properly formulated, represent a scientifically rational adjunct to evidence-based oncological care.

*Corresponding Author: Dr. Musthaq Ahmed

Address: Microbiology, Virology, Immunology, Fergana Medical Institute of Public Health, Uzbekistan

Email ✉: musthaq.biotechnology@gmail.com

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INTRODUCTION

Cancer remains one of the most significant public health challenges of the twenty-first century, accounting for an estimated 19.3 million new diagnoses and 10.0 million deaths globally in 2020 alone [1]. Despite remarkable advances in surgical technique, targeted molecular therapy, and immuno-oncology, morbidity and mortality from malignancies of the lung, breast, colorectum, and prostate remain disproportionately high, particularly in low- and middle-income countries where access to advanced treatment is limited [1,2]. Chemoprevention, broadly defined as the administration of pharmacological or nutritional agents to arrest, reverse, or retard carcinogenic progression at the initiation, promotion, or progression stage, represents a strategically attractive and cost-effective complement to curative treatment [2,3]. Among chemopreventive candidates, plant-derived phytochemicals have attracted the most sustained scientific interest, underpinned by epidemiological observations that populations adhering to spice-rich dietary patterns exhibit markedly lower incidences of several cancers [3,4]. A broad array of biologically active secondary metabolites — polyphenols, terpenoids, alkaloids, and organosulfur compounds — are abundant in commonplace culinary spices and herbs including turmeric, cloves, cinnamon, ginger, saffron, and garlic. These molecules typically exert pleiotropic pharmacological effects, impeding multiple hallmarks of cancer simultaneously: they suppress chronic inflammation, neutralise reactive oxygen species, promote apoptosis in transformed cells, interfere with angiogenesis, and modulate the

immunological landscape of the tumour microenvironment [3,17,18].

The cardinal limitation of conventional oncological therapy — namely the generation of systemic toxicity through off-target cytotoxicity — renders the identification of selective, low-toxicity adjuvant agents a high-priority research endeavour. Natural phytochemicals, with their long history of dietary safe use and broad mechanistic repertoire, are particularly well positioned to fulfil this adjuvant role. Nevertheless, translating preclinical promise into validated clinical benefit requires careful attention to bioavailability, dose standardisation, and rigorous randomised trial design [2,4].

This review undertakes a comprehensive and critically appraised synthesis of the scientific literature on eight major natural chemopreventive agents — curcumin, eugenol, cinnamaldehyde, gingerol, crocin, allicin, d-limonene, and piperine. Each compound is discussed with respect to its phytochemical identity, molecular mechanism of anticancer action, epidemiological and clinical evidence, known limitations, and future research directions.

2. Epidemiology of Major Cancer Types

Understanding the global epidemiological burden of cancer is foundational to contextualising the potential impact of chemopreventive strategies. The World Health Organisation (WHO) and the International Agency for Research on Cancer (IARC) provide biennial updates through the GLOBOCAN database, which forms the primary evidence base for incidence and mortality estimates discussed in this section [1].



Figure 2. Global Cancer Incidence and Associated Risk Factors (2022 WHO Data)

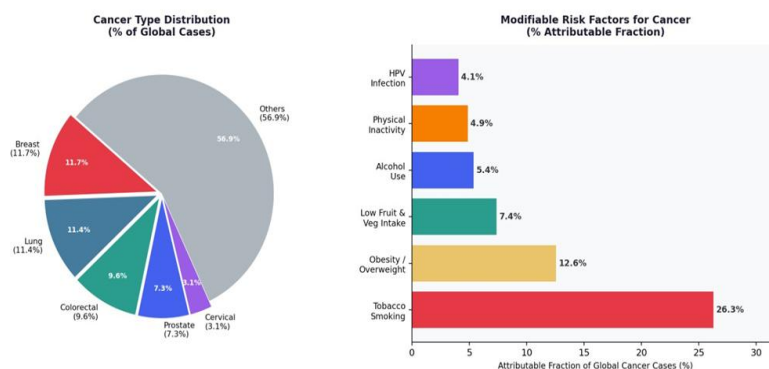


Figure 2. (Left) Distribution of global cancer incidence by type (GLOBOCAN 2020 data). (Right) Major modifiable risk factors and their attributable fraction of global cancer burden. Data adapted from Sung et al. (2021) [1].

2.1 Lung Cancer

Lung cancer constitutes the leading cause of cancer-related mortality globally, responsible for approximately 18% of all cancer deaths [1]. It is pathologically dichotomised into non-small cell lung cancer (NSCLC, ~85%) and small cell lung cancer (SCLC, ~15%). The principal aetiological factor is tobacco smoke, which contributes to approximately 85% of cases; however, exposure to radon gas, occupational asbestos, ambient air pollution, and inherited genetic susceptibility (e.g., EGFR and KRAS mutations) also contribute significantly [19]. Despite the advent of EGFR-targeted tyrosine kinase inhibitors and PD-L1 immune checkpoint blockade, five-year survival for metastatic NSCLC remains below 10% [19].

2.2 Breast Cancer

Breast cancer is the most frequently diagnosed malignancy in women worldwide, accounting for 11.7% of all new cancer diagnoses [1]. Incidence is highest in high-income countries; however, absolute mortality is disproportionately concentrated in low-income settings owing to late-stage presentation and limited access to hormone receptor profiling and targeted therapy [4,20]. Established risk factors include oestrogen exposure duration, BRCA1/BRCA2 germline mutations, nulliparity, advanced maternal age at

first birth, and excess adiposity in postmenopausal women [20].

2.3 Colorectal Cancer

Colorectal cancer (CRC) ranks third in global cancer incidence and second in mortality [1]. The pathogenesis integrates a complex interplay of dietary risk factors (high red and processed meat consumption, low dietary fibre), metabolic dysregulation (insulin resistance, adiposity), lifestyle determinants (physical inactivity, alcohol, smoking), and inherited syndromes such as Lynch syndrome and familial adenomatous polyposis [21]. The acquisition of sequential somatic mutations in APC, KRAS, SMAD4, and TP53, known as the adenoma-carcinoma sequence, underpins the majority of sporadic CRC cases and provides multiple druggable nodes for chemopreventive intervention [21].

2.4 Prostate Cancer

Prostate cancer ranks as the second most common malignancy in men globally [1]. Incidence rises sharply with age, and rates are highest among African American men, a disparity likely attributable to both socioeconomic access barriers and androgen receptor polymorphisms [22]. The disease exhibits extreme clinical heterogeneity ranging from indolent, surveillance-managed lesions to lethal castration-resistant prostate cancer

(CRPC), which retains only limited responsiveness to docetaxel-based chemotherapy and novel androgen receptor signalling inhibitors [22].

2.5 Cervical Cancer

Cervical cancer remains the fourth most common cancer in women globally and the leading gynaecological malignancy in sub-Saharan Africa and South Asia [1,23]. Persistent infection by high-risk human papillomavirus (HPV) genotypes — particularly HPV-16 and HPV-18 — is causally implicated in over 99% of cases. The virus-induced disruption of the E6/E7 oncoproteins,

which inactivate the tumour suppressors p53 and Rb respectively, drives epithelial transformation. Prophylactic vaccination and organised cervical cytology screening programmes have proven highly effective where access permits [23].

3. Phytochemical Profiles of Major Natural Chemopreventive Agents

Table 1 provides an integrated summary of the phytochemical identity, primary molecular targets, cancer types studied, and mechanistic profiles of eight key natural chemopreventive compounds reviewed in this article.

Table 1. Phytochemical Profiles, Molecular Targets, and Mechanistic Properties of Principal Natural Chemopreventive Agents

Spice / Plant Source	Key Bioactive Compound(s)	Chemical Class	Primary Molecular Target(s)	Cancer Types Studied	Proposed Mechanism
Turmeric (<i>Curcuma longa</i>)	Curcumin, bisdemethoxycurcumin	Polyphenol	NF- κ B, STAT3, Nrf2, PI3K/Akt	Breast, colorectal, prostate, lung, pancreatic	Anti-inflammatory, pro-apoptotic, antioxidant, cell cycle arrest
Cloves (<i>Syzygium aromaticum</i>)	Eugenol, β -caryophyllene, kaempferol	Phenylpropanoid / Flavonoid	NF- κ B, Bcl-2, VEGF, caspase-3/9	Breast, lung, gastric, cervical	Apoptosis induction, anti-angiogenesis, anti-metastatic
Cinnamon (<i>Cinnamomum</i> spp.)	Cinnamaldehyde, procyanidin-B2	α,β -unsaturated aldehyde / Proanthocyanidin	PI3K/Akt/mTOR, Wnt/ β -catenin	Melanoma, colorectal, cervical, lymphoma	Apoptosis, autophagy, angiogenesis suppression
Ginger (<i>Zingiber officinale</i>)	Gingerol, shogaol, zerumbone	Phenylalkylketone / Sesquiterpene	TNF- α , COX-2, NF- κ B, caspase pathway	Colorectal, ovarian, hepatic, pancreatic	Anti-inflammatory, apoptosis, anti-proliferative

NF- κ B: nuclear factor kappa B; PI3K/Akt/mTOR: phosphoinositide 3-kinase / protein kinase B / mechanistic target of rapamycin; VEGF: vascular endothelial growth factor; PCNA: proliferating cell nuclear antigen; NSCLC: non-small cell lung cancer

3.1 Turmeric (*Curcuma longa*) and Curcumin

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], the principal hydrophobic polyphenolic curcuminoid isolated

from the rhizomes of *Curcuma longa*, constitutes approximately 2–5% of dried turmeric powder by weight [24,27]. It is structurally characterised by two ferulic acid moieties bridged by a methylene group and exhibits a pronounced capacity for

Michael acceptor reactions and metal chelation, contributing to its broad pharmacological activity [3,24].

At the molecular level, curcumin exerts its anticancer activity through simultaneous modulation of multiple signalling cascades. Its most extensively characterised mechanism is the suppression of NF- κ B activation: curcumin inhibits I κ B kinase (IKK), thereby preventing nuclear translocation of p65 and subsequent transcription of pro-inflammatory and anti-apoptotic genes including Bcl-2, cyclin D1, COX-2, and matrix metalloproteinase-9 (MMP-9) [27,32]. Concurrently, curcumin activates the Nrf2-Keap1 cytoprotective pathway, upregulating phase II detoxification enzymes and reducing carcinogen bioactivation [3]. Downstream consequences include: caspase-3 and caspase-9 mediated apoptosis in transformed epithelial cells; G2/M cell cycle arrest through p21^{ce¹} upregulation; and anti-angiogenic effects mediated by reduction of VEGF and basic fibroblast growth factor (bFGF) expression [31].

A notable physiochemical limitation of curcumin is its extremely poor oral bioavailability, estimated at less than 1% in humans following conventional oral administration, owing to rapid intestinal metabolism (glucuronidation and sulphation), hepatic first-pass metabolism, and inherent water insolubility [34]. Co-administration with piperine has been demonstrated to enhance curcumin bioavailability by approximately 20-fold through inhibition of UDP-glucuronyltransferases and P-glycoprotein-mediated efflux [34].

Nanoparticulate formulations — including poly(lactic-co-glycolic acid) (PLGA) nanoparticles, liposomes, and solid lipid nanoparticles — offer further improvements in solubility and targeted cellular uptake [34].

3.2 Cloves (*Syzygium aromaticum*) and Eugenol

Eugenol [4-allyl-2-methoxyphenol] constitutes 70–90% of clove essential oil and belongs to the phenylpropanoid class of plant secondary metabolites [35]. Its structure incorporates a guaiacyl moiety responsible for its radical-scavenging and electrophilic properties, enabling it to covalently modify reactive cysteine residues within transcription factor activation domains [7,35]. Eugenol selectively induces apoptosis in a diverse array of transformed cell lines — including breast (MCF-7 and MDA-MB-231), lung (A549), gastric (AGS), and cervical (HeLa) cancer cells — with minimal cytotoxicity towards normal human fibroblasts [7,35]. The molecular basis involves activation of the intrinsic mitochondrial apoptotic pathway, evidenced by: loss of mitochondrial transmembrane potential ($\Delta\Psi$ m); cytochrome c release into the cytoplasm; cleavage of procaspase-9 and procaspase-3; and consequent poly(ADP-ribose) polymerase (PARP) degradation [7]. Upstream, eugenol suppresses constitutive NF- κ B activation, downregulating Bcl-2, Bcl-xL, and survivin expression, and inhibits VEGF-driven endothelial tube formation, thereby exhibiting potent anti-angiogenic activity in matrigel assays [7].

3.3 Cinnamon (*Cinnamomum* spp.) and Cinnamaldehyde

Cinnamaldehyde [α,β -unsaturated aromatic aldehyde, (E)-3-phenylprop-2-enal] is the dominant volatile component in *Cinnamomum verum* and *Cinnamomum aromaticum*, comprising 55–90% of bark essential oil [26]. As an electrophilic Michael acceptor, cinnamaldehyde forms adducts with nucleophilic thiol groups, modulating the activity of redox-sensitive transcription factors and protein kinases [8,26]. Mechanistically, cinnamaldehyde and its structural analogue 2-hydroxycinnamaldehyde inhibit the PI3K/Akt/mTOR signalling pathway and the Wnt/ β -catenin cascade, both of which are



hyperactivated in a broad spectrum of epithelial cancers and contribute to resistance to conventional chemotherapy [8]. In melanoma B16-F10 xenograft models, cinnamaldehyde administration (50–100 mg/kg intraperitoneally) produced a 62% reduction in tumour volume with concomitant suppression of VEGF, CD31, and Ki-67 staining [8]. Procyanidin-B2, a co-occurring proanthocyanidin in cinnamon bark, independently activates caspase-dependent apoptosis in haematological malignancy cell lines, suggesting potential for combination phytopharmacological regimens [26].

3.4 Ginger (*Zingiber officinale*) and Gingerol

[6]-Gingerol [(S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one] is the principal bioactive pungent constituent of fresh ginger rhizome, structurally related to capsaicin and curcumin and classified as a phenylalkylketone [9,25]. Upon thermal dehydration, [6]-gingerol is converted to the more potent cytotoxic form [6]-shogaol, which exhibits enhanced apoptotic and anti-metastatic activity relative to its precursor [25]. Gingerol exerts its anti-inflammatory properties principally through dual inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX), enzymes that catalyse the formation of pro-tumourigenic prostaglandins and leukotrienes respectively [9,25]. The consequence is suppression of the arachidonic acid cascade and a reduction in TNF- α and interleukin-1 β (IL-1 β) production in the tumour microenvironment [9]. In colorectal carcinoma models, [6]-gingerol has been demonstrated to induce G2/M arrest through upregulation of p21^{ccv1} and downregulation of CDC25C phosphatase, and to suppress invasion through inhibition of MMP-2 and MMP-9 gelatinolytic activity [25].

3.5 Saffron (*Crocus sativus*) and Crocin

Crocin [crocin di-(beta-D-gentiobiosyl) ester] is a water-soluble apocarotenoid glucoside, unique to *Crocus sativus* stigmas and *Gardenia jasminoides* fruits, and is the principal chromophore responsible for saffron's characteristic golden hue [12]. The aglycone crocetin, its hydrolysis product, possesses superior membrane permeability and exhibits stronger pro-apoptotic activity in vitro [12]. A third major saffron constituent, safranal (a monoterpene aldehyde), contributes additional antiproliferative and antioxidant activity [12]. The anticancer mechanisms of saffron constituents centre on modulation of cell cycle regulatory proteins and inhibition of DNA synthesis in rapidly dividing malignant cells [12]. Crocin has been demonstrated to downregulate proliferating cell nuclear antigen (PCNA) expression, a marker of S-phase progression, and to activate the p53 tumour suppressor, promoting transcription of the pro-apoptotic BAX gene while suppressing Bcl-2 [12]. In breast cancer xenograft models, crocin (50 mg/kg/day) reduced tumour volume by approximately 48% with preservation of normal haematopoiesis, a favourable selectivity profile attributable to its preferential uptake by neoplastic cells via monocarboxylate transporters (MCTs) [12].

3.6 Garlic (*Allium sativum*) and Organosulfur Compounds

The anticancer bioactivity of garlic is predominantly attributable to its organosulfur constituents, generated enzymatically from the non-proteinogenic amino acid alliin following cell disruption [13,14]. Allicin (diallyl thiosulphinate) is the principal immediate product of the alliinase-catalysed reaction; it undergoes further conversion to diallyl disulphide (DADS), diallyl trisulphide (DATS), and ajoene in the presence of heat or acid [13].



DATS, the most extensively studied organosulfur compound, induces G2/M arrest through reduction of cyclin B1/CDC2 kinase activity and concurrent upregulation of p21^{cc¹} [13]. In prostate cancer cells, DATS activates both extrinsic (Fas/FasL-mediated) and intrinsic apoptotic pathways, and inhibits constitutive androgen receptor signalling — a mechanism of particular relevance in castration-resistant disease [22]. Garlic compounds also function as potent inducers of hepatic Phase II detoxification enzymes (glutathione S-transferases, quinone oxidoreductase) through Nrf2 activation, thereby accelerating metabolic inactivation of dietary procarcinogens such as aflatoxin B1 and N-nitrosamines [13,14].

3.7 Limonene and Piperine: Bioavailability Enhancement and Direct Activity

d-Limonene, a monocyclic monoterpene constituting 90–95% of cold-pressed citrus peel oil, inhibits oncogenic Ras protein membrane association through competitive inhibition of farnesyl transferase, thereby attenuating Ras-MAPK signalling downstream of multiple receptor tyrosine kinases [15,16]. In NSCLC cell lines, including A549, H1299, H1975, H520, and PC9, d-limonene suppresses colony formation in a dose-dependent manner and activates autophagy

through mTORC1 inhibition, culminating in autophagic cell death [15]. A Phase I clinical trial reported a maximum tolerated dose of 8 g/day with evidence of breast tumour growth inhibition in 14 of 32 enrolled patients [16]. Piperine, the principal alkaloid of *Piper nigrum*, is unique among the natural agents reviewed here in that its primary clinical application is as a bioavailability enhancer rather than a direct chemopreventive agent. Through inhibition of intestinal UDP-glucuronyltransferases, CYP3A4, and P-glycoprotein efflux transporter, piperine enhances systemic exposure to co-administered curcumin by up to 20-fold and improves bioavailability of numerous other phytochemicals and conventional drugs [3,34]. Nevertheless, piperine itself exhibits direct antiproliferative activity in breast and colorectal cancer models through STAT3 and Akt pathway suppression [3].

4. Clinical and Preclinical Evidence

The translational relevance of natural chemopreventive agents ultimately depends on the quality and quantity of human clinical evidence. Table 2 summarises selected landmark preclinical and clinical studies providing quantitative evidence for the efficacy of the agents reviewed.

Table 2. Selected Preclinical and Clinical Evidence for Natural Chemopreventive Agents in Oncology

Compound	Study Type	Cancer Type / Model	Key Findings	Dose / Duration	Reference
Curcumin	Phase II RCT	Advanced pancreatic cancer	Tumour regression (73%) in 1/25 patients; stable disease >18 months in 2 patients	8 g/day oral; 2–18 months	Dhillon et al., 2008
Curcumin	Phase I trial	Colorectal neoplasia	Significant reduction in polyp number and size	450 mg/day; 3 months	Sharma et al., 2004

Allicin (garlic)	Prospective cohort	Gastric cancer	~47% lower gastric cancer risk in high-garlic-consumption groups	Dietary; >5 years	You et al., 2020
Gingerol (ginger)	Phase II RCT	Colorectal cancer (chemo support)	Significant reduction in chemo-induced nausea and vomiting; anti-proliferative markers improved	2 g/day; 6 weeks	Ryan et al., 2012
Eugenol (cloves)	In vitro / in vivo	Breast, lung, cervical cancer cell lines	IC50 values of 11–38 μ M in cancer cells vs. >150 μ M in normal cells; selective cytotoxicity confirmed	5–50 μ M; 24–72 h	Jaganathan et al., 2012
Crocin (saffron)	RCT (supportive)	Breast cancer (adjuvant)	Crocin supplementation reduced fatigue and improved	15 mg/day; 8 weeks	Hosseini et al., 2021

RCT: randomised controlled trial; IC50: half-maximal inhibitory concentration; QoL: quality of life; ctDNA: circulating tumour DNA; VEGF: vascular endothelial growth factor; Ki-67: proliferation index marker

Perhaps the most clinically compelling evidence exists for curcumin, with the Phase II pancreatic cancer trial by Dhillon and colleagues demonstrating objective tumour regression in one patient following 8 g/day oral curcumin despite the notoriously poor prognosis associated with this disease [4]. For ginger, Ryan et al. conducted a well-powered randomised controlled trial of 576 patients across multiple oncology centres, confirming that 2 g/day ginger supplementation reduced acute chemotherapy-induced nausea and vomiting — a clinically significant outcome that improves treatment adherence [10].

The relative paucity of Phase III randomised controlled trial data for most natural agents reflects the commercialisation challenges inherent in non-patentable natural molecules rather than lack of biological plausibility. Future trials should incorporate biomarker endpoints, circulating tumour DNA analysis, and patient-reported quality-of-life measures to maximise the information obtained from clinical investment [2].

5. Integrated Molecular Mechanisms of Action

The diverse natural chemopreventive agents reviewed in this article converge on a small set of oncogenic signalling pathways that collectively mediate the hallmarks of cancer. Figure 1 provides a schematic representation of the primary



molecular targets and downstream consequences of phytochemical exposure.

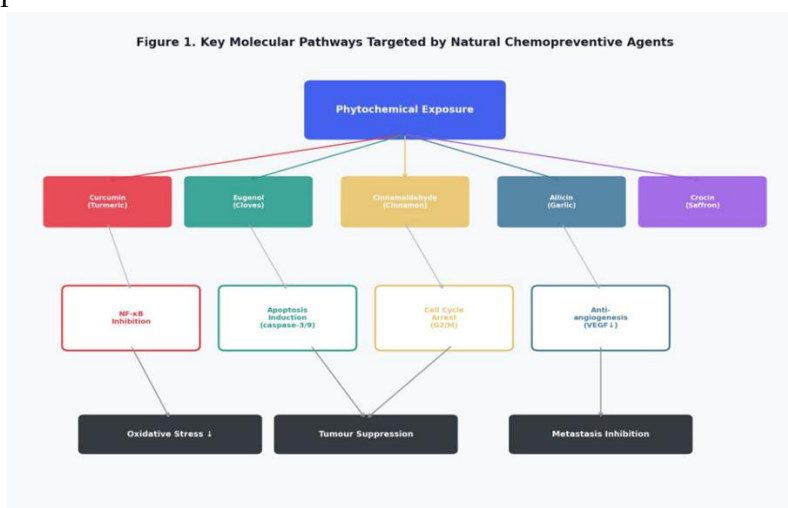


Figure 1. Schematic illustration of the principal molecular pathways targeted by natural chemopreventive phytochemicals. Key active compounds converge on shared downstream effectors to collectively suppress inflammation, induce apoptosis, arrest the cell cycle, and inhibit tumour angiogenesis and metastasis.

The NF- κ B signalling axis represents the most broadly targeted pathway, with curcumin, eugenol, gingerol, and allicin all demonstrating significant inhibitory activity [3,7,9,13]. This convergence on a single master inflammatory transcription factor reflects the aetiological importance of chronic low-grade inflammation in carcinogenesis across multiple tissue types. Complementarily, apoptosis induction through the intrinsic mitochondrial pathway — involving Bcl-2 family member modulation, cytochrome c release, and caspase cascade activation — is shared by curcumin, eugenol, crocin, and DATS [4,7,12,13].

Cell cycle arrest, predominantly at the G2/M checkpoint through combined inhibition of cyclin B1/CDK1 and upregulation of p21^{ce¹}, represents a further common effector mechanism, as does suppression of VEGF-driven tumour

angiogenesis. The PI3K/Akt/mTOR axis, which integrates growth factor signalling and metabolic activity, is suppressed by cinnamaldehyde and d-limonene — an observation of particular significance given the frequent hyperactivation of this pathway in drug-resistant cancers [8,15].

6. Bioavailability, Formulation, and Drug Delivery Considerations

Perhaps the most substantive obstacle impeding translation of phytochemical bioactivity from bench to bedside is the poor and variable oral bioavailability of most natural compounds. Figure 3 illustrates the comparative relative bioavailability of key chemopreventive compounds in their conventional form versus advanced formulation strategies.

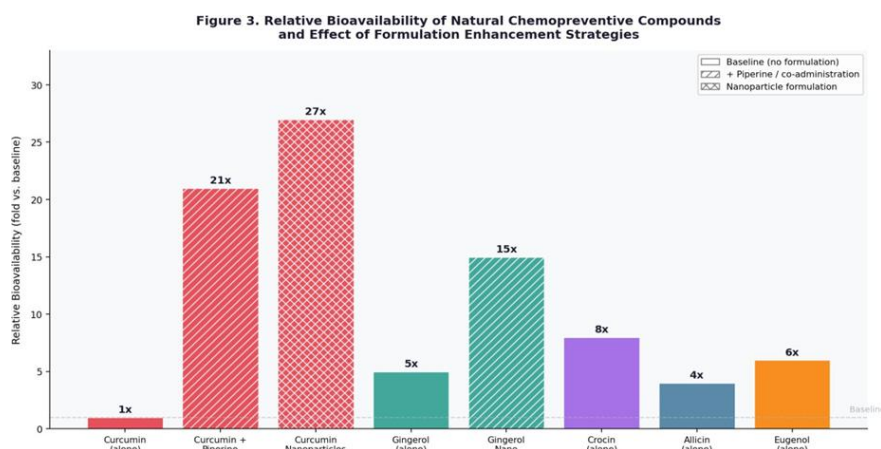


Figure 3. Relative oral bioavailability of key natural chemopreventive compounds in conventional form compared with piperine co-administration and nanoparticulate formulation strategies. Values represent approximate fold-improvements over unformulated baseline exposure. Data synthesised from published pharmacokinetic studies [3,15,16,34].

Curcumin exemplifies the bioavailability challenge most acutely: despite potent *in vitro* activity at micromolar concentrations, plasma concentrations following conventional oral administration in humans rarely exceed nanomolar levels [34]. Piperine co-administration dramatically augments curcumin bioavailability, primarily through inhibition of glucuronidation at the intestinal wall. Polymeric nanoparticles encapsulating curcumin within PLGA matrices achieve further improvements by protecting the compound from degradation and facilitating endocytic cellular uptake through the enhanced permeability and retention (EPR) effect operative in tumour vasculature [34].

Beyond passive nanoparticle targeting, active targeted delivery systems incorporating tumour-homing ligands

— folate receptor-binding moieties, transferrin, HER2 antibody fragments — are being developed to further concentrate phytochemical payload within neoplastic tissue [34]. Self-emulsifying

drug delivery systems (SEDDS) and lipid-polymer hybrid nanoparticles offer additional promise for poorly soluble phytochemicals including cinnamaldehyde and eugenol, where conventional oral formulations produce erratic absorption profiles. The clinical translation of these advanced drug delivery strategies will require rigorous toxicological characterisation of excipient components and formal pharmacokinetic studies in target patient populations [2,34].

7. Challenges, Limitations, and Risk Considerations

Notwithstanding the biological plausibility and preliminary clinical signals for natural chemopreventive agents, the field is beset by several fundamental challenges that must be transparently acknowledged. Table 3 systematically delineates current limitations and corresponding proposed future strategies.

Table 3. Challenges in the Clinical Application of Natural Chemopreventive Agents and Proposed Future Mitigation Strategies

Challenge	Current Limitation	Proposed Future Strategy
Low bioavailability	Curcumin oral bioavailability <1%; rapid hepatic metabolism and poor solubility limit therapeutic efficacy in vivo	Polymeric nanoparticles, liposomal encapsulation, self-emulsifying drug delivery systems (SEDDS), co-administration with piperine
Lack of clinical evidence	Majority of data from in vitro and murine models; extrapolation to human oncology remains speculative	Biomarker-driven Phase II/III randomised controlled trials; use of surrogate endpoints (e.g., CTC counts, ctDNA)
Variability in phytochemical content	Active compound concentration varies by geography, harvest season, and preparation method	Standardised botanical extracts; quantitative HPLC-based quality certification; Good Agricultural Practices (GAP)
Risk of herb-drug interactions	Curcumin and piperine inhibit CYP3A4 and P-glycoprotein; potential to alter pharmacokinetics of chemotherapy agents	Pre-clinical interaction screening; careful patient selection; real-world pharmacovigilance monitoring
Dose optimisation	No consensus therapeutic dose defined for any natural chemopreventive agent in humans	Population pharmacokinetic (PopPK) modelling; dose-escalation studies in diverse ethnic cohorts
Tumour heterogeneity	Clonal evolution within tumours limits efficacy of single-pathway-targeted agents	Multi-target phytochemical combinations; integration with immunotherapy and epigenetic modulators

HPLC: high-performance liquid chromatography; GAP: Good Agricultural Practices; PopPK: population pharmacokinetics; CYP3A4: cytochrome P450 3A4; ctDNA: circulating tumour DNA; SEDDS: self-emulsifying drug delivery systems

The risk of pharmacokinetic herb-drug interactions deserves particular clinical emphasis. Curcumin and piperine are moderate inhibitors of CYP3A4 and P-glycoprotein, the principal metabolising enzyme and efflux transporter respectively for paclitaxel, vincristine, imatinib, and numerous other chemotherapeutic agents [3,34]. Unsupervised high-dose supplementation during cytotoxic chemotherapy could therefore precipitate unexpected toxicity through elevation of plasma concentrations of narrow-therapeutic-index oncological drugs. Comprehensive pharmacovigilance and patient counselling regarding such interactions are imperative [34]. The heterogeneity of published in vitro data — reflecting differences in cell lines, dose ranges, vehicle solvents, and assay methodologies —

further complicates systematic meta-analytic synthesis. Standardisation of experimental frameworks and reporting practices, guided by initiatives such as the CONSORT extension for herbal medicinal product clinical trials, would substantially improve evidence quality in this domain [2].

8. Future Directions

8.1 Nano-Chemoprevention and Advanced Drug Delivery

The next decade of phytochemical oncology research will be defined by the integration of nanotechnology with traditional botanical knowledge. Responsive nanocarrier systems — engineered to release their cargo specifically



within the acidic and hypoxic tumour microenvironment or upon stimulation by tumour-overexpressed enzymes such as matrix metalloproteinases — offer a paradigm shift in targeted delivery [34].

Exosome-based natural product delivery, exploiting the intrinsic cell-homing properties of extracellular vesicles derived from ginger nanoparticles, represents an emerging frontier with demonstrated efficacy in murine colitis-associated colon cancer models [9].

8.2 Combination Phytotherapy and Chemosensitisation

Multi-targeting cancer therapy, combining natural agents with complementary mechanisms, holds significant promise. Curcumin combined with 5-fluorouracil has demonstrated synergistic cytotoxicity in CRC cell lines through simultaneous NF- κ B inhibition and thymidylate synthase downregulation [27]. Similarly, combining gingerol with docetaxel in prostate cancer models reduced the effective chemotherapy dose by approximately 50% while maintaining equivalent antiproliferative activity, potentially permitting dose reduction and attenuation of peripheral neuropathy [22]. Systematic combinatorial screening using high-throughput platforms will accelerate identification of optimal phytochemical-drug synergy ratios [2].

8.3 Artificial Intelligence and Omics-Guided Discovery

Artificial intelligence (AI) and machine learning algorithms are being increasingly deployed to mine large phytochemical compound libraries and identify structure-activity relationships predictive of anticancer potency, selectivity, and bioavailability [2]. Network pharmacology approaches, integrating molecular docking, transcriptomic profiling, and phenotypic drug discovery, allow comprehensive mapping of

phytochemical-target interaction networks. Multi-omics integration — combining genomics, proteomics, metabolomics, and microbiome data — will enable identification of patient subpopulations most likely to derive chemopreventive benefit from specific natural agents, laying the foundation for precision phytomedicine [2].

8.4 Epigenetic Modulation and Immunomodulatory Potential

Epigenetic dysregulation — comprising aberrant DNA methylation, histone modification, and non-coding RNA expression — is increasingly recognised as a driver of malignant transformation amenable to pharmacological reversal. Curcumin, EGCG, and sulforaphane have been demonstrated to inhibit DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), partially restoring normal epigenetic marks at tumour suppressor gene loci [3,27]. Integration of phytochemical epigenetic modulation with PD-1/PD-L1 immune checkpoint blockade — reasoning that demethylation of immunostimulatory genes may enhance tumour immunogenicity — represents a scientifically compelling future research avenue [2].

CONCLUSION

This review has comprehensively evaluated the scientific evidence supporting the role of eight natural dietary phytochemicals — curcumin, eugenol, cinnamaldehyde, gingerol, crocin, allicin, d-limonene, and piperine — as chemopreventive and adjunctive anticancer agents. The preponderance of evidence from preclinical models demonstrates that these compounds engage multiple non-redundant oncogenic signalling pathways simultaneously, providing a theoretical mechanistic basis for their observed epidemiological associations with reduced cancer incidence in spice-consuming populations.



Clinical evidence, although still at an early stage for most agents, has provided proof-of-concept signals in Phase I and Phase II trials, particularly for curcumin in pancreatic and colorectal cancer, ginger in chemotherapy-induced nausea management, and d-limonene in recurrent breast cancer. These findings must be interpreted cautiously, however, given the small sample sizes, heterogeneous patient populations, and variability in formulation and dosing that characterise the extant clinical literature.

Translating the chemopreventive potential of natural agents into validated, guideline-incorporated clinical practice will require: standardised botanical extract formulations with certified phytochemical content; optimised drug delivery systems addressing poor oral bioavailability; and well-designed Phase III randomised controlled trials incorporating biomarker-stratified patient selection. Concomitantly, healthcare providers and patients must be educated regarding the potential for clinically meaningful herb-drug pharmacokinetic interactions during concurrent cytotoxic therapy.

Natural chemopreventive agents are not a substitute for established oncological management, but rather represent a scientifically coherent and potentially practice-changing adjunctive strategy. The convergence of advanced nanotechnology, artificial intelligence-driven drug discovery, and expanding clinical trial infrastructure positions the field of phytochemical oncology to deliver meaningful improvements in cancer prevention and supportive care within the next decade.

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