CHAPTER N0.

09

Phytochemicals as Chemopreventive Agents: Mechanisms and Clinical Insights

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ABSTRACT: Carcinoma is a significant worldwide health concern, with its prevalence and mortality increasing substantially in countries with low or middle incomes. Preventative methods that are reliable, inexpensive, and durable are thus essential. Phytochemicals, or bioactive molecules produced from plants, are being investigated as prospective cancer-preventing medicines because of their capacity to influence several molecular processes associated with malignancy. The current article focuses on the impact of significant plant chemical categories such as polyphenols as well as terpenoids, alkaloid substances, and organosulfur molecules in fighting cancer. Antioxidant protection, control of carcinogens breakdown, modification of cell signaling systems like NF-κB, PI3K/Akt, and Wnt/β-catenin, epigenetic modification, apoptotic stimulation, angiogenesis suppression, and immunological regulation are some of the means by which these substances work. The curative properties of important phytochemicals like curcumin, resveratrol, epigallocatechin gallate, sulforaphane, lycopene, and quercetin is supported by data from in vitro, in vivo, and preliminary clinical investigations. Yet, their translational effectiveness is limited by issues with poor distribution, uneven medical results, and unpredictable kinetics. Potential methods to improve the effectiveness of treatment are provided by recent advancements in nanotechnologies, lipid-based formulations, and tailored nutrition techniques. All things considered, phytonutrients are an essential component of dietary and cancer chemotherapy avoidance, and they have tremendous opportunity to be incorporated into next cancer treatment tactics.
Keywords: Phytochemicals, chemoprevention, terpenoids, polyphenols, nutrigenomics, bioavailability

INTRODUCTION

In the majority of nations worldwide, cancer has become the leading cause of premature death. Because demographic shifts, including increasing numbers of people and aging, have a significant impact on the disparate patterns of cancer prevalence in various regions, it is anticipated that the number of cancer patients worldwide will increase over the course of the next fifty years. We project that the prevalence of the various cancers altogether will double by 2070 compared to 2020, taking into account that the most recent rates for the majority of categories of cancer remain unchanged. While estimated rises in national burden decrease as national HDI levels rise, the largest increases are anticipated in lower-resource settings, in nations currently assigned a low HDI. We address how gradual, population-based approaches with feasible objectives may avoid millions of future cancer diagnoses globally, with a particular focus on a thorough evaluation of preventive measures aimed at nicotine use, overweight and obesity, and papillomavirus (HPV) infection. The consumption of tobacco will continue to be the main avoidable trigger of cancer unless there is a significant shift in the way cancer prevention is delivered, and being overweight or obese may offer similar possibilities for early detection (Soerjomataram and Bray, 2021).

Because of the rise in mortality and disability it causes, cancer has emerged as a significant threat to global health. Globally, there were nearly 18.1 million new instances of cancer in 2020. In wealthy countries, early identification, cancer avoidance, management, and therapy have gotten better over time, resulting in lower mortality and longer life expectancies. But in low- and middle-income nations (LMICs), things are different. Under the collaboration of national plans and local communities, broad and effective cancer prevention initiatives may enhance early detection, cancer education, and oncologic infrastructure—all of which are critical factors in cancer mortality and longevity. Sustainability and affordability are crucial for cancer detection and therapy because they allow for effective administration of cancer pain while taking into account the resources and circumstances of developing nations. Governments, especially those in LMICs, must guarantee universal health coverage of medical expenses or free or reasonably priced access to cancer medications (Huang et al., 2023).

Herbal products play an efficient role in treating various types of cancer because of the phytochemicals present in the plants, which are used for the development of various types of drugs. Either the production of medicinal drugs is challenging, but it gives numerous beneficial effects with fewer side effects (Muhammad et al., 2022). Chemical compounds or substances that are generated naturally by living things are known as natural products. Organic goods are now useful in healthcare thanks to advancements in current technology. It has been documented that both macromolecules and micro-molecules

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can stop the growth of tumors. Various forms of human cancer can be prevented by using natural substances and their byproducts. Natural products have been used extensively all over the years to cure human illnesses, including the invention of penicillin. One effective method for finding biologically active substances with distinctive structures and modes of action is natural product investigation. Natural products are an excellent resource for the development of anticancer and cancer prevention medications (Mali, 2023). Chemotherapeutic drugs are used for the prevention and mitigation of cancer by halting or stopping the division of DNA damage. Tamoxifen trials were done on breast cancer patients, which significantly reduced the aggressive breast cancer. Phytochemicals like Capsaicin, cucurbitacin B, isoflavones, catechins, lycopenes, and various other dietary components also have suppressive effects on the cancer cells (Ranjan et al., 2019).

CLASSIFICATION OF CHEMO-PREVENTIVE PHYTOCHEMICALS

Unchecked cell growth brought on by genetic, environmental, and lifestyle factors is the root cause of cancer. In wealthy nations, it can be prevented by advanced treatments, but in developing nations, it is fatal due to a lack of awareness and therapies. Cancer prevention is the use of synthetic or natural agents to inhibit or postpone the growth of cancer. Because they regulate cancer-promoting pathways, modulate signaling molecules, and offer antioxidant defense, phytochemicals derived from medicinal plants are essential. This review highlights the value of plant-based substances in creating potent, all-natural anticancer strategies by five main chemo-preventive phytochemical classes and their potential to lower cancer risk also mentioned in Table 1 (George et al., 2021).

Polyphenols

Water-soluble, naturally occurring antioxidants known as polyphenols protect against cancer and oxidative stress-induced damage. They are secondary compounds of plants that stop the formation of tumors, trigger apoptosis, and stop the spread of cancer. Dietary polyphenols, which are paired with abundant plant-derived foods, can enhance chemoprevention when combined with traditional cancer treatments by scavenging reactive oxygen species (Sharma et al., 2018). Organic bioactive substances, particularly dietary phenolics, represent a potential chemotherapy defense due to the intricate nature of cancer and the adverse effects of drugs. Apoptosis, autophagy, cell cycle arrest, and telomerase repression are all made possible by their functional groups. Clinical and in vivo research demonstrates anti-angiogenic and therapeutic properties against a range of human cancers, either by itself or in combination with chemotherapy (Bakrim et al., 2022).

Terpenoids

Retinoids and carotenoids have pro-apoptotic, anti-tumor, and antioxidant properties. Dietary carotenoids lower the risk of a number of illnesses and cancers by regulating the immune system, the expression of genes, and cell proliferation. Time- and dose-responsive chemo-preventive and curative properties are demonstrated by compounds such as lutein, lycopene, and β-carotene, which act through antioxidant, signaling, and immune pathways (Milani et al., 2017). Steroid or triterpenoid glycosides that resemble soap, saponins have a variety of anticancer effects, such as inducing apoptosis, promoting autophagy, and causing cell-cycle arrest. Despite encouraging outcomes, toxicity and drug-likeness concerns have prevented the FDA from approving any saponin-based anticancer medications. In order to improve efficacy and lower toxicity, recent research investigates combination treatments and delivery methods (Elekofehinti et al., 2021).

Alkaloids

Although Nuclear Factor Erythroid 2-Related Factor 2 NRF2 controls redox balance, inflammation, and cyto-protection, its overactivation in cancer encourages drug resistance and survival. By regulating oxidative stress, antioxidant synthesis, and cancer cell death, alkaloids like berberine, evodiamine, and trigonelline function as NRF2/KEAP1 pathway inhibitors, increasing the sensitivity of cancer cells to chemotherapy (Gjorgieva Ackova et al., 2023). Piperine, an alkaloid found in black pepper, has anticancer effects toward colorectal cancer by causing apoptosis, stopping the cell cycle, and changing pathways like Wnt/β-catenin, PI3K/Akt/mTOR, and NF-κB. It improves the effectiveness of chemotherapy, but it has problems with bioavailability that can be solved with nanotechnology. This makes it an appealing, versatile option for preventing and treating colorectal cancer (Chidananda et al., 2025).

Organosulfur compounds

Myrosinase changes glucoraphanin, the main compound in broccoli, into sulforaphane (SFN), a powerful phytochemical that may help fight cancer. SFN inhibits or impedes the growth of cancer by changing many cellular pathways. Numerous studies elucidate its mechanisms; however, extensive reviews on its overarching proactive function in human cancers are still scarce (Kaiser et al., 2021). Organosulfur substances may exert additional impacts on colorectal tumors through their modulation of the microbiota in the gut or their beneficial

Table 1. Major classes of chemo preventive phytochemicals, sources, and mechanism of action

Phytochemical Class	Representative Compounds	Major Dietary Sources	MOA
Polyphenols	Curcumin, Resveratrol, EGCG, Quercetin	Turmeric, grapes, green tea, onions	Antioxidant activity, apoptosis induction,epigenetic modulation
Terpenoids	Lycopene, β-carotene, Lutein, Saponins	Tomatoes, carrots, leafy vegetables, legumes	Cell-cycle arrest, immune modulation, anti-angiogenic effects
Alkaloids	Berberine, Piperine, Evodiamine	Barberry, black pepper, Medicinal herbs	NRF2/KEAP1 inhibition, apoptosis induction, chemosensitization
Organosulfur Compounds	Sulforaphane, Allicin	Broccoli, garlic	Phase 2 enzyme activation, HDAC inhibition, suppression of metastasis

impact on intestinal mucosal health. We concentrate on their immediate consequences, including the inhibitory effect of multidrug-resistant proteins, the induction of apoptosis (through the inhibition of histone deacetylases, elevation of oxygen radicals, activation of p53, suppression of β-catenin, disruption of the mitochondrial membrane, etc.), the activation of TGF-β, binding to tubulin, the blocking of vascular growth and metastasis mechanisms, and the suppression of tumor stem cells, among other actions (McAlpine et al., 2024).

MECHANISMS OF ACTION OF PHYTOCHEMICALS IN CANCER PREVENTION

Below is described the MOA of phytochemicals for cancer prevention.

Antioxidant Defense and Free Radical Scavenging

Polyphenols, including flavonoids, phenolic acids, and stilbenes, function as robust antioxidants by immediately destroying reactive oxygen species (ROS) and augmenting endogenous defense mechanisms through the Nrf2/ARE signaling pathway. When Nrf2 is turned on, it increases the levels of important antioxidant enzymes like SOD, CAT, and GPx, which get rid of superoxide and hydrogen peroxide. These plant-based chemicals lower the number of mutagenic incidents and the start of cancer by keeping the redox equilibrium in cells and stopping damage caused by oxidative stress (Lekhak and Bhattarai, 2024).

Modulation of Carcinogen Metabolism

By inhibiting cytochrome P450 (CYP1A1, CYP2E1) activity, phytochemicals lower the activation of procarcinogens. At the same time, they activate Nrf2 to trigger Phase II enzymes, specifically GST, NQO1, and UGT. This concurrent regulation efficiently decreases mutagenic tension by reducing DNA adduct development and promoting the removal of electrophilic cancer-causing agents (Carvalho, 2025). Chirumbolo demonstrates that plant flavonoids alter the enzymes that metabolize xenobiotics in the liver by preventing CYP-mediated oxidation and promoting the glucuronidation and sulfation pathways. The buildup of cancer-causing substances, especially those originating from polycyclic aromatic hydrocarbons and heterocyclic amines, is prevented by this modification of the metabolic activity of enzymes (Chirumbolo et al., 2018).

Regulation of Cell Signaling Pathways

Plant-based compounds inhibit PI3K/Akt/mTOR, MAPK signaling, and NF-κB, which are processes essential for the continued existence and growth of cancer cells. Resveratrol and genistein are two examples of compounds that inhibit the transcription of inflammatory cytokines, block IKK phosphorylation, and induce apoptosis. Because of their multipurpose nature, several tumor-promoting pathways can be inhibited at once (Hashem et al., 2022). Suvarna's review centers on the PI3K/Akt axis, emphasizing how berberine, curcumin, and quercetin block subsequent targets like mTOR and GSK-3β by suppressing Akt phosphorylation. This alteration limits the metabolism, growth, and angiogenesis of cancer cells, highlighting phytochemicals as potential supplements for particular cancer treatments (Suvarna et al., 2017).

Epigenetic modulation

Phytochemicals function as epigenetic regulators by hindering DNMTs and HDACs. The CpG islands of suppressed tumor suppressor genes (such as p16 and RASSF1A) are demethylated by substances like EGCG and curcumin, which restores the transcription of those genes. Additionally, they reverse chromatin condensation linked to carcinogenesis by increasing histone acetylation (Khan et al., 2024)

Induction of Apoptosis and Inhibition of Proliferation

According to Rahman's study, plant compounds cause the mitochondrial membrane potential to change, the Bax/Bcl-2 ratio to rise, and cytochrome c to be released, all of which trigger intrinsic apoptosis. Curcumin and apigenin are two examples of compounds that activate caspase-9 and caspase-3, causing programmed cell death and chemotherapy-resistant cancer cells to become more sensitive (Rahman et al., 2021). By altering cyclins (D1, E) and CDK inhibitors (p21, p27), flavonoids and alkaloids induce cell-cycle arrest at the G1 and G2/M phases. Diminished tumor development and improved therapy outcomes are the results of inducing apoptosis and suppressing proliferative signaling (via PI3K/Akt) (Rudzińska et al., 2023).

Anti-Inflammatory and Immunomodulatory Effects

Natural substances such as curcumin and resveratrol reduce the production of COX-2, TNF-α, and IL-6 by inhibiting the inflammation-related transcription factors NF-κB and STAT3. This anti-inflammatory effect lessens persistent inflammation, which is an initial contributor to cancer development and tumor-triggering cytokine signaling (Lekhak and Bhattarai, 2024). The immune-regulating capacity of plant chemicals that increase cytotoxic T-lymphocyte and NK-cell activity is highlighted by Shuvalov. They prevent tumor immune evasion by balancing Th1/Th2 responses, enhancing immune surveillance, and blocking immunosuppressive factors like TGF-β and IL-10 (Shuvalov et al., 2023).

Inhibition of Angiogenesis and Metastasis

Polyphenols inhibit epithelial–mesenchymal transition (EMT) markers like Vimentin, Twist, and Snail as well as angiogenic signaling. Phytochemicals lower the risk of metastasis and the flexibility of the tumor microenvironment by suppressing glycolytic metabolism and inhibiting hypoxia-induced VEGF expression (Fakhri et al., 2024).

PRECLINICAL AND CLINICAL INSIGHTS

Evidence From *In Vitro* and *In Vivo* Studies

Numerous in vitro investigations demonstrate that distinct botanical compounds (curcumin, EGCG, resveratrol,

sulforaphane, quercetin, and lycopene) suppress the growth of cancer cells, trigger apoptosis (mitochondrial depolarization, caspase activation), halt cell cycle checkpoints, and alter signaling (NF-κB, PI3K/Akt, MAPK). Although effective plasma/tissue levels in animals are frequently higher than those attainable through dietary intake, prophylactic administration of phytochemicals has been shown to hinder tumor development, minimize metastasis, and decrease the rate in complementary in vivo rodent xenograft and tumor-induction models (Choudhari et al., 2020). At minimal, dietary-associated doses, this recent in vivo study using sulforaphane (SFN) in breast cancer models revealed up to approximately 31% tumor progression diminution, lowered proliferation metrics, and modified immune-cell infiltration; in vitro and 3D models replicated migration/invasion prevention and diminished EMT indicators (Pogorzelska et al., 2024).

Human Clinical Trials of Key Phytochemicals

The following phytochemicals are featured in this particular review: EGCG (some cancer prevention and adjuvant investigations), sulforaphane (pilot trials showing pharmacodynamic impacts on detoxification enzymes and on surrogate proliferation markers), lycopene (several prostate studies with mixed PSA/Ki-67 results), curcumin (multiple early-phase trials; enhanced inflammatory indicators, occasional tumor marker reductions), resveratrol (small trials demonstrating target regulation but few definitive clinical endpoints), and quercetin (few trials; more preclinical than clinical evidence). The article emphasizes that the majority of human trials are small, use alternative biomarkers instead of cancer incidence/survival, and usually utilize various protocols, limiting pooled recommendations (Vrânceanu et al., 2022).

Limitations and Controversies in Clinical Efficacy

A few translation errors can be explained by the fact that in vitro anticancer levels of EGCG (and many polyphenols) are frequently far greater than what can be achieved in plasma following oral dosing. Disparities in biomarker selection, associations between food and medications, inadequate uniformity of the active component content, and variability brought about by various nutritional designs are also documented. More effective pharmacokinetic and pharmacodynamic (PK/PD) studies, nanotechnologies or delivery systems to increase tissue levels, and standard outcomes (incidence or progression) to settle disputes are all emphasized in the paper (Markowska et al., 2025).

BIOAVAILABILITY AND PHARMACOKINETIC CHALLENGES

Factors affecting absorption and metabolism

According to Shi and colleagues, the following variables influence phytochemical bioavailability: (a) fundamental physical and chemical characteristics, such as solubility, molecular size, polarity, and stability in the gut; (b) digestive variables, such as pH, gastric emptying, and reactions with the food matrix; and (c) host biology, including intestinal carriers, intestinal and hepatic phase II conjugation, such as SGLT and OATPs; first-pass metabolism, which converts the parent molecules into more or fewer active substances, and gut microbiota. The review highlights the significant inter-individual variation caused by the structure of the microbiome and genetics (SULT, UGT polymorphisms), both of which account for human pharmacodynamic consequences and uneven plasma exposures (Shi et al., 2022).

Strategies to Enhance Bioavailability

Lipid carriers (liposomes, solid-lipid nanoparticles, and nanoemulsions) for the delivery of phytochemicals are systematically evaluated by Patel. The following information was gathered: (a) lipid carriers boost solubility and shield labile phytochemicals from enzymatic or gastric breakdown; (b) in animal PK/PD studies, encapsulation significantly boosts oral absorption and cellular uptake (e.g., improved tissue levels of curcumin and EGCG); and (c) lipid systems facilitate lymphatic transport, partially avoiding first-pass hepatic conjugation. The review concludes that lipid nanocarriers are among the most clinically promising ways to enhance phytochemical pharmacokinetics, despite mentioning translational obstacles such as scale-up, stability, and regulatory barriers (Patel et al., 2024).

SAFETY, TOXICITY, AND DRUG INTERACTION

Dose-Dependent Effects and Long-Term Safety

Although low-to-moderate nutritional exposures (food sources) are generally well tolerated, concentrated extracts or high-dose supplements may cause side effects, most commonly gastrointestinal symptoms, changed liver enzymes, and, infrequently, idiosyncratic hepatotoxicity. There are gaps in long-term (>1 year) safety data and inconsistent documentation of hepatic or hematologic surveillance, but systematic analyses of curcumin clinical trials show good overall tolerability at typical trial doses (up to ~4 g/day) with mostly mild GI complaints. According to these reviews, safety signals are rare but poorly described because most trials are brief and small (Zeng et al., 2022).

Potential Interactions with Conventional Chemotherapeutics

Two pragmatic issues are highlighted in a thorough analysis of herb-drug interactions in cancer treatment: first, phytochemicals that block CYP3A4 or UDP-glucuronosyltransferases may increase the plasma levels of supportive or chemotherapy medications (increasing toxicity); secondly, powerful antioxidant or anti-inflammatory effects taken in conjunction with cytotoxic regimens may decrease the stated oxidative stress-induced cytotoxicity of certain agents. Therefore, until thorough scientific association data are accessible, the authors advise cautious co-administration, particularly during the peri-chemotherapy window, preclinical PK/PD interaction screening, and the documentation of supplement use in cancer research trials (Gandhi et al., 2025).

Regulatory Perspectives

The majority of phytochemicals sold as dietary supplements in the United States are governed by the DSHEA (1994), which places a significant amount of pre-market control on manufacturers and prioritizes post-market surveillance. As a result, efficacy assurances are restricted and safety oversight is reactive. Regulatory structures vary by jurisdiction. Consequently, instead of requiring pre-approval proof of efficacy or safety as required for drugs, the FDA regulation prioritizes labeling, Good Manufacturing Practices, and adverse event reporting. Rapid commercialization is made possible by this regulatory model, but it also adds to product composition, dosage, and purity variability, which makes pharmacovigilance and clinical safety evaluation more difficult (Gandhi et al., 2025).

FUTURE PERSPECTIVES

The future perspectives for phytochemical-based chemoprevention are listed below, which, if we adopt further, will help us to fight against cancer easily and also enable us to prevent this disease from spreading.

Personalized Nutrition and Precision Oncology Approaches

In order to stop health issues, precise nutritional advice that takes into account lifestyle, phenotype, and genotype can maximize the consumption of foods high in phytochemicals. It talks about the computational methods and decision-making tools that convert pharmacogenetic-like and polygenic risk data into individualized dietary suggestions, including the timing and dosage of phytochemical administration. In order to show clinical utility, the authors stress integration with clinical oncology (e.g., perioperative nutrition, survivorship care) and demand randomized studies that contrast genotype-guided phytochemical interventions with conventional dietary recommendations (Singar et al., 2024).

Role of Nutrigenomics and Metabolomics

Braicu and associates examine how dietary phytochemicals affect the risk of carcinogenesis by interacting with the genome and epigenome to modify gene expression, DNA methylation, and miRNA networks. They cite research on both humans and animals in which nutrient-gene interactions changed the pathways of biomarkers (inflammatory and DNA repair genes), and they contend that nutrigenomic analysis can be used to determine which people are most likely to gain from exposure to particular phytochemicals. According to the paper, nutrigenomics serves as a mechanistic link between host genotype, diet, and cancer-related modification (Braicu et al., 2017).

Translational Potential and Emerging Research Directions

A scientific key is advocated by Russo's review, which calls for a shift from single-compound in vitro studies to systems-level, clinically focused research that takes population heterogeneity, PK/PD, and bioavailability into account. To speed up translation, it suggests uniform objectives (metabolic/epigenetic biomarkers, validated surrogate endpoints) and multimodal approaches (better dosages, multifaceted therapies, biomarker-driven trials). In addition to highlighting new technologies (organoids, humanized models, and nanodelivery), Russo emphasizes that effective clinical translation requires consistency and uniform documentation (Russo et al., 2024).

CONCLUSION

Through a variety of mechanisms, including antioxidant defense, modification of carcinogen metabolism, signaling pathway regulation, and epigenetic reprogramming, phytochemicals constitute a potent link between nutrition and cancer prevention. Although there are still issues with limited bioavailability and inconsistent human responses, preclinical and clinical research on important compounds—curcumin, resveratrol, EGCG, sulforaphane, lycopene, and quercetin—shows encouraging anticancer effects. Their therapeutic potential is being increased by developments in lipid-based carriers, complementary dosage forms, and nanotechnology. Combining nutrigenomics, metabolomics, and customized diets will allow precise cancer prevention adjusted to individual risk profiles. Phytochemicals may develop into essential, evidence-based components in subsequent tumor mitigation strategies with standardized safety, regulatory monitoring, and translational research.

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