

Cancer Chemoprevention through Plant-Derived Compounds

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ABSTRACT

Cancer remains a leading global cause of morbidity and mortality, prompting the exploration of preventive strategies beyond conventional treatments. Cancer chemoprevention, which involves the use of natural or synthetic agents to impede, delay, or reverse carcinogenesis, has gained significant attention, particularly through the study of plant-derived compounds. Phytochemicals such as curcumin, resveratrol, epigallocatechin gallate (EGCG), quercetin, and sulforaphane have demonstrated diverse mechanisms of action, including antioxidant and anti-inflammatory effects, modulation of enzyme activity, regulation of signaling pathways, and induction of apoptosis. Epidemiological and preclinical studies highlight the contribution of fruits, vegetables, herbs, spices, legumes, and nuts to reduced cancer risk, supported by the presence of bioactive compounds with chemopreventive potential. Clinical investigations, especially on curcumin, resveratrol, and EGCG, provide evidence of efficacy, although challenges such as poor bioavailability, lack of standardization, and regulatory hurdles persist. Advances in nanotechnology, extract standardization, and multidisciplinary collaborations offer promising strategies to overcome these barriers. Collectively, the integration of plant-derived compounds into preventive and therapeutic approaches underscores their potential in reducing cancer incidence and improving global health outcomes.

Keywords: Cancer chemoprevention, Plant-derived compounds, Phytochemicals, Antioxidant and anti-inflammatory activity, and Cancer prevention strategies.

INTRODUCTION

Cancer chemoprevention entails the use of natural or synthetic agents to impede, delay, or reverse carcinogenesis [1]. At the molecular level, these substances act on specific pathways that govern tumor development, progression, and metastasis. The search for effective chemopreventive compounds has increasingly focused on phytochemicals, bioactive substances naturally found in plants. Plant-derived compounds exhibit diverse mechanisms of action, such as antioxidant activity, anti-inflammatory effects, enzyme regulation, and modulation of signalling pathways implicated in oncogenesis. Human studies have shown that compounds like curcumin, resveratrol, and epigallocatechin gallate (EGCG) influence processes related to cancer development [2]. For centuries, humans have consumed such substances through fruits, vegetables, herbs, spices, legumes, and nuts. The finding that plant-derived compounds exert chemopreventive effects is intuitively consistent with this dietary tradition. Cancer currently represents a leading cause of fatality worldwide, with approximately 14 million new cases and 8.2 million deaths reported annually. Although research has improved the outcome of many cancer treatments, a comparable reduction in cancer incidence is an as-yet-unrealised goal. Cancer chemoprevention focuses on the use of natural or synthetic agents to retard or reverse the process of carcinogenesis prior to the development of invasive malignancy [3]. While the tumourigenic cascade has yet to be fully characterised, the process of induction and development appears to consist of at least three discrete and uninterrupted steps: initiation, promotion, and progression that occur sequentially. Tumourigenesis, therefore, represents a temporal event spanning months, if not years, prior to reaching full malignancy. Because the majority of efforts have focused on treatment options for advanced cancer, these interventions often prove ineffective as cancer cells become widespread and increasingly resistant to most cytotoxic drugs. Attempts to develop compounds able to target initiation or promotion and reverse chemo- and/or radio-resistance have given rise to a new and more effective treatment strategy, cancer chemoprevention [1, 2, 3]. Prenylated chalcones and flavonoids from non-edible plants

demonstrate multiple chemopreventive capabilities relevant to tumors of several tissue origins. Curcumin, obtained from the rhizomes of *Curcuma longa*, represents arguably the most widely studied natural product with chemopreventive potential. Quercetin, obtained from various agricultural crops and found ubiquitously in tea, fruit, vegetables, and red wine, has shown the capacity to exert protective effects at the initiation and promotion stages. Sulforaphane, found in cruciferous vegetables such as broccoli and cauliflower, induces phase II enzymes and oxidative stress response [1, 2, and 3].

Overview of Plant-Derived Compounds

Plant-derived compounds have generated significant interest as cancer chemopreventive agents. Natural compounds abundant in dietary fruits, vegetables, spices, legumes, nuts, and other plant sources have been shown to elicit antitumoral activities in various experimental models [4]. Phytochemicals are secondary metabolites produced by plants with functions such as ultraviolet protection and herbivore deterrence, encompassing polyphenols, flavonoids, terpenoids, carotenoids, aldehydes, and volatile oils. Several of these categories have demonstrated promising chemopreventive activity [4].

Mechanisms of Action

Plant-derived compounds provide a variety of possible mechanisms of cancer chemoprevention [1, 4]. In overview, phenolic compounds function as antioxidants, quenching free radicals and interfering with lipid peroxidation. Flavonoids possess anti-inflammatory activity by inhibiting enzymes such as cyclooxygenase (COX), lipoxygenase, and nitric oxide synthase that are involved in the production of inflammatory agents, and suppressing transcription factors like nuclear factor- κ B that regulate those genes. Plant-derived compounds also influence carcinogen metabolism by modulating the activity of phase I and II enzymes, hindering the conversion of procarcinogens to carcinogens and promoting detoxification, respectively [1, 4].

Antioxidant Properties

Antioxidants play a pivotal role in cancer chemoprevention. Epidemiological investigations associate elevated consumption of fruits, vegetables, and beverages with a reduced incidence of breast, colon, prostate, and lung cancers. These health benefits are generally attributed to plant-derived polyphenolic compounds, which include catechins, genistein, anthocyanins, resveratrol, curcumin, apigenin, and quercetin [4]. These polyphenols hold significant potential as therapeutic agents for malignant diseases due to their influence on numerous signaling pathways, ability to arrest cellular proliferation, promotion of apoptosis, and inhibition of angiogenesis [5]. Increasing evidence also supports that the effectiveness of chemopreventive drugs is enhanced when combined with phytochemicals; mixtures of plant polyphenols often exhibit biological activity that surpasses that of their individual constituents [4]. The modulation of cancer-signaling pathways by polyphenols is well documented. Citrus flavanones such as naringenin downregulate the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and simultaneously activate antioxidant defense mechanisms. Quercetin suppresses breast cancer progression through inhibition of the Akt/mTOR pathway and induction of autophagy. Epigallocatechin-3-gallate (EGCG) inhibits carcinogenesis by targeting mitogen-activated protein kinases (MAPK), growth factor signaling, activator protein 1 (AP-1), nuclear factor kappa B (NF- κ B), topoisomerase I, and matrix metalloproteinases. Curcumin prevents tumorigenesis via activation of nuclear factor erythroid 2-related factor 2 (Nrf2), restoration of p53 function, and regulation of inflammatory mediators [3].

Anti-inflammatory Effects

Plant-derived compounds are recognized for their anti-inflammatory properties, which play a role in inhibiting processes associated with cancer development and progression [6]. Inflammation is a key factor in the initiation, promotion, and progression of carcinogenesis; consequently, agents capable of modulating inflammatory responses are under investigation for their chemopreventive potential. Flavonoids, a subgroup of phytochemicals, demonstrate significant anti-inflammatory effects through their ability to influence multiple molecular pathways directly implicated in cancer-related inflammation [6].

Modulation of Enzyme Activity

In cancer chemoprevention, some plant-derived compounds modulate the activity of carcinogen-metabolizing enzymes. Sulforaphane, an isothiocyanate present in cruciferous vegetables, and curcumin, a polyphenol in turmeric root, both share this mode of action proven to have cancer-preventive effects. Additionally, quercetin, a flavonol found in many fruits, vegetables, and grains, is linked with these processes [3]. The chemicals involved in this function generally affect two groups of enzymes: Phase I and Phase II. Phase I involves cytochrome P450 enzymes, whereas Phase II encompasses conjugation enzymes [6]. Phase I enzymes, such as cytochrome P450 oxidase, can convert procarcinogens into reactive electrophilic metabolites known as proximate carcinogens. Examples of Phase I enzymes include aryl-hydrocarbon hydroxylase, NADPH-cytochrome P450 reductase, and NADPH dehydrogenase. In contrast, Phase II conjugation enzymes, including glutathione S-transferase, quinine reductase, glucuronosyl transferase, epoxide hydrolase, and nitro reductase, catalyze reactions that alter proximate carcinogens into stable, nontoxic, and water-soluble compounds readily excretable via bile or urine [3, 6].

Key Plant-Derived Compounds

The chemopreventive activity of several plant-derived compounds has been explored in preclinical and clinical studies. Among them, curcumin, resveratrol, epigallocatechin gallate (EGCG), quercetin, and sulforaphane have received more attention [4]. Curcumin is a polyphenol obtained from *Curcuma longa* that has chemoprotective properties through detoxification of carcinogenic agents, inhibition of pro-inflammatory processes and enzymes involved in carcinogen activation, regulation of apoptosis, and suppression of the nuclear transcription factor NF- κ B. Resveratrol is a stilbene found in high concentrations in the skin of red grapes, red wine, peanuts, and blueberries that exhibits a broad spectrum of anti-inflammatory, antiproliferative, antiangiogenic, proapoptotic, and antioxidant properties through the modulation of multiple signaling pathways. EGCG, the principal component of green tea, exhibits chemopreventive effects in several in vitro and in vivo models, acting mainly as a suppressor of NF- κ B activation and modulator of the EGFR pathway [4]. Other molecular targets include vascular endothelial growth factor (VEGF), activator protein (AP-1), signal transducer and activator of transcription 3 (STAT3), cyclooxygenase-2 (COX-2), and cyclin D1. Quercetin, a widespread flavonoid in fruits, vegetables, tea, and red wine, partly shares the same targets as EGCG but also affects mitogen-activated protein kinases (MAPKs) and PI3K/Akt signaling, enhancing antioxidant enzymes' activity. Sulforaphane occurs in cruciferous vegetables like Brussels sprouts, cabbage, and cauliflower and exerts its chemopreventive potential by inducing mammalian phase 2 enzymes, resulting in the detoxification of potential carcinogens [4].

Curcumin

Curcumin is a naturally occurring polyphenol found in turmeric (*Curcuma longa*), mainly cultivated in India and Southeast Asia. It constitutes about 5% of turmeric root powder, mainly as curcumin (diferuloylmethane) [7]. Traditionally used in Chinese medicine and Ayurveda, curcumin has antioxidant, anti-inflammatory, and antiproliferative properties. It acts as a free radical scavenger, inhibits oxidative damage, and enhances antioxidant enzymes like glutathione-S-transferase and NRF-2. Curcumin downregulates transcription factors such as NF- κ B, reducing expression of inflammatory genes, including COX2, LOX, iNOS, and cytokines such as TNF α and IL-6. It also inhibits genes involved in cell survival, induces apoptosis, and exhibits anti-angiogenic effects [7]. Curcumin has been extensively studied for its potential role in cancer prevention and therapy, displaying anti-tumor, anti-invasion, and antimetastatic effects and the ability to circumvent chemoresistance in vitro. It sensitizes drug-resistant tumors and influences molecular mechanisms through signal transduction pathways. Acting as a multi-targeted therapy, curcumin affects various cancers, including colorectal, gastroenterological, and prostate cancers [8]. Nanoformulations improve their bioavailability and therapeutic efficacy. Clinical studies highlight its potential as a chemopreventive agent, although further research is necessary to fully elucidate its mechanisms and optimize its application in cancer treatment [7, 8].

Resveratrol

Resveratrol, a polyphenolic stilbene derivative naturally found in grapes and red wine, has attracted significant interest due to its potential anti-neoplastic, antioxidant, anti-inflammatory, and neuroprotective effects [9]. The compound's anti-cancer properties appear to result from interactions with multiple cellular signaling pathways that regulate apoptosis, cell cycle control, inflammation, angiogenesis, and metastasis [10]. Resveratrol restricts oncogene expression and activates tumor-suppressing genes and various transcription factors as part of its chemopreventive action [9, 10]. Additionally, the compound targets cancer stem cells and influences the tumour microenvironment, potentially enhancing the effectiveness of chemotherapy while simultaneously reducing its side effects.

Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate (EGCG), the most abundant catechin in green tea, demonstrates chemopreventive and anticancer activities in vitro and in vivo. It exerts preventive and therapeutic effects against various malignancies, including lung, head and neck, skin, digestive tract, prostate, breast, ovarian, and colon cancers [11]. Recent research examines EGCG's capacity to target deregulated signaling pathways and noncoding transcripts in different cancers with a focus on JAK/STAT, Wnt/ β -Catenin, TGF/SMAD, NOTCH, SHH/GLI, and TRAIL-mediated cascades [12]. EGCG inhibits tumorigenesis of the lung, oral-digestive tract, and prostate. It suppresses tobacco-specific nitrosamine-induced lung tumorigenesis and also cisplatin- or dimethylarsinic acid-induced lung tumors. EGCG inhibits diethylnitrosamine-cycled liver tumors through insulin-like growth factor-signaling blockade. Oral administration of EGCG remains effective against prostate cancer cell growth in xenograft models by proapoptotic up-regulation. Anticancer effects also emerge in cervix, breast, colon, pancreas, and bladder cancers. In ovarian cancer, diet-derived gallated catechins prevent TGF- β -mediated epithelial-mesenchymal transition (EMT), cell migration, and vasculogenic mimicry. EGCG blocks TGF- β 1/Smad signaling pathways to suppress EMT and invasion in anaplastic thyroid carcinoma and inhibits TGF- β 1-induced EMT and acetylation of Smad2 and Smad3 in A549 lung cancer cells. EGCG attenuates TGF- β -mediated EMT via suppression of Smad2 and Erk1/2 signaling pathways in non-small cell lung cancer [11, 12]. EGCG inhibits colorectal cancer

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stem cells by Wnt/ β -Catenin pathway repression. Wnt/ β -Catenin signaling regulates MGMT gene expression in cancer, and its inhibition prevents chemoresistance. EGCG preferentially curtails O6-Methylguanine DNA-Methyltransferase expression in glioblastoma cells. In head and neck cancer, it represses β -catenin transactivation and promotes β -catenin degradation. Growth inhibition of breast cancer cells occurs via β -catenin signaling inactivation. EGCG diminishes pancreatic cancer cell growth, invasion, and migration partly through Akt-pathway blockade and EMT suppression; combined treatment with Gemcitabine enhances efficacy. It attenuates head and neck cancer stemness by Notch-pathway repression and exhibits anticancer activity against cholangiocarcinoma cells. EGCG curbs proliferation of colorectal cancer cells through Notch signaling modulation, targets cancer stem-like cells, and enhances chemosensitivity [11, 12]. In nasopharyngeal carcinoma, EGCG sensitizes cells to TRAIL-mediated apoptosis by NF- κ B activation.

Quercetin

Quercetin, a ubiquitous flavonoid found in various plants, exhibits potential chemopreventive effects against cancer. As a polyphenolic compound, it influences numerous cellular processes associated with carcinogenesis. Quercetin modulates gene expression, alters microRNA profiles, and impacts signaling pathways linked to tumor development [13]. Its capacity to inhibit various kinases contributes to the suppression of the proliferation of malignant cells. Furthermore, quercetin may potentiate the effects of standard chemotherapeutic agents, enhancing their therapeutic efficacy. Addressing limitations related to bioavailability and metabolism remains critical for optimizing its clinical application. Collectively, the multi-targeted actions of quercetin underpin its significance as a candidate in cancer chemoprevention and therapy [13].

Sulforaphane

Sulforaphane (SFN) is a biologically active isothiocyanate derived from the glucosinolate glucoraphanin contained in broccoli. It undergoes enzymatic hydrolysis either during preparation and mastication or via bacterial microflora in the colon. SFN demonstrates a wide range of anticancer effects related to interference with multiple hallmark cancer pathways. The compound modulates the cellular antioxidant system by elevating free glutathione and stimulating antioxidant enzymes such as NAD(P)H: quinone oxidoreductase 1, heme oxygenase 1, and glutathione S-transferase through activation of the nuclear factor erythroid 2-related factor 2 (NRF2)–Kelch-like ECH-associated protein 1 signaling pathway. It also targets proteins, including oncogenes, transcription factors, epigenetic regulators, and inflammatory and apoptotic mediators, thereby affecting multiple cellular signaling pathways. SFN regulates gene expression at different stages: transcriptionally by inhibiting activity or expression of DNA-binding factors (e.g., NF- κ B, STAT3, AP-1, c-Myc, Sp-1), post-transcriptionally by modulating microRNAs, and epigenetically by inhibiting histone deacetylase activity and DNA methyltransferases [14]. The compound exhibits high bioavailability; upon oral administration, plasma concentrations may reach low micromolar levels, and urinary excretion occurs within 12–24 h. In animal models, repeated intraperitoneal administration results in plasma and intracellular concentrations exceeding 20 and 100 μ M, respectively. Production of SFN from broccoli sprout extract is also observed in the lung and cardiovascular tissues of treated rats. Broccoli sprout ingestion reduces HDAC activity in human peripheral blood mononuclear cells, consistent with effects detected in cell-based and animal experiments. SFN selectively targets cancer cell lines while sparing normal cells, enhancing its potential as a chemopreventive compound. Epidemiological studies associate regular intake of cruciferous vegetables and other glucosinolate-rich plants with decreased risk of prostate, lung, colorectal, breast, ovarian, and pancreatic cancers [15].

Sources of Plant-Derived Compounds

A variety of plant-derived compounds isolated from food sources, especially fruits, vegetables, herbs, and spices, offer promising chemopreventive potential [3]. Edible plants also constitute a major source of natural chemopreventive agents [4]. The regular inclusion of legumes and nuts in the diet further contributes to chemopreventive compounds in human nutrition. Plant-derived compounds presenting diverse chemical structures and biological functions contribute to chemoprevention by diverse mechanisms.

Fruits and Vegetables

Fruit and vegetables are the principal sources of phytochemicals and, thus, produce important health benefits. Epidemiological evidence supports the ability of a fruit- and vegetable-rich diet to prevent the formation of different tumors [2]. Edible vegetables and fruits present in the daily diet contain a large panel of phytochemicals with antioxidant, anti-carcinogenic, and chemopreventive activities [16]. Some phytochemicals, which can be classified into several categories including phenolic acids (e.g., ellagic acids), flavonoids (e.g., quercetin), carotenoids, and vitamins, also display antiproliferative activity toward tumor cells with low toxicity. Such investigations have been the driving force in the search for additional chemopreventive phytochemicals present in fruits and vegetables. Most recently, one important class of dietary phytochemicals, ellagitannins (ET), has been studied in depth for its interesting chemopreventive properties and anticancer activities. Researches are mainly

concentrated on the chemistry, sources, pharmacokinetics, efficacy, and molecular mechanisms of these polyphenols [2, 16].

Herbs and Spices

Herbs and spices have been widely used as food flavorings and folk medicines for thousands of years. Numerous studies have documented their antioxidant, anti-inflammatory, and immunomodulatory effects, which may be related to the prevention and treatment of diverse cancers, including those of the lung, liver, breast, stomach, colorectum, cervix, and prostate. Several contain bioactive compounds such as curcumin, thymoquinone, piperine, and capsaicin, which induce apoptosis, inhibit tumor proliferation, migration, and invasion, and sensitize tumors to therapy [17]. The antioxidant, anti-inflammatory, and immunomodulatory properties of these compounds support their potential in cancer prevention and treatment [18]. Oxidative stress, inflammatory processes, and immune responses have been linked to cancer development and metastasis; spices may help modulate these mechanisms by inhibiting COX-2 expression and β -catenin activation, suppressing pathways such as leukotriene A4 hydrolase and beta-catenin-dependent signaling, inhibiting inflammatory factors including NF- κ B, inducing apoptosis, and enhancing chemosensitivity. The Wnt pathway plays a significant role in the pathology of many cancers, and dietary factors that induce apoptosis may delay cancer growth. Different herbs, hops, and fruits also exhibit antioxidant activity, indicating potential for cancer prevention and therapy [17, 18].

Legumes and Nuts

Legumes and nuts regularly contribute to dietary chemoprevention through assorted vitamins, mineral micronutrients, protein, and phytochemicals. Legume protein and associated hydrolysates modulate enzymatic and molecular measures of oxidative stress, inflammation, and AhR-myriad signaling pathways [19]. Tree nuts provide complex mixtures of tocopherols, tocotrienols, and phenolic compounds that collectively mediate antioxidant function, receptor activity, cell cycle regulation, and pro-apoptotic processes [20].

Clinical Trials and Evidence

Several plant-derived compounds have been subjected to clinical trials focusing on their efficacy in cancer chemoprevention. Curcumin is one of the most widely studied phytochemicals in this regard. Because of its broad spectrum of molecular targets and its ability to inhibit multiple cancer-related signaling molecules, curcumin has progressed to phase III clinical trials [21]. Resveratrol has also undergone human studies; at low doses, it can mimic caloric restriction and activate the sirtuin pathway [2]. Preclinical and translational evidence indicate that resveratrol inhibits all three stages of carcinogenesis initiation, promotion, and progression and exerts chemopreventive activity at physiologically relevant doses. Epigallocatechin-3-gallate (EGCG), a well-documented chemopreventive agent from green tea, is currently being investigated in ongoing clinical trials that examine its effects on colorectal adenomas, prostate cancer, and lung cancer. Other compounds, such as the isothiocyanate sulforaphane and the flavonol quercetin, have demonstrated promising chemopreventive activities and also warrant further clinical evaluation [4].

Efficacy of Curcumin

Cancer chemoprevention comprises the spectrum of strategies aimed at retarding, reversing, or impeding the carcinogenic process before the emergence of a neoplasm or its clinical manifestation. Numerous plants and their constituents have demonstrated the ability to prevent, inhibit, delay, or reverse carcinogenesis. Plant-derived compounds exert multiple chemopreventive actions, including powerful antioxidant and anti-inflammatory effects, inhibition of cytochrome P450 enzymes, induction of detoxifying phase II enzymes, prevention of DNA adduct formation, modulation of epigenetic alterations, inhibition of cell proliferation, and the promotion of apoptosis. These compounds are abundant in fruits, vegetables, herbs, spices, legumes, seeds, and nuts [1, 5]. Among the hundreds of plant-derived compounds that have garnered significant scientific interest in the prevention of various malignancies, curcumin, resveratrol, epigallocatechin-3-gallate (EGCG), quercetin, and sulforaphane stand out. Their chemopreventive properties have been evaluated extensively in clinical settings, with curcumin, resveratrol, and EGCG undergoing the most rigorous scrutiny. The examination of curcuminoids for cancer chemoprevention in clinical trials has, however, unveiled several challenges and underscored the necessity for further research to elucidate and validate these compounds' efficacy [19, 20].

Resveratrol in Cancer Prevention

Resveratrol, a polyphenolic stilbene derivative found in grapes, red wine, and other plants, has gained considerable interest due to its anti-carcinogenic properties encompassing cellular and molecular mechanisms. Evidence demonstrates that resveratrol exerts antioxidant, anti-inflammatory, and neuroprotective activities [20]. Its anti-cancer effects involve modulation of signaling pathways related to apoptosis, cell cycle regulation, inflammation, angiogenesis, and metastasis. Resveratrol restricts oncogene expression, activates tumor-suppressor genes, and regulates transcription factors. Moreover, it targets cancer stem cells that contribute to treatment resistance and disease recurrence [20]. Resveratrol influences the tumor microenvironment and sensitizes cancer cells to chemotherapeutic agents, which may enhance treatment efficacy and reduce side effects. These properties are

largely attributed to effects on mitochondria, which are central to energy production, signaling, and apoptosis processes intimately linked to cancer development and progression. Delineating the molecular targets and mechanisms of resveratrol clarifies its potential applications in chemoprevention, therapy, and neuroprotection [9]. Resveratrol also potentiates the toxicity of arsenic trioxide (As₂O₃), a potent therapeutic agent for acute promyelocytic leukemia and lung tumors hindered by multi-drug resistance (MDR). In lung adenocarcinoma A549 cells, resveratrol enhances As₂O₃-induced apoptosis [22]. The combination induces greater genotoxicity and oxidative stress than either agent alone, synergistically increasing cytochrome c release, Fas and FasL expression, and apoptotic cell death. Chemosensitization of resistant cancer cells represents a promising field in oncology [22]. Resveratrol appears relevant not only for cancer chemoprevention but also for treatment by targeting fundamental pathways of carcinogenesis and host defense. It displays synergistic effects with chemotherapeutics such as 5-fluorouracil and cisplatin that sensitize cancer cells. A multidisciplinary strategy combining resveratrol with conventional therapies may reduce adverse toxicities to non-target tissues, decrease MDR development, and improve overall therapeutic outcomes [20, 22].

EGCG and Breast Cancer

Among the multitude of phytochemicals associated with anticancer properties, epigallocatechin-3-gallate (EGCG) is one of the most powerful. Derived from tea, EGCG acts broadly against cancer, inflammation, and oxidative stress. Specific EGCG mechanisms related to chemoprevention include radical scavenging, NF- κ B inhibition, caspase-3 activation, and modulation of tumor formation and proliferation. Its effects under different conditions are remarkable, with EGCG alone or combined with other anticancer agents successfully applied to prevent breast, lung, colonic, liver, prostate, and skin cancer in vitro and in vivo. Recent trials also highlight the role of this flavonoid in the regulation of genetic alterations during carcinogenesis [21, 22]. Given that breast cancer is now the most commonly diagnosed cancer worldwide and a major cause of mortality, a favorable effect of EGCG on this type is highly desirable. Rangnekar et al. proposed EGCG for the chemoprevention of different breast cancer subtypes, alone or combined with appropriate chemotherapeutics. Huang et al. evidenced epigenetic effects, such as TIMP-3 gene demethylation, that reverse tamoxifen resistance and inhibit proliferation in MCF-7 breast cancer cells. In a more prophylactic setting, Crozier et al. demonstrated in a population-based case-control study that pretreatment with green tea catechins was associated with a lower risk of breast cancer. Furthermore, the role of EGCG in affecting other pathways involved in breast cancer development was demonstrated by regulating HYAL-1 hyaluronidase expression [20, 21, 22].

Challenges in Research

Plant-derived compounds can be grouped into four categories: phenolics, carotenoids, alkaloids, and nitrogen-containing compounds. Algicolous fungi isolated from marine environments also produce a number of metabolites that represent a major and expandable source of marine natural products for the discovery of new drugs and novel compounds related to human health. Consumption of medicinal plants and their derived compounds has been part of the human diet since prehistoric times and remains an effective approach to screen large numbers of natural compounds with chemopreventive and therapeutic properties [2]. Despite their beneficial effects, the use of plant-derived compounds still relies on tradition rather than evidence-based medicine, and their actual efficacy has been poorly evaluated in human clinical settings. Many phytochemicals with chemopreventive properties have demonstrated only poor bioavailability, thus limiting their application in clinical trials. Promising strategies to overcome this challenge include the development of synthetic analogs or the use of appropriately engineered nanocarriers to deliver and protect those agents from early inactivation. In parallel, the low level of extraction reproducibility presents a further limitation in the clinical application of plant-derived compounds, since even slight modifications to the production protocol may result in significantly different phytochemical profiles and associated properties [3]. Many countries still allow the use of therapeutic products containing medicinal plant extracts without requiring the completion of extensive preclinical and clinical testing. The existing lack of standardized in vitro and in vivo testing protocols and the absence of homogenous regulatory processes for their approval confine their use outside those jurisdictions to either clinical trials or anecdotal experiments [2, 3].

Bioavailability Issues

Plant-derived compounds may contribute to cancer chemoprevention [4]; however, their potential remains largely unexplored. Bioavailability represents a critical barrier to clinical efficacy. Modifications during digestion, metabolism, and systemic absorption often limit the concentrations that reach target tissues [23], although interactions among different phytochemicals can modulate these effects. Conventional evaluations typically measure urinary excretion as a proxy for bioavailability, but many researchers advocate for advanced delivery systems to enhance plasma concentrations and tissue targeting. Lipid-based carriers form a strategic approach to improve water solubility and stability, reduce rapid systemic clearance, mitigate intestinal and hepatic metabolism, and facilitate selective uptake by cancer cells. Quantification of tissue levels of chemopreventive agents is essential to elucidate the mechanisms of action of both nanoparticles and phytochemicals while minimizing toxicity [4, 23].

Overcoming these bioavailability challenges forms an essential step toward realizing the full clinical potential of plant-derived chemopreventive compounds.

Standardization of Extracts

The ability to define the principal phytochemicals present in crude extracts is essential for controlling extract composition before proceeding to chemopreventive activity testing. Variation in phytochemical composition due to geographical origin, plant variety, or cultivation system can occur. In addition, the phytochemical profile may fluctuate with the harvesting period, processing, and storage. Developing a standardization process to monitor the phytochemical profile of crude extracts during their preparation is thus of primary interest. Phytochemical analysis of *Aristolochia tagala* (AT) and *Curcuma caesia* (CC) extracts showed the presence of phenols, flavonoids, terpenoids, alkaloids, and tannins. According to [24], these extracts contain a variety of phytochemicals that exert antioxidant and anticancer activities. Phenolics and flavonoids act directly as antioxidants by scavenging free radicals, by chelating metals involved in the Fenton reaction, and may also act indirectly as signaling molecules that lead to the induction of detoxification enzymes [24]. Both CC and AT contain a high amount of phenolic compounds, while large quantities of flavonoids were detected in AT only. In contrast to CC, AT was the only extract in which alkaloids and tannins were identified. Terpenoid content was very high in both plants on a dry weight basis (2.85 and 3.15 mg/g, respectively) [24].

Regulatory Hurdles

Several obstacles limit the research and translational development of cancer chemopreventive agents. Extract standardization and screening for potential genotoxic and other toxic compounds represent additional challenges limiting drug development pipelines [5]. Post discovery, pharmaceutical companies face a scarcity of cost-effective, rapid protocols to assess efficacy and investigate molecular targets of new chemopreventive agents. Many companies prefer evaluating the modulation of biomarkers known to participate in carcinogenesis, rather than conducting extensive epidemiological or invasive in vivo dose-response studies. However, the limited number of well-established carcinogen-associated biomarkers reduces the applicability of this approach. Epidemiological studies remain essential for both identifying chemopreventive agents and defining specific subsets of cancers for clinical development, representing a significant regulatory hurdle in the validation of new agents [2]. Consequently, most drug candidates advance to clinical development only after extensive preclinical investment, imposing a heavy burden on academic researchers who typically lack resources for comprehensive preclinical evaluations. In contrast, pharmaceutical companies reach this stage with a relatively small pool of candidates, each rigorously scrutinized through clinical and scientific disciplines, contravening the current academic model and regulatory prerequisites for candidate qualification [25]. The IND-enabling phase, comprising toxicology, pharmacokinetics, formulation, and regulatory components, poses a formidable barrier to progressing new drug entities, especially for academic and small biotechnology developers with limited drug development experience [26]. The high costs and extensive time required to transition agents from preclinical development to human clinical trials deter researchers from engaging in this critical phase despite advancing promising candidates to early preclinical studies. Overcoming these regulatory obstacles necessitates enhanced collaborative efforts among academia, the pharmaceutical industry, and regulatory agencies to streamline the advancement of promising preventive agents, thereby maximizing the impact of chemoprevention in reducing disease-related morbidity and mortality.

Future Directions in Research

Although some plant-derived compounds have shown promising results in the chemoprevention of cancer, unequivocal clinical evidence of their efficacy is still scarce. Future research should focus on identifying subjects likely to benefit from preventive administration of these compounds, circadian modulation of their action, reliable measures of their pharmacokinetics and pharmacodynamics, and appropriate preclinical models mimicking real clinical intervention [4]. Furthermore, the use of plant-derived compounds in combination with traditional antineoplastic drugs is particularly interesting because this approach generally exhibits synergistic effects and reduces the toxicity of chemical drugs. In addition, the control of cancer hallmarks by these compounds is only partially understood, and an accurate description of the molecular pathways involved in the former is essential for a more rational design of effective chemoprevention strategies [4]. The development of new chemopreventive agents to offer additional possibilities remains highly desirable. Although only a limited number of plant-derived compounds have recently been subjected to extensive investigations, the necessarily extensive screening of natural products already provides several candidates of remarkable chemopreventive potential. Unveiling their mechanisms of action should be developed in parallel with the studies currently examining the most promising lead compounds [4].

Personalized Nutrition

Population-level cancer risk remains very high, yet currently, preventive recommendations and intervention strategies remain generic and population-averaged [27]. The growing accessibility of low-cost consumer genotyping has driven the rapid expansion of personalised or precision nutrition, in which dietary composition is individualized in accordance with genotype; thus, across a population of many individuals, there is broad-reaching scope for individualised preventive intervention. In contrast to nutrigenetics, in which genetic variation modulates the physiologic response to a given nutrient, the nutrigenomic perspective considers the broader range of diet-induced modulations in gene expression and global changes in metabolic processes, emphasising the significance of single-nucleotide polymorphisms and epigenetic effects acting on health and disease susceptibility [27]. Such approaches provide excellent opportunities for the effective design of individual-specific and chemically rational dietary intervention strategies.

Integration with Conventional Therapies

The integration of plant-derived chemopreventive agents with conventional anticancer drugs shows promise for enhanced therapeutic outcomes. A few preclinical studies have demonstrated ameliorative effects of curcumin and quercetin against toxicity induced by anticancer drugs, while there is scant evidence on the combined anti-cancer activity of such mixtures [4, 5]. A complex polyphenolic mixture (flavonoids, phenolic acids, and coumarins) extracted from *Cycas revoluta* upregulated intrinsic and extrinsic apoptotic genes to eradicate different cancer subtypes and synergized with 5-fluorouracil in targeted chemotherapeutic applications [4]. Propolis flavonoids formulated in nanoscale emulsions synergistically inhibited tumour growth in an animal model of melanoma [2]. When combined with metformin, resveratrol induced apoptosis and reduced colon tumour formation in an in vivo cancer model. Several vegetable extracts that show anticancer effects in animal models modulated signalling pathways that simultaneously control cell fate and metabolism (e.g., AMPK, mTOR, Akt/PKB, PARP, HIF-1 α , and HDACs). These plant-derived compounds exhibit a marked synergistic effect on the action of a range of targeted chemotherapeutic agents. Integration and experimentation will be necessary to support wider use of natural compounds in clinical oncology.

Exploration of New Compounds

The search for new molecules from natural products with cancer prevention potential has not yet been exhausted. Present-day research also focuses on designing and identifying novel semisynthetic compounds with a strong chemopreventive profile. Other promising areas of research include synergistic cancer chemoprevention involving either a mixture of phytochemicals or phytochemicals in combination with conventional cancer therapies. As has been noted previously, new trends in clinical trials research also include a focus on chemopreventive agents in which the compound is derived from a phytochemical source. New developments include cancer chemoprevention based on nutritional genomics and the identification of novel dietary compounds in fruits and vegetables [20, 21]. The failure to introduce a greater number of chemopreventive agents into clinical use may be attributable to several factors. One particular source of confusion stems from misleading information on the levels of plant-derived phytochemicals in whole foods and the uses of plant extracts, which contain different levels and proportions of bioactive compounds. Furthermore, the bioavailability of many plant-derived compounds is often not taken into account, which further confuses the situation. Another major problem preventing the use of clinical trials with cancer chemopreventive agents especially concerns the long-term use and safety [20]. A large proportion of these substances is still considered to be functional foods and is therefore not subjected to the rigorous toxicity testing applied to pharmaceuticals. Consequently, for most plant-derived molecules with cancer chemopreventive potential, a tumor-inhibitory effect has been described mainly in preclinical studies, and only a few compounds have made it to clinical trials [21].

Public Health Implications

Scientific evidence confirms the positive contribution of phytochemicals capable of interrupting one or more phases of carcinogenesis when present at the target organs [21]. Key compounds with marked chemopreventive properties, curcumin, resveratrol, epigallocatechin-3-gallate, quercetin, and sulforaphane, are available in fruits, vegetables, herbs, spices, legumes, and nuts [2]. The scientific rationale relates primarily to intake at the population level of fruit, vegetables, etc., rich in these compounds [4]. Much remains to be done to establish the extent of risk reduction achievable at the population level. Nutritional and education programs can be conceived with this objective and the current knowledge. The concept is clear and already applies to other diseases.

Dietary Recommendations

Policies set by the U.S. Department of Health and Human Services provide guidance to inform, educate, and motivate Americans to adopt healthy behaviors, contribute to preventing the development of chronic diseases, and promote health. Public awareness can contribute substantially to increasing knowledge regarding the avoidance of cancer risk factors. Adopting a well-balanced, low-calorie diet rich in plant foods and reduced in processed, meat, and saturated fats, together with good hygiene habits, physical activity, and reduction of carcinogen exposures, is a

model health choice relevant to all the major cancers [28]. Considering the tumor-preventing properties of natural phytochemicals, dietary recommendations could be supplemented with the promotion of a rich and varied intake of fruits, vegetables, legumes, nuts, and whole grains. Thus, a balanced and prudent diet would be complemented for an additional chemopreventive effect by a well-determined content of phytochemicals [2]. The Dietary Approaches to Stop Hypertension diet, emphasizing fruit, vegetable, and low-fat dairy intake, along with reduced saturated and total fat intake, and the Mediterranean diet, which privileges intake of minimally processed foods, plant-based foods, and olive oil, along with a moderate intake of fish, are recommended models of chemopreventive dietary profiles. Plant-based dietary recommendations already in place in many programs to promote weight loss and reduce the risk of heart disease are also likely to have beneficial effects on risk reduction across many cancer types [28]. Development of intervention and prevention programs based on a better understanding of plant-derived chemopreventive compounds may significantly reduce cancer risk at the population level, and continued efforts in these directions appear worthwhile.

Educational Programs

Several nutritional surveys have documented the disconnect between dietary recommendations and actual eating patterns of the population. The food choices of most individuals with limited culinary skills are heavily influenced by advertisements and food-label claims [3, 4]. Although nutrition experts have developed dietary guidelines to convey health recommendations (for example, My Plate, 10 Good Health Guidelines, Canadian Healthy Eating Index), consumers need simple tools to help them make wise choices in a chaotic food environment. Because the pathway from food intake to public health may involve a number of confounding factors, it is also necessary to investigate public knowledge and awareness of nutrition and health-related issues. Similarly, educational programs should be designed to reach the health professionals through continuing education and others who influence the behavior of the public, such as teachers and day care personnel, because these sectors of the community play a large role in shaping health education messages [3].

CONCLUSION

Plant-derived compounds represent a powerful and sustainable avenue for cancer chemoprevention, complementing existing therapeutic strategies. Extensive evidence from epidemiological, preclinical, and clinical studies highlights the ability of phytochemicals such as curcumin, resveratrol, EGCG, quercetin, and sulforaphane to target multiple stages of carcinogenesis through antioxidant, anti-inflammatory, pro-apoptotic, and signaling-modulatory mechanisms. Despite challenges of bioavailability, dosage optimization, and regulatory approval, advances in nanotechnology, formulation science, and standardized extraction techniques are steadily addressing these limitations. By bridging traditional knowledge with modern scientific innovation, plant-based chemopreventive agents offer a cost-effective and culturally relevant approach to reducing the global cancer burden. Future success will depend on multidisciplinary collaboration, robust clinical validation, and the integration of phytochemicals into evidence-based public health policies.

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CITE AS: Awafung Emmanuel (2025). Cancer Chemoprevention through Plant-Derived Compounds. EURASIAN EXPERIMENT JOURNAL OF MEDICINE AND MEDICAL SCIENCES, 7(1):49-58