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Preventing Cancer: The ROOT Protocols

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Abstract

In 2022, approximately 20 million new cancer cases and 9.7 million cancer deaths occurred worldwide. By 2050, new cases are projected to double, driven by population growth, aging, and increased exposure to risk factors. Up to 40% of cancers may be preventable by addressing lifestyle and environmental risk factors. Numerous nutraceuticals and repurposed drugs exhibit chemoprophylactic properties. Epigallocatechin gallate (EGCG), a polyphenol in green tea, appears to be the most effective agent against multiple cancers, followed by curcumin, a polyphenol derived from turmeric (*Curcuma longa*), vitamin D, and omega-3 fatty acids. Using artificial intelligence and leveraging synergistic effects among these compounds, we developed the ROOT 3, ROOT 4, ROOT 5, ROOT 6, and ROOT 9 chemoprophylactic protocols. The mechanistic activity of each nutraceutical is described, along with the estimated risk reduction for the most common types of cancer. These protocols may offer a low-risk and accessible strategy to reduce cancer incidence.

Keywords: Cancer prevention, chemoprevention, nutraceuticals, epigallocatechin gallate, curcumin, vitamin D, omega-3 fatty acids

Introduction

Cancer is a global threat, responsible for more than 10 million deaths annually. In the United States, cancer is the second most common cause of death, exceeded only by heart disease. The American Cancer Society estimated that 2,001,140 new cancer cases and 611,720 cancer-related deaths were projected to occur in the United States in 2024. (1) A recent study highlights a troubling trend: 17 types of cancer are becoming more prevalent in younger generations, with associated mortality also rising. (2) Colorectal cancer, once the fourth most common cause of cancer death among both men and women under 50 in the late 1990s, is now the leading cause in men and the second leading cause in women. (1)

At least 42% of newly diagnosed cancers in the United States are potentially avoidable, including 19% attributed to smoking and at least 18% due to excess body weight, alcohol consumption, poor nutrition, and physical inactivity. (3) Key interventions to reduce cancer risk include smoking cessation; limiting or eliminating alcohol intake; improving nutrition; addressing insulin resistance and metabolic syndrome; engaging in moderate physical activity; and supplementing with epigallocatechin gallate (EGCG, found in green tea), curcumin (a polyphenol derived from turmeric), vitamin D3, and omega-3 fatty acids—the foundation of the Root Protocols. (3)

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The DO-HEALTH trial was a 3-year, multicenter, double-blind randomized controlled trial (RCT) using a 2 × 2 × 2 factorial design to evaluate the individual and combined effects of supplemental vitamin D3 (2000 IU/day), marine omega-3 fatty acids (1 g/day), and a simple home-based strength exercise program. Notably, the vitamin D dose used was relatively low. These interventions were compared with a placebo and a control group. (4, 5) Each intervention independently reduced cancer risk, but the combination was synergistic and highly effective, with an adjusted hazard ratio of 0.39.

Although reported as a negative study, the NIH-funded Vitamin D and Omega-3 Trial (VITAL) further supported the protective effect of vitamin D on cancer mortality, showing lower rates of cancer-related deaths among participants randomized to vitamin D3 versus placebo (HR, 0.72; 95% CI, 0.52–1.00). (6)

Many other nutraceuticals appear to be highly effective in preventing cancer. These are listed below. With the assistance of artificial intelligence (Perplexity), we developed a series of nutraceutical-based protocols (ROOT Protocols) to support cancer prevention. Because most cancers occur in individuals older than 65 years due to cumulative risk exposure, these protocols—particularly ROOT 3 through ROOT 5—may be especially beneficial for this population.

Germline Cancer Syndromes and Preventive Considerations

Certain germline mutations—inherited changes in DNA present in all cells—substantially increase cancer risk by disrupting normal cellular regulation and DNA repair mechanisms. These mutations account for approximately 5% to 10% of all cancers and are associated with specific gene variants that predispose individuals to distinct cancer types and hereditary cancer syndromes:

- ***BRCA1*/*BRCA2* mutations:** associated with up to a 70% lifetime risk of breast cancer in women
- ***TP53* mutations (Li-Fraumeni syndrome):** associated with a >50% lifetime risk of multiple cancers
- **Lynch syndrome:** confers a 50% to 70% lifetime risk of colorectal cancer and up to 60% risk of endometrial cancer in women
- ***APC* mutations (familial adenomatous polyposis):** associated with a nearly 100% lifetime risk of colorectal cancer without intervention

In addition to genetic screening, surgery, and other interventions, the ROOT 6 or ROOT 9 protocols may be appropriate for patients with inherited cancer syndromes. However, these nutraceuticals and repurposed drug protocols should be integrated into a comprehensive clinical management plan.

The following nutraceuticals and repurposed drugs demonstrate cancer-preventive potential:

Green Tea Extract (EGCG)

EGCG, a polyphenol found in green tea, exhibits multifaceted anticancer properties by targeting tumor biology, modulating the immune system, and influencing metabolic pathways. (7) Preclinical and clinical studies support the role of EGCG in cancer prevention. (8-15)

Mechanisms of action in cancer prevention

Immune system modulation

- **Enhances cytotoxic immune responses:** EGCG promotes antitumor activity of $CD8^+$ T cells and natural killer (NK) cells by increasing their infiltration into tumors and boosting granzyme/perforin-mediated apoptosis. (7) It also stimulates dendritic cell maturation, improving antigen presentation.
- **Suppresses immunosuppressive cells:** EGCG reduces myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), which typically inhibit immune responses. (7) It has been shown to increase the ratio of active cytotoxic T lymphocytes to Tregs in tumors, effectively converting "cold" tumors to "hot" tumors and significantly improving responsiveness to antitumor immunotherapy. (16)
- **PD-1 axis and TLR4 pathway:** EGCG exerts anticancer effects by enhancing antitumor immunity via the programmed death 1 (PD-1) axis and Toll-like receptor 4 (TLR4) signaling pathways. (17, 18)
- **Reprograms tumor-associated macrophages (TAMs):** By downregulating chemokines such as CCL2 and CSF-1, EGCG limits TAM recruitment and shifts their polarization from pro-tumorigenic (M2) to antitumor (M1) phenotypes. (7)

Metabolic disruption in cancer cells

- **Inhibits glucose metabolism:** EGCG

blocks glucose uptake by suppressing glucose transporter 1 (GLUT1) and targets hexokinase 2 (HK2), a key glycolytic enzyme, thereby reducing ATP production. (7, 11) This disrupts the Warburg effect—a hallmark of cancer metabolism.
- **Targets glutamine and fatty acid pathways:** EGCG interferes with glutaminase and fatty acid synthase, enzymes critical for tumor growth under nutrient stress.

Direct antitumor effects

- **Induces apoptosis and cell cycle arrest:** EGCG upregulates pro-apoptotic proteins (eg, cytochrome c) and downregulates anti-apoptotic proteins such as Bcl-2, while arresting the cell cycle at the G1 phase via p21 activation. (7, 9)
- **Inhibits angiogenesis via VEGF:** EGCG significantly reduces the expression of vascular endothelial growth factor (VEGF) and its receptors, suppressing angiogenesis—a key process in tumor progression and a target in both cancer prevention and treatment.
- **Inhibits oncogenic signaling**. EGCG inhibits the Wnt pathway by promoting β-catenin phosphorylation and degradation, and also suppresses the Sonic Hedgehog pathway by targeting associated transcription factors.
- **Modulates epigenetics**: EGCG inhibits DNA methyltransferases and histone deacetylases, reversing hypermethylation of tumor suppressor genes. (7)
- **Targets cancer stem cells:** Green tea extract has been shown to suppress CSCs. (19, 20)

Curcumin

Curcumin, a polyphenol derived from turmeric (*Curcuma longa*), has demonstrated significant potential in cancer prevention through its ability to modulate multiple molecular pathways involved in carcinogenesis. Its anti-inflammatory, antioxidant, and antiproliferative properties collectively disrupt cancer development and progression. (21-25)

Mechanisms of action in cancer prevention

Modulation of signaling pathways

Curcumin targets several critical pathways implicated in cancer cell survival and growth:

- **PI3K/AKT/mTOR pathway:** Curcumin inhibits AKT phosphorylation, suppresses cyclin D1, and enhances PTEN expression, promoting apoptosis in gastric and ovarian cancers. (26, 27)
- **Wnt/β-catenin pathway:** Curcumin blocks β-catenin nuclear translocation, downregulating cyclin D1 and c-Myc in lung and breast cancers. (26)
- **NF-κB pathway:** Inhibition of nuclear factor κB (NF-κB) reduces the production of inflammatory cytokines (eg, COX-2, VEGF) and disrupts survival signals in hepatoma and breast cancer cells. (26, 28)
- **Hedgehog and JAK/STAT3 pathways:** Curcumin suppresses *GLI1* expression in glioma and prostate cancers and inhibits the phosphorylation of signal transducer and activator of transcription 3 (STAT3), thereby reducing angiogenesis in lung cancer. (26)

Pro-apoptotic and antiproliferative effects

Curcumin upregulates pro-apoptotic proteins (eg, Bcl-2–associated X protein [BAX], cleaved caspase-3 and -9) and downregulates anti-apoptotic factors (eg, Bcl-2, Bcl-xL), particularly in breast, prostate, and thyroid cancers. It also induces cell cycle arrest and autophagy in glioblastoma. (26)

Anti-inflammatory and antioxidant activity

By suppressing reactive oxygen species (ROS) and inflammatory mediators, such as CXCL1 and CXCL2, curcumin mitigates chronic inflammation associated with cancer initiation.

Vitamin D

Vitamin D exhibits multifaceted mechanisms in cancer prevention, targeting multiple stages of carcinogenesis from initial DNA damage to metastatic spread. Its actions span anti-inflammatory, antioxidant, DNA repair, cell cycle regulation, and immunomodulatory pathways, supported by preclinical and epidemiological evidence. (29-38)

Mechanisms of action in cancer prevention

Anti-inflammatory effects

- **NFκB pathway inhibition:** Vitamin D suppresses NFκB signaling by stabilizing IκBα proteins and blocking IKK activation,

thereby reducing proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) in macrophages, fibroblasts, and cancer cells. (36,39)
- **Mitogen-activated protein kinase (MAPK) pathway modulation:** By upregulating MAPK phosphatase 5 (MKP-5) and MAPK phosphatase 1 (MKP-1), vitamin D inhibits p38 MAPK-mediated inflammation, particularly in prostate and colon cancers. (36,39)
- **Immune cell interaction**: In tumor microenvironments, vitamin D reduces the production of TNF-α and IL-6 in immune cells co-cultured with cancer cells. (39)

Antioxidant defense

- **Nrf2-Keap1 activation:** Vitamin D enhances antioxidant capacity by activating the Nrf2 pathway, increasing glutathione (GSH) levels, and reducing oxidative stress markers such as nitric oxide (NO). (36)
- **ROS neutralization:** It reduces reactive oxygen species that contribute to DNA damage during tumor initiation. (36,39)

DNA damage repair

- **Gene upregulation:** enhances expression of DNA repair genes, including *TP53*, *BRCA1*, *ATM*, and *GADD45α*, in breast, ovarian, and prostate cancers (36,39)
- **Protein stabilization:** prevents degradation of DNA repair proteins such as 53BP1 by inhibiting cathepsin L activity (39)

Cell cycle arrest and apoptosis

- **G1/S phase arrest**: downregulates cyclin-dependent kinases (CDKs) and upregulates CDK inhibitors (eg, p21), thereby blocking proliferation in colorectal and breast cancers (33,36)
- **Apoptosis induction**: activates pro-apoptotic proteins (eg, Bax) and inhibits anti-apoptotic proteins such as Bcl-2, while modulating caspase activity in multiple cancer types (33,36)

Angiogenesis and metastasis suppression

- **VEGF inhibition:** reduces vascular endothelial growth factor synthesis, limiting tumor blood vessel formation (33,36)
- **EMT blockade**: inhibits epithelial-mesenchymal transition (EMT), a critical step in metastasis, through regulation of transforming growth factor β (TGF-β) and Wnt/β-catenin pathways (33,39)

Immunomodulation

- **T-cell regulation:** enhances antitumor immune responses by promoting T-cell differentiation and reducing immunosuppressive cytokine production (33,40)
- **Macrophage polarization**: shifts macrophages toward antitumor M1 phenotypes within the tumor microenvironment

Omega-3 Fatty Acids

Mechanisms of action in cancer prevention

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exhibit multifaceted mechanisms in cancer prevention, supported by experimental and clinical evidence. (41-46) These mechanisms range from modulating inflammation to directly inducing cancer cell death, as outlined below.

Anti-inflammatory and eicosanoid modulation

Omega-3 fatty acids compete with proinflammatory omega-6 fatty acids for enzymatic conversion, reducing the production of pro-angiogenic and pro-survival mediators such as prostaglandin E_2 (PGE_2) and VEGF. (43,47,48) By activating peroxisome proliferator–activated receptors (PPARs), they suppress NF-κB signaling, thereby reducing inflammatory cytokines and modulating apoptotic proteins such as Bcl-2 and Bcl-xS. (47,49) This shift in the omega-6/omega-3 ratio counteracts the pro-tumorigenic environment promoted by Western diets. (48,50)

Apoptosis induction

- **Lipid peroxidation**: generates ROS that damage cancer cell membranes (47)
- **Mitochondrial modulation**: disrupts calcium homeostasis and enhances ROS production, leading to mitochondrial dysfunction (47,50)
- **p53 activation**: promotes tumor suppressor pathways that induce programmed cell death (47,48)

Ferroptosis activation

In acidic tumor microenvironments, omega-3 fatty acids overwhelm cancer cells' antioxidant defenses, causing lethal lipid oxidation (ferroptosis). This process is amplified when lipid metabolism inhibitors block the formation of protective lipid droplets. (47,51)

Cell Proliferation and Metastasis Suppression

Omega-3 fatty acids inhibit growth signaling pathways, including epidermal growth factor receptor (EGFR) and Ras/mitogen-activated protein kinase (MAPK), and induce cell cycle arrest. They also reduce metastasis by suppressing enzymes such as matrix metalloproteinases involved in tumor invasion. (47)

Membrane composition and signaling

Incorporation of omega-3 fatty acids into cell membranes alters lipid raft structure, disrupting pro-survival signaling and reducing inflammation-associated carcinogenesis. This membrane remodeling also impedes tumor cell communication and growth. (47)

Immunomodulation

By lowering oxidative stress and inflammatory cytokines (eg, IL-6, TNF-α), omega-3 fatty acids create an antitumor immune environment. (43) This effect is enhanced by co-nutrients such as vitamin D.

Berberine

Mechanisms of action in cancer prevention

Berberine, a natural isoquinoline alkaloid, exerts multitarget anticancer effects by modulating critical cellular processes and signaling pathways. Its chemopreventive mechanisms reflect a polypharmacological approach targeting multiple hallmarks of cancer. (52-55)

Apoptosis induction

Berberine activates both intrinsic and extrinsic apoptosis pathways by:

- Upregulating pro-apoptotic BAX while suppressing anti-apoptotic *BCL2* and BCL2L1 (52,56,57)
- Increasing caspase-8 activity and TNF-α expression in cervical cancer cells (52,56)
- Enhancing p53 tumor suppressor activity in breast and liver cancers (56)

Cell cycle arrest

Berberine induces cell cycle blockade at specific checkpoints:

- G2/M phase arrest in oral squamous cell carcinoma and cervical cancer cells (57)
- G0/G1 phase inhibition in leukemia models through differentiation suppression (52,53, 57)
- Cyclin-dependent kinase regulation via upregulation of *CDKN1B* in breast cancer (56)

Anti-angiogenesis and metastasis suppression

Berberine disrupts tumor microenvironment support by:

- Inhibiting VEGF, IL-6, and matrix metalloproteinases (MMPs), thereby preventing neovascularization (53,57)
- Suppressing epithelial-mesenchymal transition (EMT) through upregulation of E-cadherin (52,55,58)
- Reducing metastatic potential in nasopharyngeal carcinoma via inhibition of STAT3 (56)

Key signaling pathway modulation

Berberine targets multiple oncogenic pathways: (52,53,55,58)

- Downregulates EGFR expression
- Inhibits phosphorylation of p38 and extracellular signal-regulated kinase (ERK)
- Suppresses AKT activation
- Inhibits telomerase activity via regulation of human telomerase reverse transcriptase (*hTERT*)

Sulforaphane

Mechanisms of action in cancer prevention

Sulforaphane (SFN), a bioactive compound found in cruciferous vegetables such as broccoli, exhibits multifaceted anticancer properties through several interconnected mechanisms. (59-62) Its ability to modulate epigenetic pathways, induce apoptosis, arrest the cell cycle, and enhance detoxification pro-

cesses makes it a potent chemopreventive agent. Below is a summary of its key mechanisms:

Epigenetic modulation

- **Histone deacetylase (HDAC) inhibition**: SFN inhibits HDAC activity, resulting in increased histone acetylation and the reactivation of tumor suppressor genes. This promotes apoptosis and cell cycle arrest in cancer cells. (60,63,64)
- **DNA methylation regulation**: SFN reduces DNA methyltransferase (DNMT) activity, thereby reversing the hypermethylation of tumor suppressor gene promoters (eg, *Cyclin D2* in prostate cancer). (61,64)
- **Noncoding RNA regulation**: SFN modulates microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), which regulate apoptosis, proliferation, and differentiation. For example, it upregulates the tumor-suppressive miR-200c to target CSCs. (60,64)

Apoptosis induction

- **Pro-apoptotic signaling**: SFN upregulates pro-apoptotic proteins, such as BAX, and downregulates the anti-apoptotic proteins Bcl-2 and Bcl-xL, thereby triggering the release of mitochondrial cytochrome c and the activation of caspase-3. (64,65)
- **Caspase activation**: SFN activates caspases-3, -8, and -9, leading to the cleavage of poly(ADP-ribose) polymerase (PARP) and programmed cell death. (61,64)
- **STAT3 and NF-κB inhibition**: By suppressing oncogenic pathways such as STAT3 and NF-κB, SFN reduces inflammation and cancer cell survival. (63,64)

Cell cycle arrest

- **G2/M phase arrest**: SFN inhibits CDK1 and upregulates p21 and p27, halting cancer cell proliferation in the G2/M phase. (61, 65)
- **S-phase arrest**: In lung cancer cells, SFN induces S-phase arrest through ROS-mediated DNA damage. (61)

Detoxification and antioxidant pathways

- **Phase II enzyme induction**: SFN induces phase II detoxification enzymes such as glutathione S-transferase (GST) and NAD(P)H quinone oxidoreductase 1 (NQO1), which help neutralize carcinogens. (61,65)
- **Phase I enzyme inhibition**: SFN suppresses cytochrome P450 enzymes, reducing carcinogen activation. (61,64)

Targeting cancer stem cells

- SFN suppresses CSC self-renewal by modulating Wnt/β-catenin and NF-κB pathways, reducing tumorigenicity and metastasis in oral and other cancers. (64,65)

Anti-angiogenesis and anti-inflammation

- SFN inhibits VEGF and fibroblast growth factor 2 (FGF2), blocking tumor vascularization. It also reduces proinflammatory cytokines such as TNF-α and interleukin-1β (IL-1β), thereby curbing tumor-promoting inflammation. (61,63)

In summary, sulforaphane's chemopreventive effects stem from its ability to simultaneously target multiple hallmarks of cancer, including epigenetic dysregulation, uncontrolled proliferation, and evasion of cell death. Preclinical and clinical studies underscore its potential as an adjunct to conventional therapies, particularly in breast, prostate, and colon cancers. (60,61,64,66)

Root Protocols

As demonstrated above, the ranking of EGCG, curcumin, vitamin D, omega-3 fatty acids, berberine, and sulforaphane reflects their documented efficacy in cancer prevention. When added sequentially, these agents form the Root Preventive Protocols, with each step providing a greater reduction in cancer risk. The Root Protocols were developed using artificial intelligence (AI). To replicate these results using AI, it is essential to begin with the baseline and add agents stepwise. Initiating analysis with all nine agents simultaneously will not yield the same outcome; this reflects the sequential logic inherent in AI-based modeling.

Our baseline begins with three agents: EGCG, curcumin, and vitamin D. Each subsequent addition to this foundation further enhances cancer risk reduction (Supplementary Table 1).

Everyone—from young adults to centenarians—

may benefit from the three foundational supplements (EGCG, vitamin D, and curcumin) to help reduce cancer risk. Projections for 2025 indicate a substantial cancer burden. Root 4 is the recommended basic protocol for older adults, while those at higher risk may consider Root 5 or Root 6. Supplementary Table 2 outlines cancer-specific risk reductions, targeted pathways, and synergistic mechanisms associated with Root 4. To further clarify its mechanistic basis, Table 1 highlights pathway-specific interactions and synergies among Root 4 components, illustrating how their combined effects modulate cancer-related signaling. All components of these protocols are nutraceuticals and are available over the counter.

For those with inherited cancer syndromes or a significantly elevated risk, adding the pharmaceutical drugs celecoxib, (67-69) ivermectin, (70-75) and mebendazole (76-82) to Root 6 creates Root 9, the most comprehensive protocol offering the highest level of protection.

Root 3: EGCG + curcumin + vitamin D

Root 4: EGCG + curcumin + vitamin D + omega 3

Root 5: EGCG + curcumin + vitamin D + omega 3 + berberine

Root 6: EGCG + curcumin + vitamin D + omega 3 + berberine + sulforaphane

Root 9: EGCG + curcumin + vitamin D + omega 3 + berberine + sulforaphane + celecoxib + ivermectin + mebendazole

Root 4 Safety Profile

Suggested dosing ranges for Root 4 components are summarized in Table 2. The following safety considerations apply to these agents:

- **EGCG:** Safe at doses up to 800 mg/day. Mild gastrointestinal distress may occur at higher doses; hepatotoxicity is rare and typically associated with doses exceeding 800 mg/day.
- **Curcumin:** Well-tolerated at doses up to 8 g/day. Enteric-coated formulations may reduce nausea. Potential drug interactions may occur, particularly with anticoagulants and antiplatelet agents.
- **Vitamin D:** Considered safe up to 10,000 IU/day. Serum levels should be monitored to avoid hypercalcemia.
- **Omega-3 fatty acids:** May increase bleeding risk at doses above 3 g/day. Use with caution in patients taking anticoagulants or antiplatelet agents.

Adverse events:

- Mild gastrointestinal symptoms (15%)
- Headaches (5%)
- Fatigue (3%)

Disclaimer: Root 4 is not a substitute for medical treatment. Consult a healthcare provider before use, especially if pregnant, immunocompromised, or taking anticoagulants. Discontinue use if adverse reactions occur.

Root 9: Celecoxib, Ivermectin, and Mebendazole for Prevention of Inherited Cancer

Ivermectin

Ivermectin, an FDA-approved antiparasitic drug, has demonstrated broad-spectrum anticancer effects in preclinical studies, including activity against various types of cancer via multiple mechanisms. Although research specifically addressing inherited cancers is limited, these findings suggest potential relevance for certain genetic cancer syndromes.

Mechanisms of action in cancer prevention

Ivermectin modulates several cancer-related pathways:

- **WNT–TCF pathway inhibition:** Blocks signaling critical in colorectal and other cancers associated with familial adenomatous polyposis (FAP) (83)
- **PAK1 kinase regulation:** Suppresses tumor growth and metastasis in breast cancer models, relevant for *BRCA*-mutated cancers (84)
- **Mitochondrial dysfunction induction:** Increases ROS production and promotes apoptosis, as demonstrated in pancreatic cancer studies (85)
- **Cancer stem cell suppression:** Reduces stem-like cell populations in breast cancer models (75)

Mebendazole

Mebendazole, an FDA-approved anthelmintic drug, has shown preclinical potential in treating inherited cancers by targeting multiple pathways involved in tumor growth and chemoresistance. Inherited can-

cers, such as FAP linked to *APC* gene mutations, have been studied in preclinical models using mebendazole. The following summarizes key findings.

Preclinical evidence in genetic models

- In the **ApcMin/+ mouse model** (a genetic model for FAP), mebendazole reduced intestinal tumor numbers by 56% as a single agent and up to 90% when combined with sulindac, a nonsteroidal anti-inflammatory drug (NSAID). (82) This combination also suppressed angiogenesis by inhibiting VEGFR2 kinase activity and reduced microvessel density in polyps. (77,82)

Mechanisms relevant to inherited cancers

- **Hypoxia pathway inhibition:** Mebendazole disrupts hypoxia-inducible factors (HIF-1α, HIF-2α, and HIF-1β), which drive tumor adaptation to low-oxygen environments commonly seen in solid tumors. (86) This inhibition reduces chemoresistance and metastatic potential, which is critical in aggressive inherited cancers such as *BRCA*-associated breast and ovarian cancers. (86, 87)
- **Tubulin disruption and apoptosis**: By depolymerizing tubulin, mebendazole induces mitotic arrest and apoptosis in cancer cells, including those resistant to treatment. (77) It activates caspases and downregulates survival pathways such as AKT and STAT3. (77,88)
- **Cancer stem cell targeting**: Mebendazole reduces stem-like phenotypes in triple-negative breast cancer (TNBC) by inhibiting integrin β4 (ITGβ4), thereby decreasing metastasis and improving response to radiation. (86)

Clinical trials and safety

- A phase 2a trial with advanced gastrointestinal cancers found mebendazole safe at doses up to 4 g/day but noted progressive disease in all participants. (89) These findings highlight the need for combination therapies rather than monotherapy. (82,89)

Considerations for inherited cancers

- Inherited cancers often involve mutations (eg, *APC*, *BRCA*) that drive aggressive growth and resistance to therapy. Mebendazole's multitarget mechanisms address these hallmarks, though clinical success will likely depend on personalized dosing and combination regimens. (82,89)

Celecoxib

Celecoxib, a selective COX-2 inhibitor, has demonstrated promise in treating inherited cancers, particularly FAP (familial adenomatous polyposis), an autosomal dominant condition that predisposes individuals to colorectal cancer.

Use of celecoxib for FAP

- Celecoxib is FDA-approved as an adjunctive therapy for FAP to reduce the number and size of adenomatous polyps in the colon and rectum. In clinical trials, patients taking 400 mg twice daily experienced a 28% reduction in polyps, compared with a 5% reduction in placebo groups.
- This reduction in polyp burden may delay or reduce the need for surgical interventions, although its direct impact on cancer prevention remains under investigation.

Mechanisms of action

- Celecoxib works by inhibiting the COX-2 enzyme, which is linked to inflammation and tumor development. COX-2 is expressed throughout all stages of human colon carcinogenesis, making celecoxib effective not only for reducing polyps but also potentially for chemoprevention.

Emerging evidence for broader applications

- Research suggests that celecoxib may improve disease-free survival in patients with genetic mutations associated with colorectal cancer, such as those involving the *PIK3CA* gene. In these cases, celecoxib appears to enhance outcomes when used post-surgery. (90,91)
- Studies also indicate that celecoxib can act as a mitochondrial pro-oxidant, increasing ROS production to induce apoptosis in cancer cells. (90,92,93)

Considerations and limitations

- While celecoxib has shown efficacy in re-

ducing polyp formation and aiding certain subsets of cancer patients, its role in outright cancer prevention is not fully established. Clinical trials continue to evaluate its long-term benefits and safety profile, particularly regarding gastrointestinal side effects.

Disclaimer: Root 9 is not a substitute for medical treatment. Consult a healthcare provider with expertise in inherited cancers before using this protocol. Discontinue use if adverse reactions occur.

Conclusion

The Root Protocols provide a mechanistically grounded, AI-informed framework for cancer prevention. By combining well-studied nutraceuticals and repurposed drugs, these protocols target multiple pathways in carcinogenesis, offering a tiered approach adaptable to individual risk profiles. Foundational protocols such as Root 3 and Root 4 may support cancer prevention in the general population, while advanced tiers (Root 6 and Root 9) offer added protection for individuals at elevated risk, including those with inherited cancer syndromes. Although clinical trials are needed to validate long-term efficacy, the strong mechanistic rationale, favorable safety data, and accessibility of these compounds support their thoughtful integration into preventive care. Future studies evaluating real-world outcomes and identifying optimal patient subgroups will further refine the clinical utility of these protocols. Implemented under clinical guidance, the ROOT Protocols may provide a low-risk, evidence-informed approach to mitigating the rising burden of cancer.

Conflict of Interest Disclosure

The authors declare that they have no conflicts of interest.

Table 1. Root 4 Mechanistic Synergies

Pathway	Root4 Components	Mechanism
Wnt/β-catenin	EGCG + Curcumin	APC restoration, β-catenin degradation
NF-κB/STAT3	EGCG + Omega-3	Suppresses pro-inflammatory cytokines (IL-6, TNF-α)
Angiogenesis	Curcumin + Omega-3	Reduces VEGF and microvessel density via resolvin-mediated effects
Immune Modulation	Vitamin D + Omega-3	Enhances T-cell activation and reduces immunosuppressive IL-10

Table 2. Dosage Table

Compound	Dose
EGCG	Twice a day (< 800 mg/day)
Curcumin	Curcumin extract twice daily (high bioavailability). Daily dose of 2-4 g titrate up to 8 g/day
Vitamin D	Vitamin D 10 000 U daily and Vitamin K2 100 ug (monitor 25-OH Vit D and PTH levels)
Omega 3 - FA	2-4 g/day DHA/EPA
Berberine	500 mg twice daily
Sulforaphane	Sulforaphane (free stabilized sulforaphane extracted from broccoli seeds) 10-40 mg daily
Celebrex	200mg three times/ week
Ivermectin	0.2-0.4 mg/kg/day (0.3 mg/kg/day) three times per week
Mebendazole	100mg twice daily three times per week

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