



Phytonutrients: Harnessing Anti-Inflammatory and Anti-Cancer Potential for Health Benefits

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Abstract

Bioactive compounds known as phytonutrients, which are abundant in fruits, vegetables, whole grains, and herbs, have indicated great potential in the war against cancer and chronic inflammation. Epidemiological studies have consistently demonstrated that high-phytonutrient diets are associated with a 30–40% reduced risk for chronic diseases, including heart disease and various forms of cancer. The methodology used in this review like search tools google scholar, PubMed, and science direct for data review. Notable anti-inflammatory and anti-cancer effects have been shown by flavonoids, carotenoids, glucosinolates, phenolic acids, and stilbenes, among others. Sulforaphane, a derivative of glucosinolate, inhibits histone deacetylase (HDAC) activity linked with tumor growth, while quercetin and curcumin reduce pro-inflammatory cytokines (IL-6, TNF- α) by over 50%



Article History

Received: 01 May 2025
Accepted: 25 June 2025

Keywords

Anti-inflammatory;
Bioavailability;
Curcumin;
Flavonoids;
Resveratrol;
Phytonutrients.

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Doi: <https://dx.doi.org/10.12944/CRNFSJ.13.Special-Issue-July.04>

in vitro. Resveratrol has already been demonstrated to decrease tumor mass by 60–70% in animal models through the modification of the NF- κ B and PI3K/AKT pathways. However, challenges such as low bioavailability and metabolic instability limit clinical translation despite positive preclinical results. Enhanced three- to tenfold bioavailability has been exhibited by recent nanoformulation innovations, providing fresh therapeutic application avenues. The mechanisms through which phytonutrients exhibit anti-inflammatory and anti-cancer effects are well discussed in this review, which also points out quantitative outcomes of *in vitro*, *in vivo*, and clinical trials and discusses innovations to bypass delivery problems. Ultimately, the incorporation of phytonutrients into treatment regimens and preventative health programs could be vital to reducing the occurrence of cancer and disorders associated with inflammation globally.

Abbreviation

ARE	Antioxidant response elements	IL-6	Pro-inflammatory cytokines
AKT	A serine/threonine protein kinase	JNK	Jun N-terminal kinases
CRP	C- reactive protein	LDL	Low-density lipoprotein cholesterol
COX-2	Cyclooxygenase-2	miRNAs	MicroRNAs
CDKs	Cyclin-dependent kinases	MAPK	Mitogen-activated protein kinase
DNA	Deoxyribonucleic Acid	MMPs	Matrix metalloproteinases
DNMTs	DNA methyltransferases	MDSCs	Mycloid-derived suppressor cells
EFSA	European Food Safety Authority	NSAIDs	Nosteroidal Anti-inflammatory Drugs
EPIC	European Prospective Investigation into Cancer and Nutrition	NF- κ B	Nuclear Factor kappa-light-chain-enhancer of activated B cells
EGCG	Epigallocatechin gallate	PI3K	Phosphoinositide 3-kinase
EMT	Epithelial-to-mesenchymal transition	ROS	Reactive oxygen species
ERK	Extracellular Signal-Regulated Kinase	RNA	Ribonucleic Acid
FDA	Food and Drug Administration	STAT3	Signal Transducer and Activator of Transcription 3
GPx	Glutathione Peroxidase activity	SOD	Superoxide Dismutase
GMP	Good manufacturing practices	TNF- α	Cytokine Tumor Necrosis Factor-alpha
HDAC	Histone deacetylase	TLR2	Toll-like receptor 2
HIF-1 α	Hypoxia-inducible factor-1 α	TME	Tumor microenvironment
iNOS	Inducible nitric oxide synthase	VEGF	Vascular endothelial growth factor

Introduction

Cancer and chronic inflammation are among the topmost causes of illness and death throughout the world and are responsible for more than 60% of all deaths.¹ Naturally occurring as a defense mechanism inflammation can lead to cancer, heart disease, rheumatoid arthritis, and neurodegenerative disorders.² Proper prevention and treatment steps are essential as chronic inflammatory conditions are linked with approximately 20% of malignancies.³ A group of natural compounds in plant foods, the phytonutrients, are commonly known as

phytochemicals. These have been proven to exhibit intense anti-inflammatory and anti-cancer activities by ways such as inducing apoptosis, downregulating cytokines, modulating genes and oxidative stress.⁴ In cell lines of humans, flavonols such as kaempferol and quercetin have been shown to reduce inflammatory markers such as TNF- α and IL-6 by 40–60%. Turmeric has a polyphenol named curcumin, which suppresses the NF- κ B pathway and downregulates pro-inflammatory gene expression in preclinical models by 70–90%.⁵ In a 25–30% reduced incidence of colorectal, breast, and

lung cancer as compared to the lowest quintile, the European Prospective Investigation into Cancer and Nutrition (EPIC) study provides epidemiological proof for the preventive effects of phytonutrient-dense diets.⁶ There is evidence that clinical application of phytonutrients is constrained by considerations such as rapid metabolism, poor oral bioavailability, and variability in patient response, notwithstanding their promising therapeutic potential. Reducing systemic

inflammatory markers by half and a 30% fall in the incidence of cardiovascular disease have been attributed to dietary lifestyles like the Mediterranean diet.^{7,8} The aim of this review is to provide a detailed explanation of the anti-cancer and anti-inflammatory properties of significant phytonutrients and the importance of ways to enhance their therapeutic activity and usage in health treatment.

Table 1: Classification, sources, quantitative content, and health benefits of phytonutrients

Phytonutrient	Compounds	Dietary Sources	Average Content per 100g (approx.)	Benefits
Carotenoids	Lycopene, β -carotene, Zeaxanthin, Lutein	Carrots, kale tomatoes, spinach	β -carotene: 8285 μ g (carrots); Lycopene: 2573 μ g (tomatoes)	Vision support, reduced cancer risk, immune enhancement
Glucosinolates	Sulforaphane, Indole-3-carbinol	Brussels sprouts, Broccoli, cabbage	Total glucosinolates: 44–150 mg (broccoli)	Detoxification, anti-inflammatory, anti-cancer
Isoflavones	Genistein, Daidzein	Soy products	Genistein: 45–75 mg (soy flour)	Estrogen modulation, breast cancer prevention, bone health
Flavonoids	Quercetin, Catechins, Anthocyanins, Hesperidin	Onions, berries, apples, citrus fruits, green tea	Catechins: 80–110 mg (green tea); Quercetin: 33 mg (onions)	Anti-inflammatory, antioxidant, anti-cancer, cardioprotective
Tannins	Proanthocyanidins	Red, cocoa wine, cranberries	150–300 mg (cocoa powder)	Antioxidant, vascular protection, anti-bacterial
Phenolic Acids	Ferulic acid, Chlorogenic acid, Caffeic acid	Coffee, whole grains, berries	Chlorogenic acid: 70–350 mg (coffee)	Anti-microbial, glucose metabolism, antioxidant
Polyphenols (general)	Includes phenolic acids, flavonoids	Berries, olives, tea, cocoa	Total polyphenols: 500–1000 mg (berries, tea)	Cardiovascular health, antioxidant, gut microbiota modulation
Stilbenes	Resveratrol	Grapes, peanuts, red wine	Resveratrol: 0.3–1.89 mg (red wine); 3.5 mg (peanuts)	Neuroprotective, cardioprotective, anti-aging

Lignans	Secoisolaricir -esinol, Mataire -sinol	Flaxseeds, legumes, sesame seeds	Secoisolariciresinol: 379 mg (flaxseeds)	Antioxidant, hormone modulation, anti-cancer,
Alkaloids	Capsaicin, Caffeine	Coffee, tea, chili peppers	Caffeine: 40 mg (tea); Capsaicin: 0.1–0.9 mg (chili)	Anti-inflammatory, metabolism boosting, analgesic
Saponins	Diosgenin, Soyasaponin	Legumes, soybeans, spinach	Total saponins: 120– 200 mg (soybeans)	Anti-cancer, immune modulation, cholesterol- lowering,

Phytonutrient Classification and their Sources

Many plant foods contain phytonutrients, including flavonoids, carotenoids, phenolic acids, glucosinolates, lignans, saponins, stilbenes, and alkaloids, which exhibit several health benefits. Flavonoids found in green tea, berries, onions, and apples have cardioprotective, anti-inflammatory, and antioxidant effects.⁹ Carotenoids, like lycopene and β-carotene, enhance immunological function, cancer prevention, and vision. Phenolic acids like chlorogenic acid are potent antioxidants that affect glucose metabolism and are antibacterial in nature.¹⁰ Broccoli and cruciferous vegetables contain

glucosinolates, which maintain anti-cancer defense and detoxification. Lignans reduce cancer risk and assist in the regulation of hormones, particularly in flaxseeds.¹¹ Soybean saponins and legumes have been linked to immunological regulation and cholesterol reduction. Stilbenes, including resveratrol, possess anti-aging and cardioprotective functions.¹² Caffeine and capsaicin are alkaloids that possess analgesic, anti-inflammatory, and metabolism-increasing functions. A combination of these compounds is supplied by a diet rich in a variety of plant foods, which enhances lifespan, disease prevention, and overall health.¹³ Table 1

Role of Phytonutrients

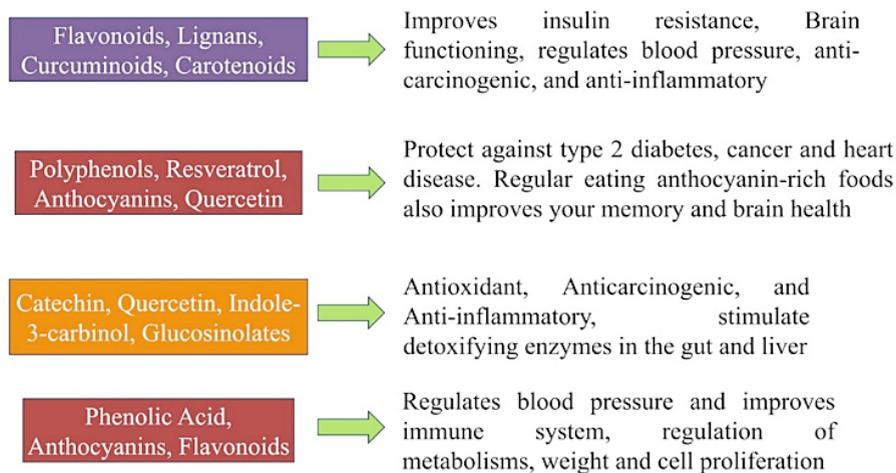


Fig.1: Phytonutrients role

Use of Phytonutrients

Natural plant compounds known as phytonutrients are increasingly being recognized as potential agents for decelerating the onset and development

of non-communicable diseases such as diabetes, cancer, cardiovascular disease, and neurological diseases. Diets rich in foods high in phytonutrients have a decreased prevalence of lifestyle diseases,

which account for 71% of all fatalities globally.¹⁴ Consuming at least 800g of fruits and vegetables daily reduces the risk of cardiovascular disease, stroke, and cancer by 24-30%, 33%, and 13%, respectively, compared to those who consume less than 200g daily.¹⁵ One of the most studied families of phytonutrients, flavonoids, have shown preventive effects against inflammation and oxidative stress, two of the factors associated with the onset of disease (Figure 1).¹⁶ A 15-20% reduction in all-cause mortality was associated with higher intake of flavonoids, especially among those who were at high risk due to alcohol or smoking. In the populations with high consumption, carotenoids such as lycopene and β -carotene were related to a 35% reduced risk of lung and prostate cancer. Phytonutrient-rich therapies have been shown to reduce LDL cholesterol, fasting blood sugar, and inflammatory markers such as C-reactive protein (CRP).¹⁷ Turmeric's curcumin polyphenol has shown encouraging results in clinical practice, reducing CRP levels by up to 65% and enhancing insulin sensitivity in type 2 diabetics by 20–30%. The authors pointed out, however, that the medicinal efficacy of high-phytonutrient-containing products is constrained by limitations such as poor absorption, metabolic variability, and non-standardization. Substances like curcumin and resveratrol can become more bioavailable due to new technologies such as liposomal delivery and nanoencapsulation.^{18,19}

Significance of Phytonutrients

Flavonoids, also known as phytonutrients, are produced by plants and provide them taste and color. With their anti-inflammatory, anti-cancer, and antioxidant activities, they are crucial to human health and the prevention of chronic diseases. Flavonoids are the most studied among over 10,000 flavonoids classified into numerous major groups.²⁰ Carotenoids, such as lutein, zeaxanthin, lycopene, and β -carotene, are known for their potent antioxidant activities and are responsible for the bright color of carrots, tomatoes, and green leafy vegetables.²¹ The health benefits of high-phytonutrient diets are backed by epidemiology. As per the World Cancer Research Fund, consuming five or more servings of fruits and vegetables daily may reduce an individual's risk of developing cancer by up to 20–30%.²² A reduced incidence of lung cancer in nonsmokers by 29% is also linked with high dietary intake of carotenoids. Phytonutrients are

also necessary for eliminating inflammation, a risk factor for many chronic illnesses.²³ In vitro and in vivo research have demonstrated that phytonutrients like curcumin, resveratrol, and epigallocatechin gallate (EGCG) are capable of significantly reducing pro-inflammatory cytokines like IL-6, IL-1 β , and TNF- α . Antioxidant defense is aided by phytonutrients through the neutralization of reactive oxygen species (ROS), protecting cells from oxidative damage and mutagenesis.^{24,25} Resveratrol and quercetin have been found in preclinical studies to increase immune surveillance in tumor environments and enhance regulatory T-cell numbers.²⁶ Aside from being essential components of public health nutrition policy, phytonutrients are also essential partners in the fight against diseases of modern living. The global burden of cancer, metabolic disorders, and chronic inflammation can be significantly reduced if their full potential is harnessed through diet or supplementation.²⁷

Anti-inflammatory Mechanism Cancer and Chronic Inflammation

Chronic inflammation, a prolonged, dysregulated immune response, is the primary cause of non-communicable illnesses like cancer, accounting for over 20% of all human cancer cases and 60% of deaths worldwide.²⁸ This condition promotes angiogenesis, genetic abnormalities, and a pro-tumorigenic environment, leading to angiogenesis and other health issues.²⁹ Chronic inflammation encourages metastasis, suppresses apoptosis, and encourages cell growth by triggering key signaling pathways such as NF- κ B, STAT3, and COX-2. Chronic inflammatory bowel disease such as Crohns disease and ulcerative colitis can increase the risk of cancer by five to tenfold.³⁰ Because of liver inflammation, individuals with a chronic hepatitis B or C infection are 25–30% at risk of developing hepatocellular carcinoma. This link between cancer and inflammation is further evidenced by quantitative clinical evidence, which indicates that elevated CRP levels are associated with a 50–80% increased risk of mortality from malignancies such as colorectal, prostate, and lung cancer.³¹ Long-term exposure to inflammatory mediators can induce epithelial-to-mesenchymal transition (EMT), which enhances metastatic risk and reduces the success of treatment. Prevention and control of cancer can significantly be influenced by preventing or reducing chronic inflammation.³² Regular use of NSAIDs

and anti-inflammatory drugs can reduce colorectal cancer incidence by 20-40%, while lifestyle changes like weight control, exercise, and increased consumption of anti-inflammatory phytonutrients can

also lower cancer risk.³³ Inflammation suppression by preventive diet including anti-inflammatory phytonutrients is a possible method to reduce the risk of cancer and improve patient outcomes.³⁴ (Figure 2)

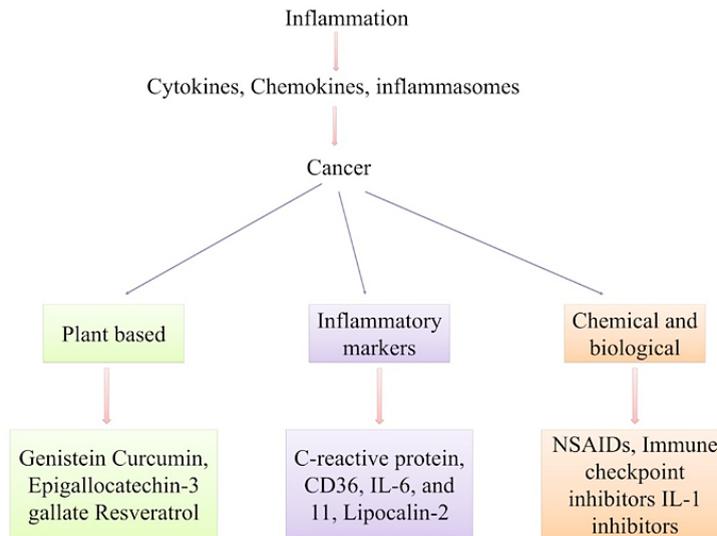


Fig.2: Inflammation, cancer and their biomarkers

Cytokines Proinflammatory Modulation

Two pro-inflammatory cytokines that are responsible for chronic inflammation and are associated with various diseases are TNF- α and IL-6. Utilize phytonutrients to treat inflammatory diseases and control their manifestation.³⁵ Leukocyte recruitment, endothelial activation, and upregulation of other inflammatory mediators such as IL-1, IL-6, and COX-2 are all mediated by TNF- α which is produced by activated macrophages.³⁶ Levels of TNF- α are often significantly higher in chronic disease states; they have been found up to ten-fold higher in levels of circulating TNF- α in rheumatoid arthritis individuals compared to health individuals. Both TNF- α and IL-6 synthesis have been reported to be reduced by several Phytonutrients.³⁷ researched anti-inflammatory drug, and clinical trials have shown that supplementation can reduce blood TNF- α by 30-50% and IL-6 by 20-40% in patients with inflammatory diseases like arthritis and metabolic syndrome.³⁸ Red wine and grapes have resveratrol, which possesses very strong cytokine-modulating effects and reduces IL-6 and TNF- α levels dramatically in type 2 diabetic individuals.³⁹ In both in vitro and in vivo conditions, the flavonol quercetin found in apples, onions, and berries has been shown to inhibit TNF- α and IL-6

production and secretion.⁴⁰ Green tea, parsley, celery, and chamomile also inhibit TNF- α and IL-6 by acting on upstream signaling molecules to downregulate them. Through their combination of antioxidant activity, blockage of signaling pathways, and transcriptional regulation, such natural compounds confer therapeutic significance towards prevention and cure of chronic inflammatory conditions.^{41,42}

Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-KB), Mitogen-Activated Protein Kinase (MAPK), Inhibition Pathways

Critical signaling cascades that regulate gene expression in inflammatory responses, immunological reactions, cell proliferation, and cell death are the NF- κ B and MAPK pathways. Exacerbation of chronic diseases such as cancer, cardiovascular disease, neurodegenerative diseases, and autoimmune disease is caused by overactivation of these pathways.⁴³ By inhibiting these critical biochemical pathways, phytonutrients, which are found in fruit, vegetables, teas, and herbs, have shown significant anti-inflammatory and chemo preventive activity. NF- κ B is a transcription factor bound to its inhibitor, I κ B α . Phosphorylation of I κ B α by the IKK complex

induces it to degrade and allows NF- κ B to enter the nucleus. This leads to the synthesis of adhesion molecules, chemokines, pro-inflammatory cytokines, and enzymes like iNOS and COX-2.⁴⁴ Curcumin, resveratrol, and quercetin are a few phytonutrients that inhibit NF- κ B activation at various points in this signaling cascade.⁴⁵ In patients with inflammatory diseases, curcumin treatment has been associated with a 50–60% reduction in NF- κ B activity and significant reductions in TNF- α and IL-6 levels.⁴⁶ The three principal families of kinases involved in mediating MAPK signaling ERK, JNK, and p38 MAPK are activated by both inflammatory and environmental stimuli. Disorders such as arthritis, atherosclerosis, and the progression of cancer are associated with the excessive activation of MAPK pathways.⁴⁷ Several phytonutrients possess anti-inflammatory effects through action on the MAPK pathway. Resveratrol inhibits inflammatory cytokine production downstream by preventing ERK1/2 and p38 MAPK activation. Through the inhibition of JNK and p38 MAPK phosphorylation, the green tea catechin EGCG reduces COX-2 and iNOS production. Apigenin inhibits the expression of inflammatory genes and inhibits MAPK phosphorylation.⁴⁸

Effect of Antioxidant

Chronic inflammation, aging, and a variety of diseases, such as cancer, diabetes, cardiovascular disease, and neurological disorders, are all affected appreciably by oxidative stress, which is a result of an imbalance between the body's antioxidant defensive mechanisms and the formation of ROS.⁴⁹ Reactive oxygen species can trigger cellular dysfunction and inflammatory responses by damaging proteins, lipids, and DNA. Due to their ability to detoxify ROS, activate endogenous antioxidant systems, and regulate redox-sensitive signal pathways, phytonutrients such as flavonoids, carotenoids, stilbenes, and phenolic acids have garnered extensive attention.⁵⁰ Direct scavenging of ROS and indirect upregulation of cellular antioxidant enzymes by phytonutrients exert antioxidant activities. Flavonoids, carotenoids, stilbenes, and phenolic acids are some of the compounds whose chemical makeup allows them to neutralize free radicals by donating electrons or hydrogen atoms. For example, quercetin has been shown to reduce the production of ROS in lipopolysaccharide-stimulated macrophages by over 70%.⁵¹ Further,

nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor regulating the expression of genes dependent on antioxidant response elements (ARE), is activated by phytonutrients. Nrf2 activation leads to enhanced detoxification and removal of ROS.⁵² Curcumin has been shown to increase nuclear translocation of Nrf2 in oxidative stress experimental models, leading to 40–60% elevation in SOD and GPx activity.⁵³ Carotenoids like lycopene and β -carotene that are potent singlet oxygen quenchers have been associated with 30% lower levels of oxidative stress markers and lipid peroxidation on regular consumption. In addition to scavenging free radicals and inducing the synthesis of antioxidant enzymes, green tea provides potent antioxidant defense.⁵⁴

Immune Cell Function and Regulation

Using influencing the activity of T-cells, macrophages, and other immune system components, phytonutrients play a crucial role in controlling immune cell function. Through the regulation of cytokine production, gene expression, cell growth, and signal transduction pathways, these bioactive plant compounds can modulate immune responses, ensure immunological homeostasis and reduce pathological inflammation.⁵⁵ The two main phenotypes of macrophages, the innate immune system's front line of defense, are M1 (pro-inflammatory) and M2 (anti-inflammatory and tissue-repairing). By altering the polarization of macrophages from M1 to M2, phytonutrients can decrease inflammation.⁵⁶ It has been shown that curcumin, a curcumin-like chemical, decreases M1 macrophage infiltration in inflammatory tissues by 60% by suppressing M1 markers and inducing M2 markers in LPS-stimulated macrophages.⁵⁷ Resveratrol, a polyphenol present in red grapes, suppresses macrophage activation and decreases TNF- α production in activated macrophages by up to 50% by inhibiting the NF- κ B and MAPK pathways. In addition, it preserves immunological balance by stimulating phagocytic function and suppressing hyperactive inflammatory responses. T-cells are key elements of adaptive immunity, particularly CD4+ helper T-cells and CD8+ cytotoxic T-cells.⁵⁸ Green tea's phytonutrients, including epigallocatechin gallate (EGCG), reduce Th1 and Th17 cytokines and induce regulatory T-cells (Tregs), which secrete anti-inflammatory cytokines, aiding in the regulation of T-cell differentiation and cytokine production.⁵⁹ Apples and onions are rich in quercetin, which

suppresses intracellular calcium signaling and MAPK activation to modulate T-cell proliferation and cytokine production.⁶⁰ Beta-glucans in oats and mushrooms possess immunomodulatory properties that enhance antigen presentation and adaptive immune responses by activating dendritic cells and macrophages through Dectin-1 and TLR2 receptors. They are promising adjuncts in immunotherapy and vaccine development due to these properties.⁶¹

Phytonutrient in Anticancer Potential

Due to their numerous bioactivities phytonutrients which occur in fruits, vegetables, cereals, and herbs, have been demonstrated to be effective in cancer prevention and complementary therapy. These compounds have anti-cancer activities through several mechanisms, including antioxidant activity, regulation of cell signaling pathways, inhibition of angiogenesis, induction of apoptosis, and suppression of metastasis.⁶² Increased intake of phytonutrient-rich foods has been linked to reduced incidence and development of cancer in research. Among the best-studied anti-cancer phytonutrients is curcumin, which is derived from turmeric and suppresses cancer cell growth by modulating numerous molecular targets.⁶³ Oral curcumin is safe and can lower inflammatory markers by 30–50% in patients with colorectal cancer by inhibiting tumor-promoting inflammation, according to clinical studies.⁶⁴ Red wine and grapes are rich in resveratrol, a stilbene that has shown potential to prevent the development, promotion, and progression of cancer. Green tea's principal catechin, epigallocatechin gallate (EGCG) has shown anti-tumor angiogenesis and anti-metastasis activities.⁶⁵ EGCG treatment greatly inhibited the potential for metastasis and decreased tumor neovascularization by 70% in mouse models. Due to its antioxidant properties and interference with androgen receptor signaling, lycopene, a carotenoid found abundantly in tomatoes is associated with reduced risk of prostate cancer.⁶⁶ Broccoli and related cruciferous vegetables contain sulforaphane, which is a histone deacetylase inhibitory chemical and a phase II detoxifying enzyme inducer; this helps avoid the growth of breast and colon cancer cells. Their cancer treatment translational applicability will be enhanced through clinical confirmation and dosage standardization.⁶⁷

Action Mechanisms of Phytonutrients

It has been shown that phytonutrients, which are bioactive compounds contained in plant foods possess anti-cancer activity through several interconnected mechanisms. These involve inhibition of angiogenesis and metastasis, induction of apoptosis, and cell cycle arrest.⁶⁸ The mechanism of apoptosis, which kills damaged or potentially malignant cells is tightly regulated. Many cancer cell lines exhibit high rates of apoptosis due to induction of intrinsic apoptosis pathways by phytonutrients like curcumin, resveratrol, and EGCG. Another significant way phytonutrients exert their anti-cancer action is through cell cycle arrest.⁶⁹ Cancer cells often bypass cell cycle regulatory checkpoints, and this leads to uncontrolled growth. By targeting significant regulatory proteins like cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors, phytonutrients can restore normal cell cycle regulation. EGCG has been shown to induce cell cycle arrest in several cancer cell lines, including prostate and breast cancer cells, at the G1 phase.⁷⁰ Curcumin and lycopene inhibit G1 arrest by activating tumor suppressors p21 and p27 and blocking cyclin D1 production, which is crucial for inhibiting angiogenesis and metastasis to control tumor development.⁷¹ Sulforaphane, curcumin, and resveratrol are some of the phytonutrients that can inhibit angiogenesis by inhibiting the expression of matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF).⁷² Curcumin inhibits MMP-2 and MMP-9 enzyme activities, while resveratrol and EGCG inhibit the NF- κ B pathway to downregulate VEGF expression. Through inhibition of cancer cell migration and formation of new blood vessels, EGCG has been found to inhibit metastasis by 60–70% in animal models.⁷³ Since phytonutrients act on multiple pathways associated with cancer development, they have the potential to inhibit tumor growth, enhance the effectiveness of traditional treatments, and decrease side effects. These processes emphasize the promise of phytonutrients as therapeutic agents in cancer prevention and therapy.⁷⁴

Gene Expression and Modulation Epigenetics

The investigation of heritable differences in gene expression that do not arise from alterations to the fundamental DNA sequence is referred

to as epigenetics. Mechanisms involve DNA methylation, histone modification, and non-coding RNA activity mediate such changes.⁷⁵ The regulation of epigenetic processes, which may impact a variety of cellular processes ranging from growth, differentiation, and stress response, is an important role of phytonutrients. The mechanisms of how phytonutrients modulate the epigenetic environment help them retain anti-inflammatory, anti-tumor, and disease-protective qualities.⁷⁶ One of the primary methods in which phytonutrients have an epigenetic influence involves DNA methylation which commonly reduces gene activity.⁷⁷ A study showed that some phytonutrients such as sulforaphane, demethylate tumor-suppression-involved genes. DNA methyltransferases (DNMTs) which could reactivate latent tumor suppressor genes such as p16INK4A which plays a critical role in the control of the cell cycle are blocked by sulforaphane.⁷⁸ Another significant epigenetic mechanism that regulates gene expression is histone modification.⁷⁹ Several post-translational modifications such as acetylation, methylation, phosphorylation, and ubiquitination can take place in histones, which are protein molecules that surround DNA.^{80,81} Curcumin of turmeric has been shown to modify histone acetylation, increasing gene expression for DNA repair, cell cycle regulation, and apoptosis. Studies show that in *in vitro* and *in vivo* models of cancer, curcumin-induced histone modifications lead to reduced tumor growth.⁸² Furthermore, phytonutrients modulate gene expression through the regulation of non-coding RNAs, particularly microRNAs (miRNAs). Green tea's epigallocatechin gallate (EGCG) is one of the phytonutrients that can regulate miRNA expression, and in doing so, influence genes involved in cell division, proliferation, and death. These epigenetic alterations maintain cellular homeostasis, regulate inflammatory processes, and help cancer cells recover normal gene expression.⁸³

Microenvironment Impact on Tumor

Tumor initiation, growth, metastasis, and drug resistance are all substantially controlled by the intricate ecology of the tumor microenvironment (TME). It is characterized by oxidative stress, hypoxia, acidity, and inflammation, all of which may impact cancer cell behavior. Phytonutrients, found in fruits, vegetables, and plant foods, alter various TME components, altering the interaction between tumor cells and their environment,

thus enhancing anti-cancer efficacy.⁸⁴ Chronic inflammation induces angiogenesis, immunological evasion, and metastasis, all of which play a role in tumor growth. The inhibiting the activation of pro-inflammatory mediators such as NF- κ B, COX-2, and pro-inflammatory cytokines, phytonutrients such as curcumin, resveratrol, and sulforaphane have the ability to suppress inflammatory pathways.⁸⁵ This reduces the release of inflammatory cytokines and chemokines, which renders the tissue environment less conducive to tumor growth. Angiogenesis is also vital for tumor growth and metastasis as well as inflammation. These have been shown to inhibit angiogenesis by targeting key elements like matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF).⁸⁶ Phytonutrients inhibit tumor formation and metastasis by decreasing the blood supply to tumors. Through the promotion of the epithelial-to-mesenchymal transition (EMT), hypoxia causes tumors to become more aggressive by allowing cancer cells to migrate to other organs and invade surrounding tissues.⁸⁷ Hypoxia-driven EMT can be reversed by phytonutrients such as resveratrol and quercetin, which inhibit the production of hypoxia-inducible factor-1 α (HIF-1 α), an essential controller of oxygen-dependent genes. Due to this inhibition, cancer cells cannot acquire the invasive properties required for metastasis.⁸⁸ Yet another property of the TME is immune evasion. The enhancing the function of immune effector cells such as T-cells and natural killer (NK) cells and inhibiting immune suppressive cells such as T-regulatory cells and myeloid-derived suppressor cells (MDSCs), phytonutrients could alter immune cell function within the TME. Their potential as complementary medicines in cancer prevention and treatment are underscored by their ability to modulate multiple pathways within the TME.⁸⁹

Radio-Chemotherapy Effects

While radiation and chemotherapy are essential treatments for most cancers, they often have severe side effects, such as drug resistance, destruction of normal tissues, and immunosuppression. The use of phytonutrients as a plant-derived bioactive compounds to conventional cancer therapy has become increasingly popular over the last few years.⁹⁰ It has been shown that phytonutrients could enhance the effectiveness of radiation and chemotherapy and decrease their side effects. Their ability to enhance immune responses

reduce toxicity and sensitize cancer cells offers an effective method to improve the efficiency of cancer treatment. By increasing the sensitivity of cancer cells to chemotherapeutic agents such as curcumin, resveratrol, and epigallocatechin gallate (EGCG) phytonutrients complement chemotherapy.⁹¹ These phytonutrients interact with a multitude of cellular pathways that are responsible for drug resistance, such as overexpression of anti-apoptotic proteins and activation of drug efflux pumps. The inhibiting P-glycoprotein, a cell membrane protein that exports chemotherapeutic drugs from cells, curcumin has been shown to sensitise resistant cancer cells to paclitaxel. This enhances the intracellular drug accumulation.⁹² Through the modulation of cell survival and death signaling pathways, resveratrol has also been shown to sensitise tumor cells to cisplatin.⁹³ Phytonutrients also possess radioprotective activity, enhancing the therapeutic value of radiation treatment and minimizing its adverse effects on normal tissues.⁹⁴ EGCG, a primary polyphenol in green tea, has shown promise in radiation therapy by radio-sensitizing tumor cells by inhibiting the Akt pathway which is responsible for DNA repair and cell survival.⁹⁵ Curcumin sensitizes tumor cells to radiation by increasing DNA damage in cancer cells but preventing normal cells from oxidative stress.⁹⁶ Through decreased oxidative stress, control of immune reaction, and protection of normal cells from damage due to radiation phytonutrients also contribute to reducing treatment toxicities. For example, through modulation of phase II detoxifying enzymes, sulforaphane, a compound found in cruciferous vegetables such as broccoli, has been shown to reduce chemotherapy-induced neutropenia and protect against organ injury.^{97, 98}

Delivery Challenges, Bioavailability, Metabolism

Curcumin, resveratrol, EGCG, and sulforaphane are a few phytonutrients that have shown promising promise in the treatment and prevention of a variety of diseases, including cancer. However, these compounds often find it difficult to reach therapeutic levels within the blood and tissues which limits their therapeutic potential.⁹⁹ The proportion of a chemical that becomes available in the circulation after introduction into the body and reaches tissues and organs is termed bioavailability. Due to their very lipophilic nature, phytonutrients such as curcumin are not readily absorbed into the circulation upon intake.¹⁰⁰ The liver's rapid first-pass metabolism

of resveratrol, a compound found in red wine and grapes, reduces its bioavailability. The principal catechin in green tea, EGCG, is rapidly broken down and mal absorbed in the intestine, reducing plasma levels.¹⁰¹ The brief half-lives of such phytonutrients in the bloodstream, which facilitate their rapid elimination from the body make these challenges even more challenging. The accessibility and biological effectiveness of phytonutrients are largely controlled by metabolism. Liver and intestinal enzymes metabolize phytonutrients upon ingestion, yielding metabolites that may be less physiologically active than the parent compounds.^{102,103} Inconsistent response to supplementation can occur because of the influence of the gut microbiota on phytonutrient metabolism. One means of enhancing the bioavailability and therapeutic action of phytonutrients is through delivery forms. New delivery forms with enhanced solubility, stability, and absorption of such chemicals have been designed due to the improvement in nanotechnology and formulation technologies. These innovative delivery techniques can potentially circumvent the disadvantages of fast metabolism and poor bioavailability, ensuring that more concentrations of phytonutrients become available in the bloodstream and arrive at the targeted tissues for their therapeutic action.¹⁰⁴

Regulatory Perspectives Dosage And Safety

Curcumin, resveratrol, EGCG, and sulforaphane are just a few among the many phytonutrients that have shown promising therapeutic effects in preventing and treating disease. Their safety profiles, optimal doses, and regulatory oversight need to be well considered to ensure safe and effective use, particularly in a clinical context. Especially when taken in bulk form or over an extended period, highly concentrated supplements can be risky to safety.¹⁰⁵ For example, EGCG prevents cancer but has been found to cause a rare instance of liver toxicity upon high-dose administration; sulforaphane is safe but can produce some mild gastrointestinal distress; curcumin causes gastrointestinal disturbances; and resveratrol enhances bleeding risk in subjects on anticoagulant therapy.¹⁰⁶ Also, some drugs' metabolism and action can be influenced by the interaction of phytonutrients with drugs metabolized by the liver's cytochrome P450 enzyme system. For phytonutrients to exert optimal therapeutic benefits and minimum adverse side effects, the appropriate dose is necessary. Doses of 500 mg to 2,000 mg

of curcumin, 150 mg to 500 mg of resveratrol, and 300 mg to 800 mg of EGCG are standard in clinical trials.¹⁰⁷ There are varying regulatory frameworks for phytonutrient supplements across countries but the majority of them regulate them as dietary supplements, which are regulated less strictly than medicines. Whereas the European Food Safety Authority (EFSA) in Europe imposes stricter limitations on health claims by manufacturers of supplements, the FDA in the United States does not certify dietary supplements as safe or effective before they are marketed. Stricter regulatory steps, such as quality control guidelines, good manufacturing practices (GMP), and more extensive clinical research on phytonutrient safety and effectiveness, are necessary to solve these issues.^{108,109}

Research Gaps and Future Directions

There are many gaps in research and future directions that need to be answered despite the increasing evidence that phytonutrients possess the potential to prevent and cure disease. Maximizing the metabolism and bioavailability of phytonutrients such as sulforaphane, EGCG, resveratrol, and curcumin is an urgent area for future research. Increasing the efficacy of these chemicals by advancing liposomal formulations, nanotechnology, and bio enhancement methods is essential.¹¹⁰ Understanding how the gut microbiota influences the metabolism of phytonutrients could possibly lead to personalized phytonutrient-based therapies through insights into the way that everyone responds differently to these chemicals. Another important research area is optimization of dosing strategies. While various doses of phytonutrient supplements have been investigated in clinical trials, standardized dosing recommendations are still not available. To determine the optimal dosage which maximizes therapeutic effects and reduces adverse effects, dose-response investigations are necessary.^{111, 112} To determine long-term implications of high-dose phytonutrient supplementation to human health, longitudinal studies of the consequences of chronic consumption will be important. Further studies will also be necessary to elucidate the molecular actions of phytonutrients. Though it has been indicated by studies that phytonutrients possess anti-inflammatory, antioxidant, and anti-cancer activity, it is yet to be determined which specific signaling

pathways and gene expression modifications these compounds induce.¹¹³ Researching how phytonutrients impact epigenetics can reveal novel therapeutic avenues for the prevention and treatment of chronic diseases such as cancer, heart disease, and neurological disorders. Finally, additional work must be conducted to enhance the regulatory landscape for phytonutrient supplements.^{114,115} Standardizing the phytonutrient composition of supplements and creating more specific guidelines for health benefit claims will improve the quality and consistency of products that consumers can buy. Creating firm standards that ensure the safety and efficacy of phytonutrient-based treatments necessitates collaboration among regulatory agencies, researchers, and the supplement industry.^{116,117}

Discussion

Phytonutrients, which are abundant in fruits, vegetables, and herbs, demonstrate significant anti-inflammatory and anti-cancer properties that are essential for health promotion. These bioactive compounds, including flavonoids, carotenoids, and polyphenols, exert their effects by modulating inflammatory pathways and oxidative stress, thereby mitigating chronic inflammation associated with various diseases. Furthermore, their capacity to regulate cellular processes, such as apoptosis and cell cycle arrest, highlights their potential in cancer prevention and treatment. Utilizing these benefits through dietary intake or supplementation offers a comprehensive approach to addressing inflammatory disorders and reducing cancer risk. Future research should aim to elucidate specific mechanisms of action, optimize bioavailability, and explore synergistic interactions among phytonutrients to enhance their therapeutic efficacy in clinical settings. Integrating phytonutrient-rich diets into public health strategies holds promise for improving overall well-being and preventing chronic diseases.

Conclusion

Fruits, vegetables, whole grains, and legumes are rich in bioactive compounds known as phytonutrients that have been shown to hold promise for preventing and treating chronic diseases such as cancer, heart disease, and inflammatory diseases. These compounds are attractive therapeutic agents due to

their anti-inflammatory, antioxidant, and anti-cancer properties. Converting these findings into therapeutic applications remains challenging, however. Because most substances are not well absorbed, rapidly metabolized, and eliminated from the body, one of the key challenges is phytonutrient bioavailability and metabolism. Breakthroughs in drug delivery systems such as liposomes, nanoparticles, and bioenhancers offer means to increase absorption and ensure effective distribution to target areas. In consideration of the diverse range of currently available dosage guidelines and limited knowledge regarding the long-term safety of high-dose phytonutrient supplementation, dosing optimization remains a challenge. Another significant area in need of more exploration is the modes of action for the phytonutrients. The specific biochemical mechanisms and gene regulation processes through which phytonutrients exert their therapeutic effects are not understood, even though their antioxidant and anti-inflammatory effects are well known. To prevent the initiation of disease, the future research must focus on understanding the epigenetic changes induced by phytonutrients and the interactions of these compounds with genetic and environmental factors. To offer comprehensive guidelines for the approval and marketing of phytonutrient-based supplements, regulatory agencies such as the FDA and EFSA will be crucial. The advantages of having foods rich in phytonutrients in the diet to reduce the risk of chronic diseases are evidenced by epidemiological and clinical studies. There will be greater opportunities to integrate phytonutrient-based therapies into mainstream medical practice as we gain a better understanding of the complexities of phytonutrient metabolism, bioavailability, and interactions with other compounds.

Acknowledgement

The authors would like to thank Graphic Era (Deemed to be University), Dehradun, Uttarakhand, India; Siksha 'O' Anusandhan University, Bhubaneswar, Odisha, India; Baba Banda Singh Bahadur Engineering College, Fatehgarh Sahib India; Invertis University, Bareilly, Lucknow, Uttar Pradesh, India; Lovely Professional University, G.T Road, Jalandhar, Punjab, India; and PSGR Krishnammal College for Women, Coimbatore, Tamil Nadu, India for the support.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed consent statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial registration

This research does not involve any clinical trials.

Permission to Reproduce Materials from other Sources

Not applicable.

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