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Phytochemicals as Anticancer Agents: Investigating Molecular Pathways from Preclinical Research to Clinical Relevance

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Abstract

Cancer remains a significant global health threat, with annual deaths projected to reach 16.2 million by 2040. Phytochemicals in different botanical sources offer promising cancer preventive strategies due to their unique biological activities, affordability, ease of use, and relatively lower toxicity. This review compiles the anticancer activities of phytochemicals in various plant-based food groups as demonstrated in preclinical models and human studies. A literature survey was performed in various research databases such as Google Scholar, PubMed, Scopus, and Web of Science to identify relevant peer-reviewed publications, including original research and review articles published between 2018 and 2025. Phytochemicals such as flavonoids, phytosterols, phenolic acids, carotenoids, and stilbenes, exert anticancer effects through anti-angiogenesis, metastasis, cell cycle arrest, apoptosis, and modulating cell signalling pathways like PI3K/Akt/mTOR/P70S6K pathway, MAPK/ERK, NF-κB, and Wnt/β-catenin as documented in *in vitro* and animal studies. Prospective human studies show that phytochemicals in different food groups, such as whole grains, nuts and seeds, fruits and vegetables, and tea extracts, exhibit anticancer effects. One significant challenge with phytochemical use is their poor bioavailability. Although

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numerous experimental studies have explored strategies to enhance phytochemical bioavailability, such as nano formulations, co-administration with bioenhancers, and structural modifications, clinical research on the pharmacokinetics, potential nutrient interactions, optimal dosing, and long-term safety of isolated or enriched phytochemicals remains limited.

Abbreviations

17HSD 17β	17β-hydroxysteroid dehydrogenases
ATA	Antcin – A
BAX	BCL2 Associated X
BCL-2	B cell lymphoma 2
BT – 20	Breast cancer cell line – 20
BT – 549	Breast cancer cell line – 549
cagA	Cytotoxin–associated gene A
CAMP	Campesterol
CAT	Catalase
CCND1	Cyclin D1
CCS	Case-control studies
CDK	Cyclin-dependent kinases
CFL2	Cofilin-2
COX	Cyclooxygenase
CS	Cohort study
DMH	Dimethylhydrazine
DNMT1	DNA methyltransferase 1
EEP:	Ethanolic extract of propolis
EGCG	Epigallocatechin gallate
EMT	Epithelial-mesenchymal transition
ERGO	Ergosterol
ERK	Extracellular signal-regulated kinase
FADD	Fas-associated protein with death domain
FOXO	Forkhead box transcription factors
G2/M	Second gap phase/Mitosis
GPX	Glutathione peroxidase
GRP78	Glucose-regulated protein 78
HCA	Heterocyclic amines
HEK293T	Human embryonic kidney 293 cells
HER2	Human epidermal growth factor receptor 2
HIF 1α	Hypoxia–inducible factor 1 alpha
hnRNPA1	Heterogeneous nuclear ribonuclear protein
H. pylori	Helicobacter pylori
HUVEC	Human umbilical vein endothelial cells
IL-6	Interleukin
JAK/STAT	Janus kinases/Signal transducer and activator of transcription
LEF -1	Lymphoid enhancer factor
MAPK	Mitogen–activated protein kinase
MBE	Muscadine grape berry extract
MCF7	Michigan Cancer Foundation 7
MDA – MB – 231	MD Anderson – metastatic breast 231
MDA – MB – 436	MD Anderson – metastatic breast 436
MEK	Mitogen–activated extracellular signal-regulated kinase
MIC 1	Macrophage inhibitory cytokine – 1
MMP	Matrix metalloproteinase
MTA 1	Metastasis-associated protein 1
MTase	Methyltransferase
mTOR	Mammalian target of rapamycin
NCD	Non-communicable diseases
NFR2	Nuclear factor erythroid 2-related factor 2
NLRP	Nucleotide-binding and leucine-rich repeat protein
NSCLC	Non-small cell lung cancer
OR	Odds ratio
P13K/AKT kinase	phosphatidylinositol 3 kinase/Akt
p53	Tumour protein
PAI-1	Plasminogen activator inhibitor-1
PAH	Polycyclic aromatic hydrocarbons
PCNA	Proliferating cell nuclear antigen
PG	Prostaglandin
PIK3CA	Phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha
PPARS	Peroxisome proliferator-activated receptors
PTEN	Phosphatase and tensin homolog
Raf	Rapidly accelerated fibrosarcoma
Ras	Rat sarcoma
RASSFIA gene	Ras association domain family member 1
ROS	Reactive oxygen species
RR	Relative risk
SITO	Sitosterol
SOD	Superoxide dismutase
STAT3	Signal transducer and activator of transcription 3
STIG	Stigmasterol
TGF-β	Transforming growth factor β

TIMP	Tissue inhibitors of metalloproteinases	TRAIL	Tumor Necrosis Factor (TNF)-related apoptosis-inducing ligand
TLR	Toll-like receptors	VEGF	Vascular endothelial growth factor
TNBC	Triple negative breast cancer		
TNF–α	Tumor necrosis factor-alpha		

Introduction

NCDs are long-term disease conditions that develop gradually due to genetic, physiological, environmental, lifestyle, and dietary factors. The most prevalent NCDs globally include diabetes, cancer, chronic respiratory diseases, and cardiovascular disorders. The incidence rate of NCDs is increasing globally and nationally.[1] Cancer, marked by uncontrolled cell proliferation and potential metastasis, is a major global health threat.[2] Projections suggest that by 2040, the global burden of cancer will reach 28 million new cases and 16.2 million deaths annually.[3] Conventional cancer treatments like surgery, chemotherapy, and radiotherapy often come with significant adverse effects. However, recent advancements in oncology have introduced innovative approaches such as ablation therapy, catalytic cancer therapy, iron-dependent cell death therapy, gene modification therapy, nanoparticle-based therapy, radionics, stem cell therapy, sonodynamic therapy, and targeted therapy. While these advanced therapies offer promising alternatives for cancer treatment, their high costs create significant barriers to accessibility, making them unaffordable for individuals from various socio-economic backgrounds.[4]

Findings from medical and nutrition research indicate that dietary agents enhance anticancer activity and regulate several physiological functions. In the field of cancer research and therapy, scientists are currently exploring numerous chemical components produced from plants that can effectively fight and prevent cancer.[5] Phytochemicals/phytoconstituents/ non-nutritive compounds present in herbs, leaves, vegetables, fruits and other plant sources have attracted considerable attention because of their prospective roles in cancer inhibition and therapy due to the complexity of their structures, their unique biological effects, affordability, ease of use, and comparatively fewer harmful side effects.[6,7] The anticarcinogenic properties of these non-nutritive compounds include modulation of molecular signaling pathways, inhibition of early-stage carcinogenesis, protein modifications, and interaction with specific molecular signals.[8]

Good nutrition is vital for maintaining metabolic homeostasis. Inclusion of specific foods and beverages in the diet can alter metabolic pathways by enhancing or diminishing them. Diets mainly comprised of plants include a broad variety of consumption habits marked by reduced animal-derived foods and a predominance of plant-based foods abundant in various phytochemical groups.[9] Herbs, spices, legumes, whole grains, vegetables, fruits, oilseeds, and nuts provide essential micronutrients, including vitamins, minerals, enzymes, and phytochemicals, all contributing to cellular protection and cancer prevention. Epidemiological and mechanistic studies suggest that adherence to a plant-based diet that is well balanced, with limited consumption of red and processed meat, is linked with a lower incidence of breast, prostate, colorectal, and lung cancers.[10,11] Regarding diet patterns for the prevention of cancer, prioritizing suitable plant-centred food selections is essential. This review systematically compiles and evaluates the phytochemicals and bioactive compounds present in various plant-based food groups, delineating their molecular mechanisms of cancer prevention as evidenced in preclinical models and human clinical studies.

Materials and Methods

This review compiles and analyzes the current scientific evidence on the anticancer potential of phytochemicals, emphasizing their molecular mechanisms and translational relevance from preclinical models to clinical applications. A literature survey was performed in various research databases such as Google Scholar, PubMed, Scopus, and Web of Science, to identify pertinent peer-reviewed publications. The search included original research articles and review papers published between 2018 and 2025. The following keywords and Boolean operators were used to refine the search:

- ("phytochemicals" OR "plant-derived compounds") AND ("anticancer activity" OR "cancer therapy")
- ("natural compounds" AND "molecular mechanisms" AND "cancer")
- ("preclinical studies" OR "*in vitro*" OR "*in vivo*") AND ("phytochemicals" AND "oncogenic pathways")
- ("clinical trials" AND "phytochemicals" AND "cancer treatment")

The manuscripts for this review article were chosen upon fulfilling certain eligibility and exclusion criteria.

Inclusion Criteria

- Studies investigating the anticancer effects of phytochemicals with mechanistic insights.
- Research papers detailing apoptotic pathways, autophagy modulation, angiogenesis inhibition, cell cycle regulation, or interactions with other oncogenic pathways.
- Preclinical studies (both *in vitro* and *in vivo*) and clinical trials evaluating phytochemical-based cancer therapies.
- Peer-reviewed publications in English with clearly defined methodologies and experimental outcomes.

Exclusion Criteria

- Studies lacking mechanistic insights or focusing solely on general phytochemical properties without cancer-specific findings.
- Non-peer-reviewed sources, conference abstracts, and unpublished reports.

Phytochemicals as Targeted Cancer Therapeutic Agents

In recent years, growing scientific evidence has highlighted the powerful role of phytochemicals in reducing cancer risk. Phytochemicals present in plant-based foods exert protective effects against cancer through multiple molecular mechanisms. Naturally occurring compounds, including flavonoids, phytosterols, phenolic acids, carotenoids, and stilbenes, help combat cancer by inducing apoptosis, inhibiting angiogenesis, and modulating inflammatory and oxidative stress pathways.[12]

Flavonoids: Flavonoids are natural compounds in plants, consisting of 2 rings of benzene connected by 3 carbon atoms, creating a C6-C3-C6 structure. They are classified into subclasses, including chalcones, dihydrochalcones, flavones, and flavanols, based on the oxidation level of the central chain and the B-ring attachment.[13] Common dietary sources of flavonoids include EGCG (cocoa and green tea), hesperidin and hesperetin (citrus fruits), quercetin (apples, berries, broccoli, grapes, red onions, and red wine), luteolin (carrots, celery, chili peppers, lettuce, and spinach), and apigenin (artichokes, chamomile, oregano, and parsley).[14] Flavonoids reduce tumor progression through apoptosis and cell-cycle regulation. Flavonoids cause G2/M phase arrest and promote cell death in breast cancer cells by altering two pathways (p53 and PTEN).[15] EGCG regulates the 67-KDa laminin receptor, influences JAK/STAT, MAPK, and PI3K/AKT signaling pathways, and affects estrogen and androgen receptors in breast and prostate tumors, respectively.[16] Quercetin, decreases BCL2 levels, and activates caspase-3 to trigger apoptosis. It sensitizes prostate cancer cells to paclitaxel by modulating proteins like GRP78 and hnRNPA1.[17] Apigenin's anti-angiogenic properties are associated with cell cycle cessation, apoptosis induction, and regulation of signaling pathways.[18]

Phytosterols

Phytosterols are plant-derived compounds resembling cholesterol, differing mainly by an extra hydrocarbon chain at the C-24 site. Over 250 phytosterols have been identified, with campesterol, β-sitosterol, stigmasterol, β-sitostanol, and campestanol being the most common in food sources.[19] These compounds show anticancer properties by enhancing pro-apoptotic signals that cause cell death by increasing calcium concentration in the cytosol and mitochondrial region. Phytosterols promote the overexpression of unfolded protein response signals and endoplasmic reticulum-mitochondria axis signals, leading to endoplasmic reticulum stress and cancer cell death. They also decrease the production of ROS, facilitating cell death via intrinsic mitochondrial apoptotic pathways or extrinsic death receptor pathways. Phytosterols hinder cell cycle progression by suppressing PCNA expression and disrupting the MAPK pathway, while also reducing cell migration and aggregation.[20] They help the immune system identify and kill cancer-causing cells.[21] β-sitosterol inhibits the propagation of human colon cancer cells by obstructing the LEF-1-mediated Wnt/β-catenin pathway. The increased expression of LEF-1 in

intestinal cancer triggers this pathway, causing the growth of tumors.[22] β-Sitosterol impedes the advancement and invasiveness of HCT116 CC cells by lowering LEF-1 levels, disrupting the pathway, and diminishing key downstream targets, including Survivin and CCND1, supporting its effectiveness as a cancer-fighting agent.

Phenolic Acids

The cancer-fighting ability of phenolic acids comes from their antioxidant effects. They act as free radical scavengers and metal binding agents, strengthen the body's antioxidant defense mechanisms, and regulate key proteins and transcription factors (NRF2).[23, 24] Their role involves blocking cell growth via the ERK1/2 pathway, D-type cyclins, and CDK, alongside hindering angiogenesis by targeting VEGF and MIC-1, suppressing oncogenic signaling (PI3K/AKT), inducing apoptosis, and inhibiting cellular migration and metastasis. Their ability to fight against cancer is amplified through epigenetic influencers and resistance regulators, effectively reducing cancer cell division, inhibiting metastasis, and promoting cell death.[25] Phenolic acids, such as caffeic, dihydro cinnamic, and p-coumaric acids extracted from propolis, along with EGCG extracted from green tea, act as epigenetic agents for TNBC.[26] Administration of coumaric acid and EGCG led to a marked decline in cell viability across four TNBC cell lines (BT-20, BT-549, MDA-MB-231, and MDA-MB-436). Molecular docking predicted that these compounds bind to the MTAse territory of human DNMT1, competing with its endogenous inhibitor SAH. While EEP did not modify overall DNA methylation, EEP and EGCG were found to cause demethylation of the RASSF1A gene in BT-549 cells. EEP treatment also influenced RASSF1 protein expression, highlighting propolis as a potential agent for epigenetic therapies aimed at DNA methylation modulation. Chlorogenic acids present in tea help mitigate disease risk by regulating signaling pathways involved in inflammation and oxidative damage, regulating essential key cellular functions such as proliferation, apoptosis, and immune responses. By interacting with specific molecular mechanisms, chlorogenic acids suppress tumor growth. Research studies of phenolic acids in ovarian cancer have identified promising anticancer effects. GA suppresses tumor development via the PTEN/AKT/HIF-1α pathway. Salicylic acid regulates multiple pathways, including Wnt/β-catenin, and targets ovarian cancer stem cells. EA prevents angiogenesis and cisplatin resistance, facilitating apoptosis. PCA reduces cancer cell growth by inducing apoptosis and regulating oxidative stress. CA enhances cisplatin cytotoxicity, while coumaric acid and ferulic acid act as adjuvants, modulating oxidative stress and signaling pathways.[27]

Stilbenes

Dietary stilbenes are polyphenolic compounds found in berries, grapes, and medicinal herbs. Certain examples of notable stilbenes are compounds such as resveratrol (trans-3,4′,5-trihydroxystilbene), abundant in grapes and red wine are known for their oxidative stress reducing, immune regulating, and cancer fighting effects. Pterostilbene (trans-3,5-dimethoxy-4′-hydroxystilbene), a more bioavailable counterpart of resveratrol found in blueberries and grapes, exhibits enhanced pharmacokinetics. Piceatannol (trans-3,5,3′,4′-tetrahydroxystilbene), present in red wine and passion fruit, functions as a tyrosine kinase inhibitor with anticancer potential. Other derivatives, such as piceid (resveratrol glucoside), astringin (piceatannol glucuronide), ε-viniferin, pallidol (resveratrol dimers), and gnetin C (a resveratrol dimer found in melinjo seeds), demonstrate anti-angiogenic and chemopreventive effects. These stilbenes control epigenetic pathways, specifically methylation of DNA, alteration of histone, and regulation of microRNA, contributing to their therapeutic efficacy, causing programmed cell death, lowering angiogenesis, and inflammatory responses.[28, 29] Methoxy-stilbenes exhibit anticancer activity by modulating key receptors and enzymes linked with the biosynthesis of estrogen in breast cancer cells.[30] Finings indicated that methoxy-stilbenes efficiently suppressed the action of two key enzymes involved in estrogen synthesis (aromatase and 17HSD17β). They are also involved in suppressing the expression of Erα, thereby weakening estrogen signalling and preventing cancer cell proliferation. MBE, a rich source of resveratrol, piceatannol, and pterostilbene, showed greater potency than resveratrol by stimulating apoptosis and enforcing cell cycle arrest.[31] Resveratrol combats photo-carcinogenesis by adjusting apoptotic inhibition proteins and governing cell cycle signalling cascades. Stilbenes prevent prostate cancer through inhibition of MTA1 signaling pathways. Resveratrol and pterostilbene suppressed MTA1 expression, leading to reduced

tumor growth, metastasis, and angiogenesis while enhancing apoptosis.[32]

Carotenoids

Carotenoids are lipophilic pigments classified into carotenes and xanthophylls, which contribute to the red, yellow, and orange colours in fruits and vegetables. Beyond their roles as antioxidants, and provitamin A sources, carotenoids demonstrate significant anticancer activity through mechanisms such as free radical neutralization, gene regulation, and modulation of inflammatory pathways. Key dietary sources of carotenoids include algae, yeast, carrots, tomatoes, citrus fruits, and various plant by-products.[33] Saponified lipophilic extract from sea buckthorn (*Hippophae rhamnoides* L.) has anticancer effects against breast cancer cell lines T47D and BT-549.[34] The extract inhibited proliferation (IC50 value: 16 µM), reduced ROS levels, and induced apoptosis (80.29% in T47D and 40.6% in BT-549). Carotenoids derived from yeast through cost-effective fermentation processes, demonstrated dose-dependent cytotoxicity against MCF7 and MDA-MB-231 cells (IC50 values: 29.11 and 7.82 µg/mL) while sparing normal HEK293T cells.[35] Similarly, carotenoids derived from *Paracoccus* sp. EGY7, identifying zeaxanthin (48.3%) as the predominant compound. The extract exhibited cytotoxicity against MDA-MB-231 cells (IC50 value: 1200 µg), inhibited cellular migration, and induced apoptosis through modulation of BAX/BCL2 ratios.[36] α-Carotene suppresses metastasis by modulating MMP2, MMP2, TIMP-1, and PAI-1, thereby impairing integrin β1/FAK/MAPK signaling without affecting primary tumor growth. β-Carotene inhibits gastric cancer progression through Notch/EMT pathway suppression, and in neuroblastoma, it downregulates MMPs, HIF-1α, and VEGF, consequently reducing metastasis. Additionally, it modulates M2 macrophage and fibroblast activation, limiting invasiveness in colorectal cancer. Overexpression of β-carotene 15,15′-oxygenase suppresses the tumorigenic potential and metastatic progression of neuroblastoma through modulation of EMT and MMP activity.[37]

Major Mechanistic Anti-Cancer Potential of Phytochemicals

Anti-angiogenesis and Metastasis

Angiogenesis is the process by which old blood vessels are converted into new ones, crucial for tumor growth, invasion, and dissemination. Phenolic compounds serve as angiogenesis blockers to inhibit the multiplication of tumor cells. Polyphenol compounds such as EGCG, ellagic acid, and genistein counteract angiogenesis by inhibiting VEGF, PDGF, HIF-1α, and MMPs. Inhibition of platelet-derived growth factor (PDGF) receptor phosphorylation and epidermal growth factor receptor also aids in anti-angiogenesis.[38] Green tea polyphenols chelate ferrous ions and stop the proliferation of cancer cells driven by HIF 1α. *In vitro* studies on prostate tumor cells showed that EGCG treatment reduced HIF 1α-mediated transcription and protein levels under normal oxygen conditions.[39] Galanin, kaempferol, myricetin, and quercetin inhibit the tubular development of HUVECs mediated by vascular endothelial growth factor and impede U937 cell adherence to HUVECs.[40] Flavonoids, including kaempferol, genistein, apigenin, rutin, and naringin, reduce the levels of vascular endothelial growth factor in cells of human breast cancer.[14] Metastasis is the process by which cancer cells travel through lymph nodes to distant organs, interchangeable with angiogenesis, invasion, cell adhesion, migration, proteolysis, and extracellular matrix destruction.[41] Many dietary polyphenolic compounds disrupt tumor cell adhesion and migration, giving them anti-invasive and antimetastatic properties, though their precise signaling pathways and molecular mechanisms remain unidentified.[42] Curcumin inhibits VEGF/VEGFR2 signalling and downstream pathways (AKT, MAPK), reducing endothelial cell proliferation and migration. It also suppresses MMP2/9 expression and EMT by modulating Wnt/β-catenin pathways.[43] Resveratrol downregulates cyclin D1/CDK4 and VEGF expression, blocking endothelial cell activation, while Quercetin hinders CAM assay angiogenesis by targeting VEGF and HIF-1α.[44] Apigenin blocks STAT3 nuclear translocation, impairing endothelial tubulogenesis, while Genistein induces apoptosis in VEGF-loaded endothelial cells by inhibiting JNK/p38 and MMP-2/9. Luteolin downregulates PURB-mediated MAPK/PI3K pathways, reducing NSCLC angiogenesis.[45]

Cell Cycle Arrest and Apoptosis

Apoptosis, a prevalent form of regulated cell death, is a critical target for various cancer therapies. Dietary cancer-fighting agents such as apigenin, chrysin, curcumin, EGCG, ellagic acid, resveratrol, and silymarin suppress carcinogenesis through the

induction of apoptosis.[46] Notably, cancer cells exhibit heightened sensitivity to these agents compared to normal healthy cells. In sarcoma cells, EGCG induces apoptosis through mechanisms including cell cycle cessation at the G2/M phase, suppression of BCL-2, and the activation of p53 and BAX.[47] In prostate cancer cells, apoptosis is accompanied by the overexpression of BAX, along with the activation of caspases (3 and 8). EGCG primarily triggers and promotes senescence and apoptosis through p53-mediated signaling, in conjunction with the role of BAX.[48] Theaflavin, a phenolic compound in black tea, contributes to apoptosis by enhancing DNA fragmentation, activating caspases (3 and 8), increasing and decreasing the levels of BCL-2.[49] Furthermore, theaflavin activates the expression of caspases 9 and 3 in prostate cancer cells, alters the BAX/BCL-2 ratio, increases the release of cytochrome c from mitochondria, and causes apoptosis via p53 expression.[50] Anthocyanins, a significant class of flavonoids, demonstrated dose-related suppression of the growth of colon cancer cells. They induce programmed cell death in colon cancer cells through DNA damage and an imbalance in BAX and BCL-2 expression. However, certain bioflavonoids, including epicatechin, rutin, chlorogenic acid, and p-hydroxybenzoic acid, do not exhibit growth-inhibiting effects.[51] Delphinidin, a naturally occurring anthocyanidin, obstructs VEGF-induced cell movement and growth by arresting the cell cycle at the G0/G1 phase. The levels of Cyclin D1 and cyclin A significantly decreased.[52] Additionally, early activation of extracellular signal-regulated protein kinase 1/2, overexpression of caveolin-1, and downregulation of Ras contribute to the antiproliferative effects of delphinidin.[53]

Modulation of Cell Signalling Pathways

Phytochemicals exhibit various biological activities like anti-inflammatory, antiproliferative, antioxidant, antimutagenic, and immunomodulatory, which help regulate cancer progression and influence cancer development by modulating multiple signaling pathways.[54] They modulate routes concerned with cancer progression and suppression, such as the PI3K/Akt/mTOR/P70S6K pathway, PPARs, Nrf2, JAK-STAT, HIF-1, TGF-β, and TLR/NLRP, as well as the MAPK, ERK, and p38 pathways.[55-57] Phytochemicals can scavenge free radicals and respond to chemical stress, activating or inhibiting diverse signaling responses. Notable phytochemicals like apigenin, betulinic acid, ascorbic acid, curcumin, resveratrol, lycopene, and sesamol have protective effects through these pathways.[58] Resveratrol decreases the capacity of colorectal cancer cells to develop and metastasize. The mechanism indicates a connection between the modulation of the peroxisome proliferator gamma receptor coactivator 1-alpha signaling pathway and AMP-activated protein kinase.[59] Resveratrol suppresses ERK1/2 phosphorylation, limits gene expression associated with tumor progression. Resveratrol and curcumin act on Ras mutations that cause continuous activation of the MEK/ERK/MEK/Raf/Ras pathway, driving cell growth and survival.[60] Flavonoids such as luteolin, apigenin, and kaempferol inhibit AKT/mTOR/P13K signalling pathway, essential for cell survival, growth, and metastasis, while promoting apoptosis by suppressing AKT phosphorylation and modulating downstream regulators (STAT3).[61] Another dietary flavonoid, Fisetin, in combination with 5-FU treatment reduced PI3K expression, AKT activation, mTOR, its downstream targets, and mTOR signaling complex in PIK3CA-mutant cells.[62] Table 1 provides an overview of the regulatory pathways modulated by phytochemicals and their impact on cancer metabolism.

In 2020, GLOBOCAN reported 19.3 million new cases of cancer worldwide, ranking India third behind the US and China. Projections indicate that by 2040, the percentage of people suffering from cancer in India will rise to 2.08 million, reflecting a 57.5% increase from 2020.[76, 77] Cancer can develop in nearly any organ or system within the human body, including the oral cavity, breast, bone, brain, stomach, intestines, lungs, renal organs, genitals, and the reproductive system. According to a recent review, the five most common cancer locations across various anatomical sites in Indian men include the stomach (4.8%), prostate (6.1%), tongue (5.9%), mouth (8.4%), and lung (10.6%). For women, the most commonly reported cancer sites were breast (28.8%), cervix (10.6%), ovary (6.2%), corpus uteri (3.7%), and lung (3.7%). Furthermore, based on estimated incidence rates, cumulative risk, and total cancer burden across all anatomical sites, the most prevalent cancers were those of the digestive system (1 in 39 individuals), breast (1 in 56), genital system (1 in 53), oral cavity (1 in 62), and respiratory system (1 in 74). Among digestive system cancers, the most frequently diagnosed

malignancies included the stomach (1 in 213), liver (1 in 276), and colorectal cancer (1 in 295). In contrast, lung cancer remained the predominant malignancy in the respiratory system (1 in 101).[78] The anticancer potential of phytochemicals derived from various food sources is supported by animal and human studies. Tables 2-6 present their correlation with a reduced incidence of conditions such as breast, lung, colon, stomach, liver, and prostate cancer, along with the underlying mechanisms of their anticancer activity. These tables also highlight the effectiveness of phytochemicals in cancer prevention and mitigation.

Table 1: Regulatory Pathways Modulated by Phytochemicals in Cancer Metabolism

Pathway	Phytochemicals	Mechanism of action	Effect on Cancer Metabolism
PI3K/AKT/mTOR One of the most frequently dysregulated signaling cascades in cancer, promoting cell survival, proliferation, and resistance to apoptosis	Curcumin, Resveratrol, Luteolin, Apigenin	Inhibits Akt phosphorylation; suppresses mTOR and downstream effectors (FOXO, STAT3)	Reduces cell survival, proliferation, and metastasis; enhances chemosensitivity.[40]
MAPK/ERK (Ras/Raf/MEK/ERK) Regulates the growth of cells. Its dysfunction is linked to uncontrolled tumour growth.	Resveratrol, Ursolic Acid, Gingerol	Blocks ERK1/2 phosphorylation; inhibits Ras/Raf activation	Suppresses uncontrolled proliferation and metastasis; induces apoptosis.[63,64]
NF-κB Key regulator of inflammation-driven tumorigenesis	Curcumin, Quercetin, Ellagic Acid	Inhibits NF-κB nuclear translocation and DNA binding	Reduces inflammation-driven tumorigenesis and angiogenesis.[61]
Wnt/β-catenin	Curcumin, Genistein	Downregulates Wnt signaling; suppresses β-catenin nuclear accumulation	Inhibits EMT and metastasis.[65,66]
Apoptosis (Intrinsic)	Luteolin, Icanin	Modulates BCL-2/BAX ratio; activates caspases via mitochondrial ROS	Triggers caspase-dependent apoptosis; reduces cancer cell survival.[67,68]
Apoptosis (Extrinsic)	Irigenin, Apigenin, Kaempferol	Activates TRAIL/DR5 and FADD pathways	Enhances death receptor-mediated apoptosis.[69]
ROS/Nrf2-ARE	Phenolic compounds	Activates Nrf2-ARE pathway; upregulates SOD, CAT, GPX	Counteracts oxidative stress; promotes detoxification and chemoprevention.[70,71]
p53 Suppressor pathway regulates cell cycle and apoptosis	Ellagic Acid, Resveratrol	Upregulates p53 and p21; downregulates cyclins (D1, E)	Induces G0/G1 cell cycle arrest; restores tumor-suppressive functions.[72,73]

Hormone Receptors	Genistein, Apigenin	Modulates ER/AR signaling; inhibits HER2/STAT3	Suppresses hormone-driven proliferation.[74,75]

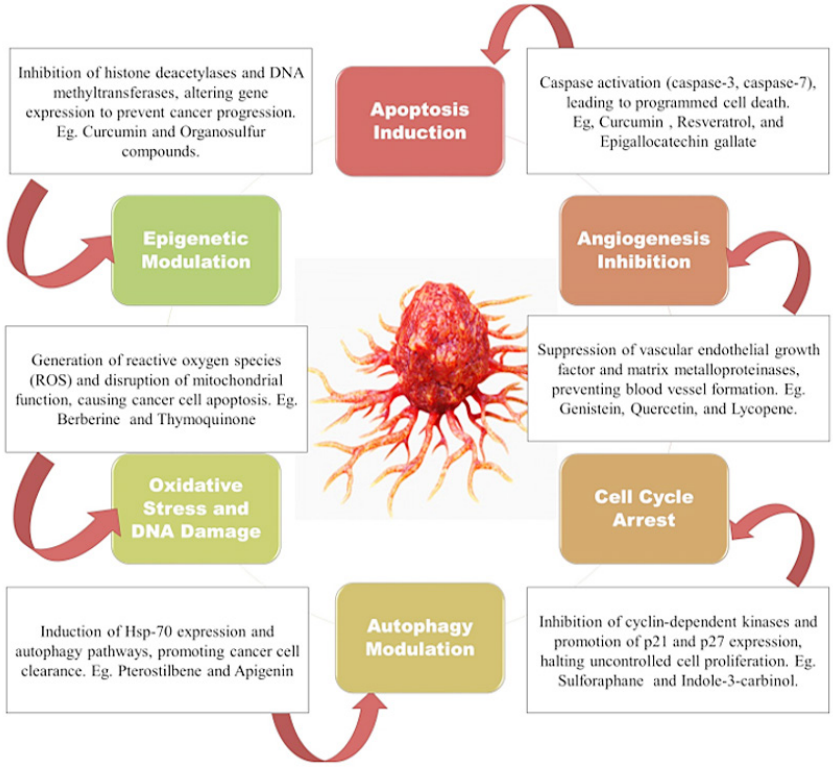

Fig.1. Anticancer mechanism of phytochemicals: Pathways and molecular targets

Challenges in the Bioavailability of Phytochemicals

Phytochemicals provide a wide range of health benefits, but their full therapeutic potential is often affected by factors such as limited bioavailability and stability. After oral ingestion, several processes, including digestion, absorption, metabolism, distribution, and excretion, affect the bioavailability of phytochemicals.[113] The structural and compositional characteristics of food matrices are crucial in determining how phytochemicals are released during digestion. These compounds are entrapped within the cell walls and influence their bioaccessibility. Food processing techniques, particularly thermal treatments, cause the release of these functional compounds by disrupting their natural cell structure.[114] These processing techniques also result in degradation of thermolabile compounds due to oxidative and hydrolytic reactions. The natural physical and chemical properties, such as crystallinity and fat solubility, determine the absorption and bioavailability. The chemical traits, such as hydrophobicity, molecular weight, can impede their solubility and transport across the gastrointestinal epithelium. Physiological factors such as changes in gastrointestinal pH, enzymatic functions, and the presence of specific transport systems also impact their absorption rate. Antinutritional factors, including phytates, tannins, and oxalates, interact with phytochemicals and form complexes, thus diminishing their bioavailability. Dietary fibers hinder the absorption of fat-soluble compounds by modifying their interaction with lipid micelles.[115] After the process of absorption, metabolism either enhances or decreases their bioactivity of phytochemicals. This metabolic process is influenced by gut microbiota, which can affect their chemical structures and biological functions.[116] Table 7 presents an overview of phytochemical bioavailability, highlighting its challenges, underlying mechanisms, and strategies for enhancement.

Table 2: Anticancer effects of phytochemicals in various animal models

Phytochemical	Type of cancer	Action
Apigenin - flavonoids	NSCLC	Regulates Bcl-2 family protein levels and triggers caspase activation, resulting in G2/M phase cell cycle arrest and apoptotic cell death in NSCLC xenograft models.[79]
Epigallocatechin - flavonoids	Breast cancer	Hinders tumor development and decreases tumor burden by triggering apoptosis and restraining the growth of human breast cancer cells in a mouse model, in addition to mitigating nitrosamine-induced lung tumor formation.[80]
	Prostate cancer	Regulates essential signaling pathways in multiple tumor models, including MAPK and PI3K/AKT, demonstrating anti-angiogenic, anti-proliferative, and pro-apoptotic effects.[81]
Gingerol - Phenolic compound	Breast cancer	Limits the expansion and metastatic potential of 4T1Br4 mammary carcinoma in a syngeneic breast cancer model. Reduces proliferation and invasiveness of lung-metastatic breast cancer cells by inhibiting Akt, p38MAPK, and EGFR pathways.[82]
Curcumin - Phenolic compound	Colon cancer	Reduces the expression of the K-RAS and β-catenin genes, COX-2, and survivin within colon tissue in Sprague-Dawley rat models.[83]
Resveratrol and Pterostilbene - Stilbenes	Prostate cancer	Inhibits MTA1-regulated miR-17 family, miR-22, and miR-34a, resulting in reduced prostatic hyperplasia, tumor growth, and the proliferation and invasion of prostate cancer cells in murine models.[32]
β-sitosterol – Phytosterol	Colon cancer	Mitigates the decline of antioxidant enzymes and reestablishes nonenzymatic antioxidant defense in a rat model of colon cancer induced by 1,2 DMH.[84]
Lutein - Carotenoid	Colon cancer	Suppresses K-RAS and AKT expression and reduces aberrant crypt foci in a DMH-induced mouse model of colon cancer.[85]

Table 3: Cancer protective properties of whole grains

Functional compounds	Cancer type	Mechanisms	Clinical evidence	
			Study design	Findings
Alkylresorcinols, Avenanthramide, anthocyanins, lignans, flavones, ferulic acid, gallic acid, dietary fiber,	Stomach	Maintains gut microbiota and inhibits the action of *Helicobacter pylori* Suppression of cell metastasis, cell growth, and promotion of Induction of apoptosis	Meta-analysis of CCS using the highest vs the lowest intake comparison	Reduced whole grain intake coupled with high intake of refined grains contributed to a 36% higher risk of gastric cancer.[86]
			Meta-analysis of 1 longitudinal study and 2 CCS	Daily intake of whole grains decreased the risk of gastric cancer by 65%.[87]
	Liver	Reduces inflammation and oxidative stress Mitigates the carcinogenic effect of hyperinsulinemia	Dose-dependent meta-analysis of 6 CS	A daily intake of 50g of whole grains decreased liver cancer risk by 23%.[88]
	Colorectal	Increases the bulk of fecal matter Decreases the transit time and prevents carcinogenic compounds from being absorbed Butyrate, a short-chain fatty acid, promotes apoptosis	Dose-dependent meta-analysis of 111 CS	Daily intake of 90g of whole grains decreased colorectal cancer risk by 17%.[89,90]
	Lung	Reduces inflammation	A prospective CS with 101,732 participants	Higher whole grain intake was associated with a 16% reduced risk of lung cancer.[91]
	Breast	Upregulation of apoptosis Inhibiting the action of the MMP–9 and MMP-2 Reduces the action of urokinase-type plasminogen activator Down-regulation of STAT5/IGF-1R and STAT3/VEGF pathways	Meta-analysis of CS and 7 CCS	A daily intake of 50g of whole grains decreased breast cancer risk by 17%.[92]
	Prostate	Reduces the levels of inflammatory biomarkers (IL 1β, TNF α, and 5-lipoxygenase) Increases the apoptotic factors (pro-apoptotic caspase 3 protein)	CCS (120 participants)	Greater adherence to a healthy diet and a higher phytochemical index were associated with reduced odds of prostate cancer (0.322).[93]

Table 4: Association between red and processed meat consumption and cancer risk

Cancer type	Mechanismsa	Clinical evidence	
		Study design	**Findings**
Stomach Liver and Breast cancer	*H. pylori* infection causes stomach cancer via two pathways Direct pathway: Induction of protein modulation and mutation of specific genes Indirect pathways: Inflammation of gastric epithelial cells.	Meta-analysis of 232 studies (33,831,063 participants)	H. pylori colonization increased stomach cancer risk by 2.56 times (95% CI, 2.18 - 3.00).[94] Red meat intake increased stomach cancer risk in *H. pylori* individuals (OR=1.85).[95]
	Interference of CagA with certain host proteins involved in the cell cycle and motility Heme iron in red meat causes the production of cancer-causing N-nitroso compounds, which lead to DNA damage and cellular oxidative stress.	Systematic review and meta-analysis of 148 prospective studies	Intake of red meat may increase the risk of breast cancer. Processed meat increases the risk of liver and breast cancer by 6% and 12%.[96,97]
Colorectal	KRAS, TP53, and APC mutations Heme iron in red meat promotes the formation of cancer-causing compounds (HCAs and PAHs)	Systematic review and meta-analysis of 40 CS	High intake of red (RR: 1.09) and processed meat (RR: 1.19) raises the risk of colorectal cancer. Daily intake of 76g of red and processed meat increases the risk of colorectal cancer by 20%.[98,89]
Prostate	Method of cooking – grilling and barbecuing, and release of nitrates, nitrites, and other carcinogenic compounds	Meta-analyses of 72 studies	Red meat intake was not linked with prostate cancer. However, consumption of processed meat increased the risk of prostate cancer.[100]

Table 5: Cancer protective mechanisms of fruits and vegetables

Functional compounds	Cancer type	Mechanisms	Clinical evidence	
			Study design	**Findings**
Lycopene, flavonols, Lignan Quercetin, Resveratrol Geinstein Flavonols Kaempferol Anthocyanins, Proanthocyanidins, Punicalagin,	Breast Liver	Lycopene demonstrated antiproliferative activity by inhibiting the multiplication of insulin-like growth factor-I-stimulated cells Dietary fibre in fruits/dried fruits interacts with oestrogen metabolism, thereby reducing its bioavailability	A prospective CS A prospective CS	High intake of tomatoes decreased the risk of breast cancer (RR: 0.87), and high intake of dried fruits decreased endometrial cancer risk (RR: 0.60).[101] High consumption of fruits and vegetables

Glucosinolate, isothiocyanates, carotenoids, dietary fibre		Lignan binds with oestrogen receptors, reducing endogenous oestrogen levels Induce apoptosis Stops the G2/M phase of the cell cycle Reduces the levels of EMT -related markers and disrupts the PI3K/AKT pathway	Meta-analysis of 9 CS(N=13,26,176)	(>5.5 servings/day), especially cruciferous, yellow-, and orange-coloured vegetables, decreased the risk of breast cancer.[102] Participants who ate more vegetables had a 39% lower chance of developing liver cancer.[103,104]
	Lung	Inhibits cancer cell growth and proliferation Promotes cell apoptosis, Reduces cell migration and adhesion, and sensitizes cancer cells to antitumor drugs	Meta-analysis of 18 prospective studies	Participants who consumed more fruits and vegetables had a lower risk of lung cancer than their counterparts. (RR: 0.92 for vegetables, and 0.82 for fruits).[105]
	Colorectal	Reduces the levels of CFL2, which is responsible for promoting actin filament and reducing cell stiffness, thereby reducing colon cancer risk Increases the release of several proinflammatory cytokines from immune cells, thereby promoting anticancer cytotoxicity	Meta-analyses of 24 observational studies (10,68,158 participants)	Increased consumption of citrus fruits, apples, watermelon, and kiwi decreased colorectal cancer risk by 9%, 25%, 26%, and 13%, with corresponding RR of 0.91, 0.75, 0.74, and 0.87, respectively.[106-108]

Table 6: Cancer protective potential of nuts, oilseeds, and tea

Functional compounds	Cancer type	Mechanisms	Clinical evidence	
			Study design	Findings
Nuts and oilseeds				
Hydroxybenzoic acid, flavones, flavanols, hydroxycinnamic acid; flavonols, catechins, flavanones, stilbenes, anthocyanins, isoflavones, lignans, ellagic acid,	Prostate	Alters the levels of inflammatory markers, including C-reactive protein, ILs, TNF-α, and cell adhesion molecules Contributes to antioxidant activity	Systematic review and dose-dependent meta-analysis	Consumption of nuts was not associated with prostate cancer risk.[109-110]
			Meta-analyses of 8 CS and 5 CCS	Daily nut consumption of 28g may offer a protective effect, lowering colorectal cancer risk by 33%.[111]
	Colon	Reduce DNA damage via down-regulation of inflammation gene expression		

Phytosterols, SITO phyto-stanols, STIG, phytostanol, ATA, ERGO, CAMP.		Decrease PG E2 production, IL-6 and IL-8 release, and COX - 2 expression		
		Tea		
Polyphenols, EGCG, epicatechin, epigallocatechin, gallocatechin gallate, epigallo -catechin	Colorectal	Polyphenols modulate multiple signaling pathways involved in cancer cell proliferation and apoptosis, including the MAPK, PI3K/Akt, Wnt/β-catenin, and 67 kDa laminin receptor pathways Inhibit new blood vessel formation (angiogenesis)	Meta-analysis of 14 studies	Tea was associated with a 24% reduction in colon cancer risk; however, considerable heterogeneity was observed, with estimates ranging from a 51% decrease to an 18% increase, suggesting the influence of population and regional differences. [112]

Table 7: Phytochemical Bioavailability: Challenges, Mechanisms, and Enhancement Strategies

Phytochemicals		**Challenges faced in bioavailability**	**Strategies to enhance the bioavailability of phytochemicals**
Flavonoids	Quercetin, Kaempferol, Naringenin, Catechins	Glycosylation slows absorption, competition for intestinal transporters, and rapid excretion. [117]	Enzyme-based hydrolysis (to convert glycosides to aglycones), co-administration with inhibitors of efflux transporters, and nanoformula -tions.[118]
Phytosterols	β-Sitosterol, Campesterol, Stigmasterol	Phytosterols are highly hydrophobic, limiting their solubility in aqueous environ -ments, leading to poor gastrointestinal absorption. Phytosterols are prone to oxidation, and their effect is reduced. [119]	Use of lipid-based delivery systems such as emulsions, micelles, or nanoencapsulation to improve solubility and enhance bioavailability. Use of microencapsulation techniques, like spray drying, to protect against oxidation.[120]
Polyphenols	Curcumin, Resveratrol, Quercetin, EGCG, and Anthocyanins	Poor water solubility, chemical instability in gastric pH, rapid metabolism (glucuronidation and sulfation), and low intestinal absorption. [121]	Nano emulsions, liposomal encapsulation, polymeric nanoparticles, and co-administration with bioavailability enhancers.[122]
Stilbenes	Resveratrol, Pterostilbene	Low aqueous solubility, leading to poor gastrointestinal absorption and bioavailability.	Use lipid-based formulations such as nano emulsions, liposomes, or solid lipid nanoparticles to improve solubility

		Rapid oxidation and photode -gradation reduce the stability of stilbenes, limiting their effectiveness.[123]	and bioavailability. Encapsulation techniques can be used to prevent oxidation.[124]
Carotenoids	β-Carotene, Lycopene, Lutein	Poor water solubility, degradation in heat and light, and reduced absorption due to binding with fiber.[125]	Lipid-based delivery systems, microencapsulation, and dietary co-administration with fats.[126]

Discussion

Cancer remains one of the most challenging NCDs to treat due to its complex pathophysiology, heterogeneity, and ability to develop resistance to conventional therapies. Chemotherapy is associated with severe side effects, including systemic toxicity and damage to non-cancerous cells. In this context, incorporating naturally derived bioactive compounds into cancer treatment regimens has emerged as a highly promising strategy. The integration of phytochemicals with conventional chemotherapeutic agents has garnered significant attention in recent years.

This review provides an in-depth over view of the role of specific phytochemicals, particularly flavonoids, phenolic acids, phytosterols, stilbenes, and carotenoids in preventing and treating cancer. These non-nutritive compounds found in whole grains, fruits, vegetables, and leaf extracts exhibit antioxidant, anti-inflammatory, and anticancer effects. Their anticarcinogenic effects are mainly mediated through the modulation of critical intracellular signaling pathways involved in cancer pathophysiology. Key signaling cascades influenced by these non-nutritive compounds include the PI3K/Akt/mTOR pathway, which controls cell growth, survival, and metabolism; the NF-κB signaling pathway, central to inflammation and immune response; and the MAPK/ERK pathway, which controls cell proliferation and differentiation. Furthermore, they play an essential role in regulating and maintaining the autophagy-apoptosis balance. Phytochemicals exert a multi-targeted mode of action by interacting with various molecular targets simultaneously, in contrast to conventional chemotherapeutic agents, which exhibit single pathway specificity while destroying cancer cells. The potential of phytochemicals to simultaneously disrupt several signalling cascades improves cancer treatment.

Extensive preclinical studies using *in vitro* and *in vivo* models have demonstrated the anticancer effects of these phytochemicals across a range of cancer types, including breast, colon, prostate, lung, and liver cancers. Moreover, clinical trials and meta-analyses of cohort and prospective studies have provided epidemiological evidence supporting the protective role of diets rich in different phytochemicals. These findings highlight the potential of plant-based diets as adjuncts or alternatives to conventional cancer therapies, emphasizing the significance of dietary interventions in cancer prevention and therapy.

Conclusion

Cancer continues to pose a significant global health burden, necessitating the development of cost-effective, safe, and widely accessible therapeutic strategies. Increasing attention is being directed toward natural products due to their easy accessibility and affordability. Among these natural compounds, phytochemicals have emerged as promising compounds for anticancer drug development. This review offers a comprehensive examination of key phytochemicals, particularly flavonoids, phenolic acids, stilbenes, phytosterols, and carotenoids as anticancer agents. The underlying mechanisms of action, including modulation of critical signaling pathways, apoptosis induction, anti-inflammatory effects, and antioxidative activity, are discussed in detail, supported by evidence from both preclinical studies and human clinical trials.

Clinical trials remain the gold standard for evaluating therapeutic efficacy and safety. While meta-analyses of cohort and prospective studies have highlighted the potential anticancer effects of dietary phytochemicals against various cancer types, several limitations persist. These include variability in the phytochemical content of foods, influenced by factors such as plant variety, cultivation conditions,

processing methods, and challenges related to bioavailability. The latter is particularly critical, as the absorption, metabolism, and systemic availability of phytochemicals can significantly impact their biological efficacy.

Although numerous experimental studies have explored strategies to enhance phytochemical bioavailability, such as nano formulations, co-administration with bioenhancers, and structural modifications, clinical research on the pharmacokinetics, potential nutrient interactions, optimal dosing, and long-term safety of isolated or enriched phytochemicals remains limited. Further well-designed human studies are essential to translate promising laboratory findings into effective, evidence-based interventions for cancer prevention and therapy.

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