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REVIEW ARTICLE

Diet-derived Flavonoids: Bridging Epidemiological Chemoprevention and Preclinical Anti-tumor Mechanisms in Clinical Oncology

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Abstract

Flavonoids are an abundantly consumed group of dietary polyphenols present in fruits, vegetables, teas, herbs and other plant-derived foods composed of a diphenylpropane (C6-C3-C6) ring structure, allowing subclassification into flavonols, flavones, flavan-3-ols, anthocyanins and isoflavones based on substitutions on the heterocyclic C ring. Multiple case-control studies and prospective cohort analyses reveal higher intake of certain flavonoid subgroups associated with reduced risk of various epithelial cancers like lung, breast, pancreatic, oral and liver. *In vitro* studies across diverse human cancer cell lines and *in vivo,* animal models demonstrate anticancer effects of select flavonoids either directly or in synergy with chemotherapy by targeting hallmark capabilities that enable tumours including resisting cell death, sustaining proliferation, inducing angiogenesis, activating invasion and metastasis. The well-explored anticancer mechanisms range from direct antioxidant activity, quenching free radicals and bolstering endogenous defenses; to anti-inflammatory signalling via NF-κB and cytokine modulation; epigenetic alterations by chromatin remodeling; to direct regulation of cell cycle controllers (CDKs, cyclins) and apoptotic mediators (caspases, Bcl-2. Early human trials mostly indicate the safe use of certain flavonoids and subclasses at tested doses however, progression to therapeutic benefit faces challenges like suboptimal systemic availability upon metabolism, unclear metabolite activities and study design limitations regarding delivery methods, combination treatments and clinical priority. In essence, dietary flavonoids exhibit pleiotropic pharmacological strengths against cancer progression warranting expanded translational research and human trials to develop formulations/delivery systems and validate targeted clinical integration, especially alongside chemotherapy regimens.

Keywords: Anticancer Activity, Epidemiological, Flavonoids, Molecular Mechanisms, Translational Research

1. Introduction

Flavonoids are a large group of polyphenolic compounds found ubiquitously in plants. Chemically, flavonoids consist of two aromatic rings linked together by a 3-carbon bridge, forming a common diphenyl propane skeleton[1,2]. Over 9,000 varietals of flavonoids have been identified and categorised into subclasses based on the oxidation state of the central pyran ring. The six major subclasses are flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, and isoflavones. Flavonoids differ in their distribution - some are found in all plant products (e.g. quercetin), while others are specific to particular foods (e.g. flavanones in citrus fruit)[3].

Based on the oxidation state of ring C, flavonoids can be further divided into different subclasses[4] (Figure 1).

- Flavonols: Contain a 3-hydroxyflavone backbone with a ketone group on ring C (e.g. quercetin, kaempferol). They are found in fruits, vegetables, tea, and red wine[5].
- Flavones: Contain an unsubstituted flavone backbone without hydroxylation on ring C (e.g. apigenin, luteolin). Found in parsley, celery, and chamomile tea[6].

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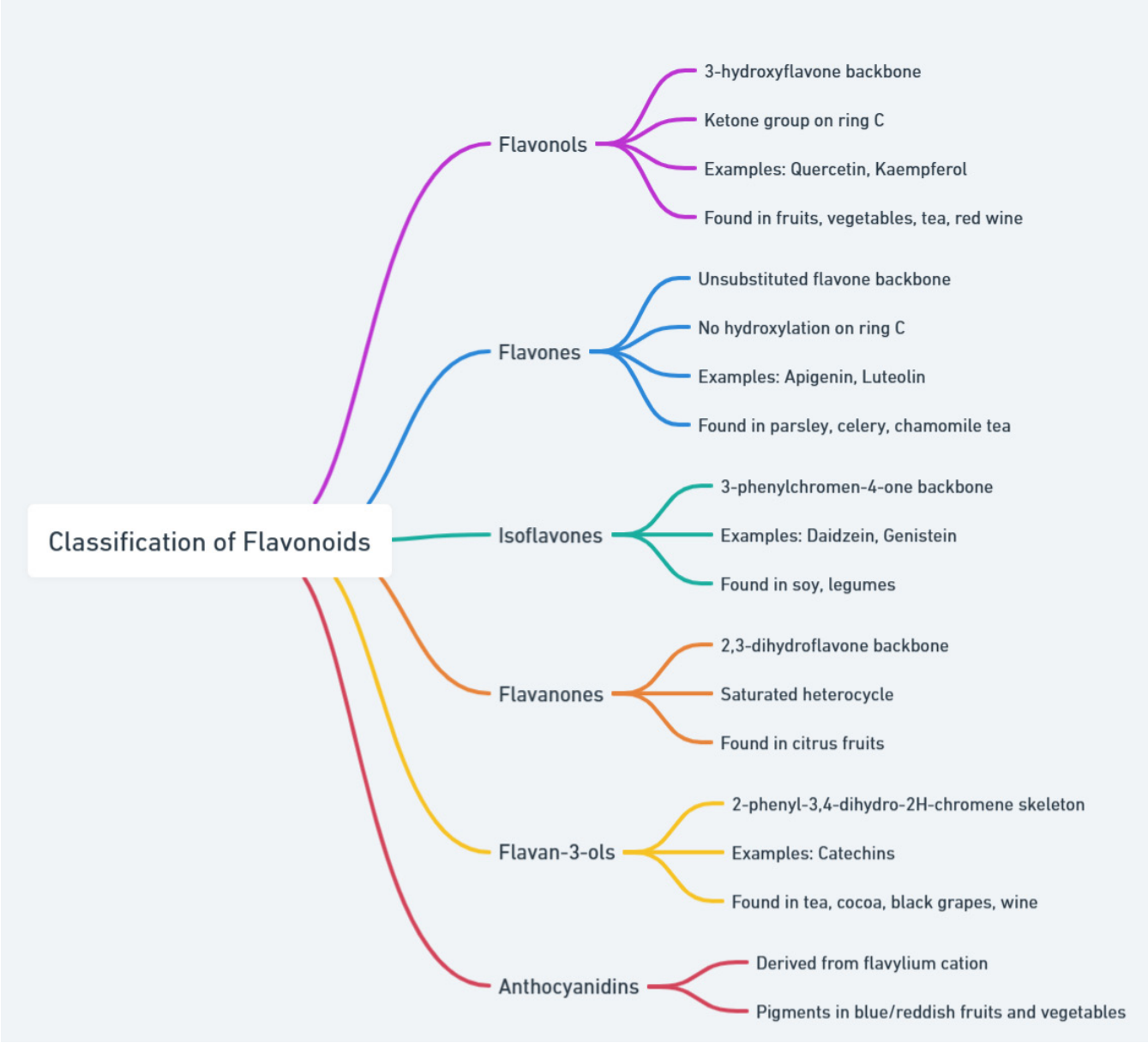

Figure 1. Classification of flavonoids.

- Isoflavones: Contain the 3-phenylchromen-4-one backbone (e.g. daidzein, genistein). Largely found in soy and other legumes[7].
- Flavanones: Contain a 2,3-dihydroflavone backbone with a saturated heterocycle. Found abundantly in citrus fruits[8].
- Flavan-3-ols: Have a 2-phenyl-3,4-dihydro-2H-chromene skeleton (e.g. catechins). Found in tea, cocoa, black grapes and wine[9].
- Anthocyanidins: Derived from the flavylium cation and are pigments in blue/ reddish fruits and vegetables[10].

This classification is based on the structural differences in ring C, while substitutions to rings A and B contribute to the diversity among the over 9,000 identified flavonoids. Hydroxylation, methoxylation, prenylation, glycosylation and polymerisation further

add to the structural heterogeneity[11]. For example, the flavonol quercetin, abundantly found in onions, apples and broccoli, contains five hydroxyl groups, whereas kaempferol only has four[12].

Dietary intake studies estimate the average person consumes about 1 gram of mixed flavonoids daily. The richest food sources are fruits, vegetables (especially onions, parsley, broccoli), tea, red wine and cocoa[13]. Herbs, spices, legumes and grains also contribute to intake. Though there is variation between regions and individual diets, flavonoid-rich items are common worldwide. The estimated per capita flavonoid intake in the United States is ~650 mg/day[14].

For centuries, flavonoids have been used in botanical medicines worldwide. The first scientific report on flavonoids was in 1930 when Szent-Gyorgyi isolated citrin from lemon peel[15]. In the 1930s flavones were shown to reduce capillary bleeding. The term 'vitamin P', for permeability vitamin, was introduced - reflecting the vascular protective benefits observed. Since then thousands of studies have evaluated flavonoids, elucidating anti-inflammatory, anti-diabetic, cardio-protective and anti-cancer effects[3]. Due to their abundance in the diet and evidence across epidemiological as well as clinical studies, regulatory agencies have recognized some flavonoids as Generally Recognized as Safe (GRAS). Well-established members include quercetin, catechins and soy isoflavones[16].

The pleiotropic effects of flavonoids on health can be attributed to their molecular mechanisms of action. Being polyphenols, flavonoids exhibit excellent antioxidant capacity intracellularly and *in vitro*[17]. However newer evidence points to their interactions with cell signalling pathways that control inflammation, angiogenesis, cell proliferation, death and differentiation[3]. They modulate pathways by altering transcription factors and binding sites on receptors as well as affect downstream kinases like MAPK[18]. Recent work also reveals their epigenetic effects via chromatin remodelling and access to promoter regions[19].

In conclusion, dietary flavonoids are an intensively studied group of plant polyphenols present in commonly consumed fruits, vegetables and plant-derived foods and beverages. Their health protective effects span anti-inflammatory, anti-diabetic, anti-viral and anti-cancer benefits. This makes understanding their pharmacological mechanisms valuable for nutrition policies and therapeutic development.

2. Flavonoids and Cancer Prevention

Numerous epidemiological research has shown a negative correlation between the consumption of flavonoids found in fruits, vegetables, tea, and other sources and the risk of developing cancer.

Meta-analysis of case-control studies from China showed total flavonoid intake associated with reduced gastric cancer risk. The highest vs lowest analysis showed an odds ratio of 0.50 (95% CI 0.40–0.61). Epigallocatechin gallate from green tea is linked to a 31% decreased risk[20,21].

European Prospective Investigation into Cancer and Nutrition examined total flavonoid subclass intake and liver cancer. The hazard ratio was 0.75 (95% CI 0.62–0.91, Ptrend = 0.004) for hepatocellular carcinoma and 0.51 for flavonol subclass when comparing top vs bottom quintiles[22].

A meta-analysis of 11 cohort studies revealed that breast cancer risk was lower for those in the highest versus the lowest quantile of flavonoid intake. Stratification by menopausal status showed stronger associations in postmenopausal women[23,24].

A meta-analysis by Grosso *et al.* investigating dietary flavonoids for the risk of oral-pharynx and larynx cancers suggested a significant risk reduction. The odds ratio for total flavonoid intake was 0.60 and 0.47 for flavan-3-ol monomers[25].

3. Proposed Mechanisms of Cancer Prevention

Multiple underlying mechanisms have been proposed that mediate the chemoprotective nature of flavonoids based on *in vitro* and animal data.

3.1 Antioxidant Activity

The phenolic structure of flavonoids enables them to act as hydrogen donors, metal ion chelators and free radical scavengers. They augment and interact with endogenous redox networks in cells.

Quercetin displays inhibition against peroxyl radicals, superoxide radicals and hydroxyl radicals. The

ortho-dihydroxy phenolic structure is crucial for this broad scavenging capacity[26].

Myricetin, containing catechol and pyrogallol moieties, effectively inhibits DNA oxidation by Fenton reagents. It demonstrates cytoprotection in tert-butyl hydroperoxide models via free radical trapping[27].

Fisetin increases the activities of glutathione peroxidase, glutathione reductase, catalase, and Nrf2 (Nuclear factor erythroid 2–related factor 2) signalling and suppresses nitric oxide generation in murine B16F10 melanoma cells treated with H_2O_2 oxidative stress inducer. This reveals its role in fortifying cellular antioxidant defences[28,29].

Benefits against DNA damage, lipid peroxidation and mitochondrial dysfunction reveal their ability to modulate cellular oxidative stress that drives carcinogenesis pathways.

3.2 Anti-inflammatory Effects

Inflammation is now recognized as a key enabler of tumour growth, promoting cell proliferation, survival, invasion and angiogenesis.

Myricetin suppresses LPS-induced inflammatory activation in macrophages by downregulation of TNFα, IL-1β, IL-6 and COX2 expression by regulating the NF-κB and MAPK/ERK pathways[30].

Similarly, apigenin inhibited LPS-stimulated TNFα production in murine peritoneal macrophages through suppression of NF-κB transcriptional activation and protein expression[31,32].

In dextran sulfate sodium-induced colitis mice models, oral supplementation of quercetin, apigenin and luteolin demonstrated protective effects by lowering myeloperoxidase activity and preserving antioxidant defences[33,34].

3.3 Modulation of Cell Signalling Pathways

Flavonoids can modulate mutagenic pathways operating in cancer via the regulation of a multitude of enzymes, transcription factors, receptors, cell cycle and death proteins.

Soy isoflavones like genistein suppress protein tyrosine kinases involved in phosphorylation of cell growth factor receptors and thereby regulate signalling pathways that control cell proliferation and differentiation[35].

Silibinin, a flavonoid in milk thistle, down-regulates COX-2, iNOS expression, and associated cytokine signalling by inhibiting the phosphorylation of MAP kinases like p38 and JNK in skin cancer models[36].

Quercetin inhibits the PI3K/Akt cascade by modulating the activation of its upstream regulators like HER2/3 and EGFR. This leads to reduced viability and migration in ovarian and cervical cancer models[37,38].

3.4 Epigenetic Effects

Flavonoids can modify gene expression through their impact on epigenetic processes, including DNA methylation, alterations in histone structure, and the arrangement of nucleosomes.

Green tea polyphenols have been shown to reactivate methylation-silenced tumour suppressor genes like p16INK4a, retinoic acid receptor β (RARβ), O6-methylguanine-DNA methyltransferase (MGMT), human mutL homolog 1 (hMLH1), and glutathione S-transferase pi 1 (GSTP1) in skin, oesophageal, and prostate cancer cells[39].

Apigenin triggers the halt of the cell cycle in human prostate cancer by causing acetylation of histone H3 and H4, which in turn activates the transcription of the p21 and p53 genes[40,41].

3.5 Induction of Apoptosis

Abrogation of apoptotic pathways is a key hallmark of malignant cells.

Silymarin causes the collapse of mitochondrial membrane potential, enhances caspase-3 activity, and downregulates Bcl-2, and Bcl-XL proteins while upregulating Bax expression to drive the intrinsic apoptotic pathway in human prostate, breast and bladder cancer cells[42,43].

Similarly, genistein demonstrates caspase-dependent apoptosis induction in MDA-MB-231 cells by suppressing Bcl-2 and Bcl-xL and activating Bax[44,45].

Fisetin selective cytotoxicity against uveal melanoma cells involves the activation of ROS-dependent mitogen-activated protein kinases triggering the caspase cascade[46–48].

Apigenin reactivates the TRAIL-R2 apoptotic pathway by upregulating death receptor expression in TRAIL-resistant prostate cancer cells[49–52].

Inhibition of angiogenesis and metastasis by interfering with VEGF-stimulated endothelial cell proliferation, migration and proteolytic enzyme activity, flavonoids can inhibit tumour angiogenesis.

Methylated flavonoids like chrysin, tamarixetin, and silibinin show anti-angiogenic properties in rodent models by targeting the VEGF/bFGF-regulated ERK /FAK/MMP pathways. This controls endothelial cell migration, invasion and tube formation[53].

Similarly, naringenin, hesperetin and nomilin among citrus flavonoids have revealed anti-angiogenic effects by downregulating VEGF, hypoxia-inducible factor 1-alpha, CD31, and vimentin expression in treated animals[54–56].

Epigallocatechin gallate competitively inhibits the binding of VEGF165 to the NP1 receptor and disrupts downstream signalling by AKT and ERK1/2 associated with angiogenesis[57,58].

Genistein also demonstrates anti-metastatic potential by downregulating matrix metalloproteinases and upregulating tissue inhibitors of metalloproteinases. Reduced cell motility and invasion are also achieved by modulation of genes like nm-23 and Kai1 that suppress metastasis[59,60].

4. Anti-cancer Effects of Flavonoids

In vitro evidence, multiple *in vitro* studies reveal the potential anti-cancer effects of different flavonoid compounds across various human cancer cell lines:

Quercetin displays anti-proliferative activity in oral (KB, CAL-27), leukaemia (HL60, HEL, K562), gastric, colon, prostate, lung, bladder, ovarian and breast (MCF7, MDA-MB231) cancer cells. It causes cell cycle arrest and apoptosis induction across models[61].

Similarly, apigenin-induced apoptosis and cell cycle arrest in pancreatic (PANC-1), prostate (PC3, 22Rv1), thyroid (BCPAP, TPC-1), cervical (HeLa, C33A) and haematological cancer cells through modulation of Bax/Bcl-2 genes and other proteins governing cell cycle progression[62].

Genistein from soy demonstrated dose-dependent cytotoxic effects in cultures of the prostate (LNCaP, DU145), gastric (MGC-803), pancreatic (MiaPaCa-2), colorectal (HCT116), metastatic brain (F98) and ovarian (SKOV3) cancer cells via regulation of apoptosis, cell growth and invasion related signalling cascades among other pathways[45,63,64].

5. Influence on Cancer Hallmarks

The anti-cancer mechanisms elucidated span across the hallmark capabilities tumour cells acquire:

5.1 Cell Cycle Arrest

Many studies reveal flavonoids like luteolin, quercetin and apigenin can induce cell cycle arrest at G0/G1 or G2/M phase by acting on cyclins, CDKs and their inhibitors like p21 and p27. Targets include Akt, FOXO and p53 pathways. The review discusses mechanisms like suppression of CDK1, CDK2, CDK4, CDK6, cyclin D1 and cyclin E1 expression in prostate, breast, cervical and liver cancer cells treated with various flavonoids. Downregulation of these cell cycle controllers causes arrest at growth phases[65,66].

5.2 Proliferation and Growth Inhibition

Flavonoids suppress proliferation signals via PI3K/ Akt, JAK/STAT, Wnt and MAP kinase pathways. Genistein and EGCG prevent the activation of growth factor receptors like EGFR, ERBB2 and downstream routes. Silibinin causes G1 arrest by hindering hyperphosphorylation of retinoblastoma protein[67].

5.3 Induction of Apoptosis

Quercetin intercalates in DNA strands triggering caspase cascade[68]. Flavanols enhance p53 transcriptional activity and loss of mitochondrial potential to prompt apoptosis via mechanisms including JNK, NF-κBand PI3K/AKT inhibition[69,70]. Isoflavones modulate Bcl-2 proteins, upregulate death receptors signalling like Fas/ FasL[62].

5.4 Synergism with Chemotherapy

Co-administration of certain flavonoids has revealed synergistic activity with conventional chemotherapy drugs:

Silibinin boosts the effectiveness of cisplatin in models of lung and ovarian cancer by altering the signalling pathways that regulate cell growth and programmed cell death[71,72].

Similarly, the combinatorial potential of quercetin has been reported with cisplatin in ovarian, hepatocellular and gastric cancers owing to complementary mechanistic regulation of apoptosis-related proteins, microRNA signalling and reactive oxygen species generation[65].

6. Most Potent Flavonoid Subclasses

Among the subclasses, evidence points to isoflavones, flavonols, and flavan-3-ols as the most potent categories exhibiting anti-cancer benefits (Figure 2).

6.1 Isoflavones

Genistein is among the most extensively studies isoflavones showing activity across diverse cancer cell lines - prostate, bladder, gastric, pancreatic, melanoma etc. Attributed to the inhibition of angiogenesis, metastasis, proliferation and induction of differentiation pathways[63].

6.2 Flavonols

Quercetin has displayed effective and selective cytotoxic effects across vast malignancies – oral, breast, lung, pancreatic, hepatoma, leukaemia etc by targeting growth factor receptors. Myricetin similarly exhibits anticancer benefits[68].

6.3 Flavan-3-ols

Tea catechins like EGCG have revealed tumour inhibitory capacity especially for cancers of the digestive tract like gastric, colon etc. Targets matrix metalloproteinases, mitochondria-mediated apoptosis and VEGF pathways[73,74].

7. Flavonoid Bioavailability and Metabolism

7.1 Absorption, Metabolism and Excretion

Flavonoid absorption primarily takes place in the small intestine, yet the amount that reaches the bloodstream

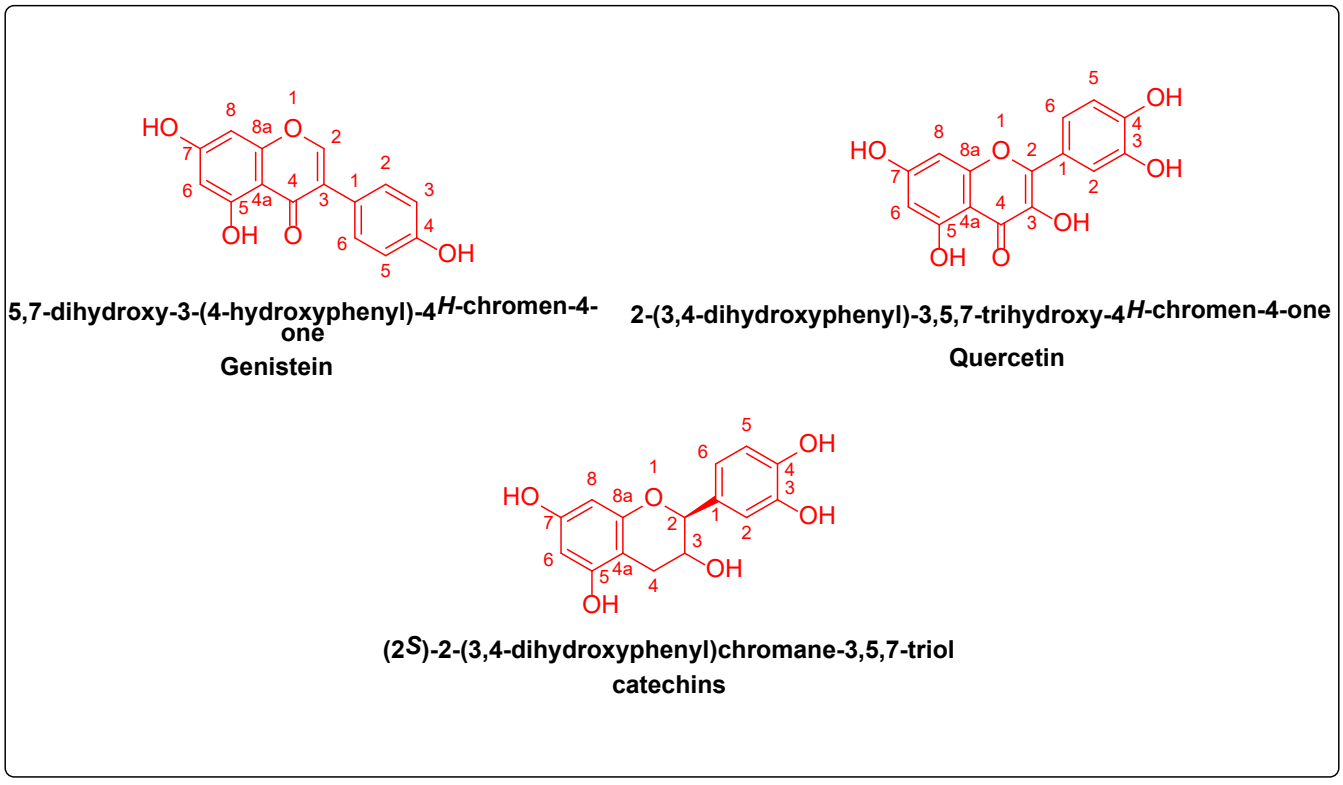

Figure 2. Most potent flavonoids.

and target tissues is affected by their release from food matrices and their stability. Intestinal, and hepatic metabolism further modify structures before secretion back into the intestine or urinary system.

In intestinal absorption, most data suggest passive diffusion of lipophilic flavonoids like isoflavones across the intestinal wall. Structural transformations by lactase phlorizin hydrolase, cytosolic β-glucosidase and membrane-bound β-glucuronidase enzymes aid this permeation. An efflux ABC transporter MRP2 limits their epithelial retention. Circulating metabolites then undergo hepatic biotransformations[75].

Colonic Metabolism Unabsorbed flavonoids pass into the colon where catabolism by resident microflora releases aglycones that may re-enterhepatic circulation through the portal vein or get eliminated via faecal excretion. Microbial enzymatic activities give rise to various phenolic acids. Faecal microbiome stability and compositions hence govern bioavailability to an extent[76].

Hepatic metabolism and elimination pathways: methylation, glucuronidation and sulfation represent the key hepatic modifications as phase II conjugation reactions to facilitate biliary and urinary secretion: Catechol-o-methyl transferase (COMT) catalyses the O-methylation of dihydroxyl groups on ring scaffolds. UDP-glucuronosyltransferase adds glucuronic acid moieties, especially at positions with a hydroxyl group, like ring C or position 7 on ring A of flavonoids. Sulfotransferases transfer sulfate groups to hydroxyl structures into sulfo-conjugated forms like quercetin-3'-sulfate before urinary elimination[77].

7.2 Factors Affecting Bioavailability

Flavonoid bioavailability exhibits extensive personal variations attributed to:

7.2.1 Dietary Source

Glycosides from onions display nearly 10 times greater bioavailability over other food matrices. Solubilizing effects of a protein-rich meal matrix can also enhance uptake than carbohydrate-rich meals[78].

7.2.2 Supplement-drug Interactions

Synergistic effects on absorption have been noted for quercetin and genistein when co-administered with fruit juice, tea or wine components like ellagic acid and EGCG possibly owing to regulated efflux transport[79,80].

7.2.3 Gut Microbial Community

Intestinal bacteria mediate metabolite production from nonabsorbable forms and hence direct systemic exposure. Prenylated chrysin metabolites are unique to mice harbouring intestinal lactobacilli. Inter-individual variability in microbiome underlies response diversity[81,82].

7.2.4 Gene Polymorphisms

Variations in metabolic or transporter enzymes like COMT, UGT and ABC efflux carriers due to single nucleotide changes alter metabolite ratios and kinetics substantially between subjects[83,84]. Quercetin bioavailability displays a nearly 10-fold range based on such genetic differences[80].

8. Strategies for Enhanced Bioavailability

Emerging approaches targeting the ADME framework to promote circulating flavonoid levels include:

8.1 Synthesis of Analogues

Structural analogues of hesperetin, and naringenin created through methylation, halogenation, and sulfonylation exhibit enhanced metabolic stability and membrane permeation. 4'-Fluoro-naringenin exhibits a tenfold increase in bioavailability compared to the native compound[85,86].

8.2 Advanced Delivery Systems

Lipid-based vesicles, nanoemulsions, and solid dispersions protect the integrity of polyphenols through GI transit while improving mucosal permeation. A quercetin nanoemulsion established nearly 20 times more absorption than unformulated control in rodent PK studies[87–89].

8.3 Modification of Sites Prone to Metabolism

Blocking positions vulnerable to sulfation, glucuronidation can retain potency. Synthetic enrichment of 7-O-glycosides demonstrates resilience

against phase II losses while preserving antiproliferative effects[90].

9. Pharmacokinetics of Flavonoid Subclasses: Absorption and Metabolism Differences

9.1 Flavanones

Glycosylated flavanones have superior systemic levels over aglycones. Hesperetin bioavailability increased 5 fold owing to sugar moieties or rutinosides[91,92].

9.2 Flavonols

Quercetin glucosides get effectively hydrolyzed by LPH and cytosolic β-glucosidase before absorption into circulation mainly as glucuronidated conjugates. About 70% of ingested quercetin enters the blood in metabolized forms[75].

9.3 Isoflavones

Genistein and daidzein show nearly 100% absorption with peak levels at 6-8 hours. However, about 75-85% circulate as glucuronides and sulfoglucuronides while only 5-20% retain active unconjugated structures due to extensive phase II metabolism[93].

9.4 Anthocyanins

Rapid phase II modifications form methylated, glucuronidated and sulfated metabolites although at very low fractions (2-5 %) owing to limited intrinsic absorption. Proanthocyanidins on polymerization are not absorbed at all in native forms[94].

In essence, the position, type and extent of substitutions govern the absorption, transformation and pharmacokinetic profiles of each flavonoid category following oral ingestion.

10. Human Clinical Trials for Flavonoids in Cancer

Both epidemiological observational studies, as well as controlled interventional trials, have been conducted to examine associations of flavonoid intake with cancer outcomes in humans.

Epidemiological Studies Multiple cohort analyses reveal beneficial correlations.

Meta-analysis of 21 population studies found high vs low analysis of total flavonoid consumption associated with significantly reduced risk for lung cancer (RR 0.81; 95% CI 0.75-0.88). The strongest reductions were shown for the flavonol and flavone subclasses[95,96].

Among 53 studies examining carotenoids and flavonoids for pancreatic cancer, higher dietary anthocyanidins, flavan-3-ols, flavones and flavonols displayed risk reductions between 14-22% in dose-response analysis[97,98].

Investigation into breast cancer recurrence among 1900+ survivors indicated >6 servings/week of fruits had a 28% lower likelihood than those with <3 servings/week[99]. A combination of fruit and vegetables, berries, and flavonoids specifically correlated with risk reductions in stratified models adjusting for confounders[100].

However, such retrospective analyses have inherent biases in measurement, reporting and control for confounders that limit causal evidence. Controlled trials help address those limitations.

10.1 Interventional Studies

A double-blind placebo-controlled study of prostate cancer patients with flavonoid supplements (600 mg/d catechins, 100 mg quercetin) revealed improvements in PSA levels, cholesterol profile without toxicity along with better functionality scores, suggesting chemopreventive benefits. Reductions were also seen in markers of inflammation, angiogenesis and apoptosis regulation[101].

Among ovarian cancer patients, 14-day preoperative soy isoflavone supplementation (200 mg/d) indicated modulation of pathways associated with cell cycle regulation, DNA repair, and apoptosis compared to the placebo group in subsequent tumour analysis indicating mechanisms that likely mediate protective actions[102].

Other studies reflect prevention potential - a phase I dose-escalation study in oral premalignant lesions indicated safe use of muscadine grape skin extract containing anthocyanins, and flavonols up to 1400 mg daily without systemic toxicity through 12 weeks while showing some histological improvements on biopsy[103].

10.2 Challenges in Translational Research

However, several challenges remain in translating preclinical knowledge into clinical therapeutic contexts:

Limited bioavailability: Intrinsic low oral absorption limits tissue exposures to exert optimal effects, especially at higher disease burden states in patients vs. preventative preclinical models[104].

Complex metabolism: Flavonoid transformations by various tissue enzymes yield metabolites with unclear functional activities in humans. A better understanding of biologically active structures and routes is essential[105].

Priorities for trials: Systemically delivered phase II/III clinical trials on formulated agents focusing on realistic tissue accumulation, pharmacodynamic biomarkers from preclinical models and clinically recommended combination regimens are lacking but are crucial to determining therapeutic index for high-risk populations[106].

In essence, epidemiological data provides support while clinical studies have largely affirmed the safety of flavonoids at used doses. Advancing efficacy-focused investigation with innovative delivery systems in targeted trials remains vital to unlocking clinical promise and supporting clinical integration for cancer patients.

11. Safety and Side Effects of Flavonoids in Cancer Patients

Flavonoids, a diverse group of polyphenolic compounds found abundantly in various plant-based foods, have garnered significant attention for their potential pharmacological activity in cancer treatment. However, a thorough evaluation of the safety profile is imperative before considering their integration into cancer therapy. This section delves into the existing literature, presenting a meticulous analysis of the safety aspects of flavonoids in cancer patients, including potential side effects and interactions with conventional cancer therapies (Figure 3).

11.1 Safety Profile

Numerous studies have explored the safety of flavonoids in both preclinical and clinical settings. GRAS by regulatory bodies, flavonoids exhibit a favourable safety profile when consumed through dietary sources. However, caution is warranted when considering therapeutic doses in the context of cancer treatment.

11.2 Preclinical Safety Assessments

Preclinical studies have provided valuable insights into the safety of flavonoids. While these compounds demonstrate low toxicity in normal cells, their effects on cancer cells are context-dependent. The diverse mechanisms by which flavonoids exert anticancer effects may also influence normal cellular functions[107]. Rigorous preclinical safety assessments are crucial for understanding potential off-target effects and establishing a therapeutic window.

11.3 Clinical Safety Data

Clinical trials investigating the safety of flavonoids in cancer patients have reported mixed findings. Most trials suggest a good tolerability profile, with minimal adverse effects observed at standard doses[108]. Frequently observed adverse effects encompass digestive issues (such as nausea and diarrhoea) and minor allergic responses. However, the incidence of adverse events varies across studies, emphasizing the need for standardized reporting and larger patient cohorts.

11.4 Possible Adverse Reaction

11.4.1 Gastrointestinal Disturbances

The most frequently reported side effects associated with flavonoid consumption in cancer patients are mild gastrointestinal disturbances. Nausea, abdominal discomfort, and diarrhoea have been reported in a subset of patients, but these effects are generally transient and reversible[109].

11.4.2 Allergic Reactions

While rare, some individuals may experience allergic reactions to specific flavonoids. Skin rashes, itching, and, in severe cases[110], anaphylaxis has been documented. Clinicians should be vigilant in monitoring patients for any signs of allergic responses, especially in those with a history of allergies.

11.4.3 Hepatotoxicity

Limited cases of hepatotoxicity have been reported, prompting the need for careful monitoring of liver

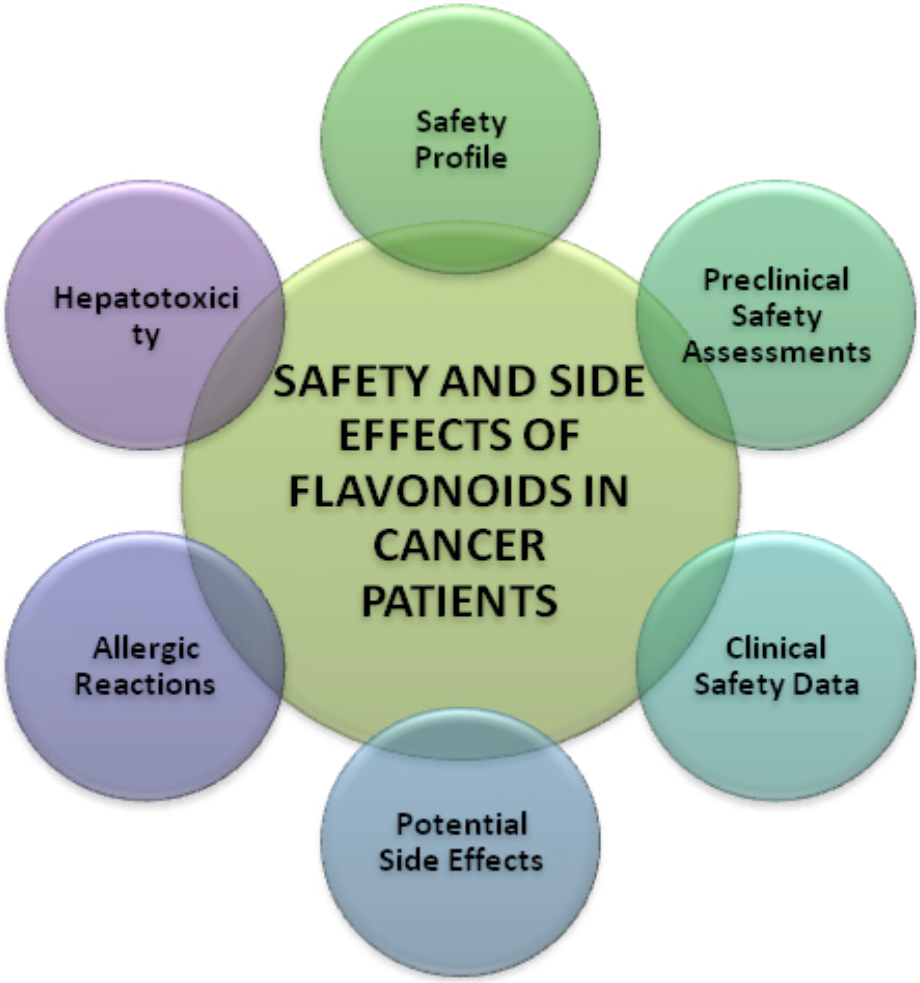

Figure 3. Safety and side effects of flavonoids in cancer patients.

function in patients undergoing flavonoid-based therapies[111]. This is particularly relevant when considering long-term treatment or high-dose regimens.

12. Interactions with Conventional Cancer Therapies

12.1 Chemotherapeutic Agents

Interactions between flavonoids and conventional chemotherapeutic agents are complex and multifaceted. While some studies suggest synergistic effects that enhance the efficacy of chemotherapy, others indicate potential antagonism or interference with drug metabolism. Close monitoring of patients receiving concurrent flavonoid and chemotherapy regimens is essential to assess both therapeutic efficacy and the risk of adverse events[112].

12.2 Antioxidant Effects and Radiation Therapy

Flavonoids are known for their antioxidant properties, which could theoretically interfere with the oxidative stress induced by radiation therapy. Studies exploring this interaction have yielded conflicting results, highlighting the need for further investigation to elucidate the impact of flavonoids on the efficacy of radiation therapy[113].

13. Future Directions and Challenges

As we navigate the evolving landscape of cancer research and therapeutic interventions, the exploration

of flavonoids as potential agents for cancer treatment has unveiled promising avenues. However, a comprehensive understanding of the future directions and acknowledgement of current challenges and limitations is essential for steering this field towards impactful clinical applications (Figure 4).

13.1 Identification of Novel Flavonoids

The vast array of flavonoids in nature offers a rich source for potential therapeutic compounds. Future research should focus on the discovery and isolation of novel flavonoids with enhanced bioavailability, specificity to cancer cells, and potent anticancer activities[114,115].

13.2 Precision Medicine Approaches

The heterogeneity of cancer necessitates a personalized approach. Future studies should investigate the potential of flavonoids in precision medicine, considering individual variations in metabolism, genetic makeup, and the specific molecular characteristics of tumours[116].

13.3 Combination Therapies

Investigating the synergistic effects of flavonoids with conventional cancer therapies holds promise. Combinatorial approaches could enhance therapeutic efficacy, reduce adverse effects, and potentially overcome resistance mechanisms that limit the effectiveness of current treatments[117,118].

13.4 Understanding Mechanisms of Action

Unraveling the intricate molecular mechanisms underlying flavonoid-induced anticancer effects is crucial[11]. Future research should employ advanced technologies, such as single-cell omics,

Figure 4. Future directions in flavonoid research for cancer treatment include.

to elucidate how flavonoids modulate signalling pathways, induce apoptosis, and impact the tumour microenvironment[119].

13.5 Exploration of Nanoformulations

Enhancing the bioavailability and stability of flavonoids through nanoformulations represents a promising avenue[120]. Nanoparticles can improve drug delivery, targeting, and release, potentially overcoming limitations related to flavonoid solubility and degradation[121].

13.6 Evaluation of Long-term Effects

Long-term safety and efficacy data for flavonoids in cancer patients are scarce[122]. Future studies should focus on conducting well-designed, longitudinal trials to assess the sustained effects of flavonoid interventions, ensuring a comprehensive understanding of their impact on cancer progression and patient outcomes[123].

13.7 Integration of Preclinical and Clinical Data

Bridging the gap between preclinical and clinical research is imperative. Future studies should emphasize the translation of preclinical findings into meaningful clinical applications, addressing discrepancies and optimizing study designs to facilitate successful transitions from bench to bedside[124–126].

14. Challenges and Limitations in Flavonoid Research for Cancer Treatment

14.1 Bioavailability Issues

The limited bioavailability of certain flavonoids remains a significant challenge. Factors such as poor

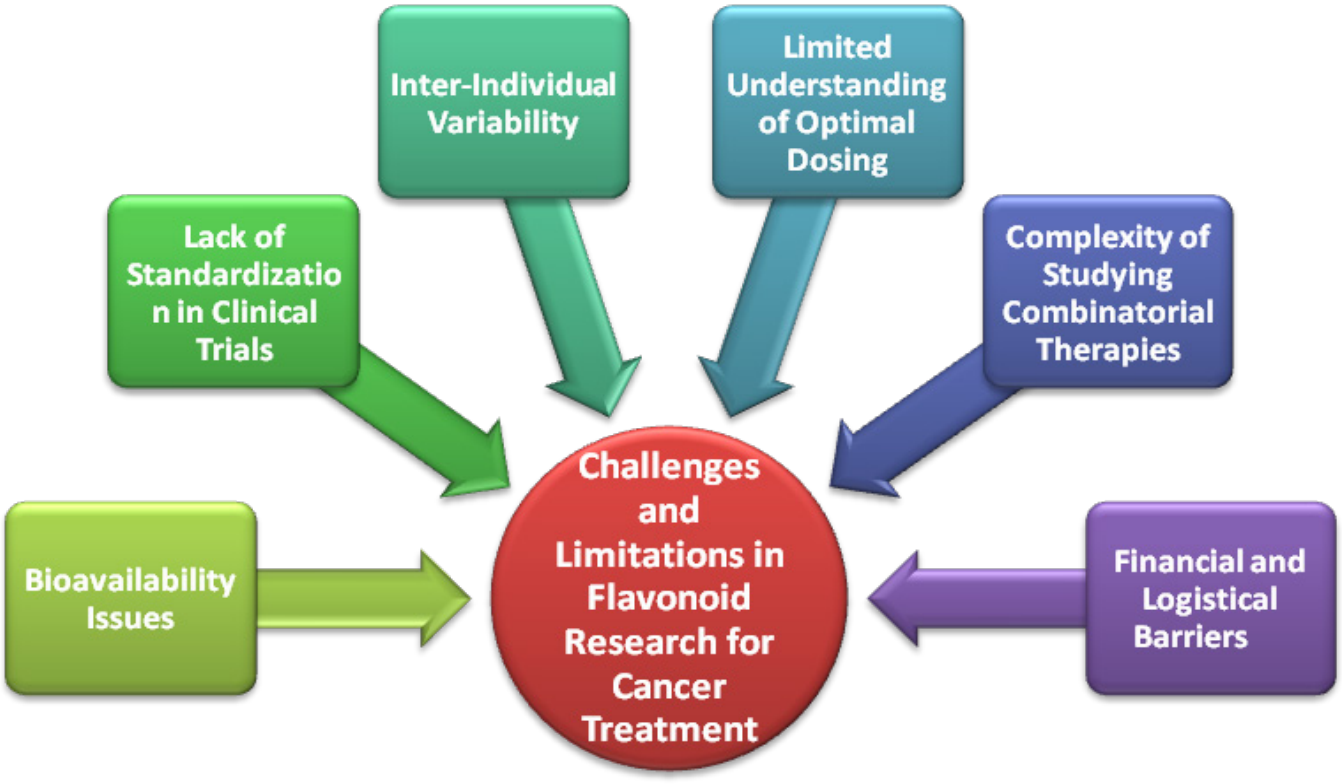

Figure 5. Challenges and limitations of flavonoids research.

absorption, rapid metabolism, and limited distribution to target tissues hinder their therapeutic potential[78,127]. Overcoming these challenges requires innovative drug delivery strategies (Figure 5).

14.2 Lack of Standardization in Clinical Trials

Inconsistencies in the design and reporting of clinical trials hinder the comparison of results across studies[128]. Standardization of protocols, outcome measures, and reporting criteria is essential for generating reliable evidence and drawing meaningful conclusions[129].

14.3 Inter-individual Variability

The response to flavonoid treatment varies among individuals due to genetic, dietary, and lifestyle factors[130,131]. Future research should explore ways to tailor flavonoid interventions to specific patient profiles, considering factors such as gut microbiota composition and genetic polymorphisms[132].

14.4 Limited Understanding of Optimal Dosing

Determining the optimal dosage and duration of flavonoid treatment remains a challenge[133]. Future research should focus on establishing dose-response relationships, considering factors such as patient characteristics, cancer type, and stage[134].

14.5 Complexity of Studying Combinatorial Therapies

Investigating the interactions between flavonoids and conventional cancer therapies presents methodological and logistical challenges[135]. Standardized methodologies and rigorous study designs are needed to assess the safety and efficacy of combination therapies accurately[136].

14.6 Financial and Logistical Barriers

Conducting large-scale clinical trials and research initiatives requires significant financial and logistical resources[137]. Collaborative efforts between academia, industry, and regulatory agencies are essential to overcome these barriers and facilitate robust research endeavours[138].

15. Conclusion

Flavonoids are an abundantly consumed group of dietary polyphenols present in fruits, vegetables, teas, herbs and other plant-derived foods. Composed of a diphenylpropane (C6-C3-C6) ring structure, over 9,000 varietals exist classified as flavonols, flavones, flavan-3-ols, anthocyanins and isoflavones based on substitutions on the heterocyclic C ring. Extensive epidemiological evidence from case-control and prospective cohort studies reveals higher flavonoid subclass intake is associated with reduced risk of various epithelial cancers like lung, breast, pancreatic, oral and liver. Supporting *in vitro* analysis across diverse human cancer cell lines and *in vivo* animal models demonstrates direct and synergistic anticancer effects of certain flavonoids by targeting proliferation, cell cycle, apoptosis, metastasis and angiogenesis pathways. The well-elucidated mechanisms range from antioxidant activity, quenching free radicals and bolstering endogenous defences; to anti-inflammatory signalling via NF-κBand cytokine modulation; epigenetic alterations by chromatin remodelling; to direct regulation of cell cycle controllers (CDKs, cyclins) and apoptotic proteins (caspases, Bcl-2). Synergism with various chemotherapy drugs has been elucidated for enhanced anticancer efficacy. While early human trials mostly indicate safe use and potential chemopreventive efficacy, the realization of therapeutic benefit faces challenges like suboptimal systemic availability upon metabolism, unclear metabolite activities and study design limitations regarding delivery methods, combination treatments and clinical priority. In essence, dietary flavonoids exhibit multifaceted anticancer strengths warranting expanded translational research and human trials to develop formulations/delivery systems and validate targeted clinical integration.

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17. References

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