

Targeting Oxidative Stress and Inflammation in Cancer Prevention: The Emerging Role of Flavonoids

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ABSTRACT

Flavonoids are a large category of natural substances found in many fruits, vegetables, and medicinal plants. They have gained substantial attention due to their possible role in cancer prevention. Increasing evidence suggests that oxidative stress and chronic inflammation are interconnected and contribute to cancer development. These processes can damage DNA, create genetic instability, and support tumor growth. Flavonoids function as potent antioxidants by directly neutralizing damaging reactive oxygen and nitrogen species, enhancing the body's own antioxidant systems, and regulating redox-related cellular signals. Also, they exhibit significant anti-inflammatory properties by affecting key molecules such as NF- κ B, COX, LOX, and iNOS. This action contributes to a reduction in the production of inflammatory substances. Research conducted in laboratories and with animals indicates that flavonoids can inhibit excessive cell growth, induce programmed cell death (apoptosis), obstruct the formation of new blood vessels (angiogenesis), and enhance the efficacy of standard cancer treatments.

Despite the promising findings from laboratory and clinical research, the application of flavonoids as treatments still encounters challenges such as their restricted absorption, rapid degradation in the body, and variability in individual responses. This review discusses their mechanisms of action, what research has revealed, and the possible future of flavonoids as natural antioxidants and anti-inflammatory substances. Also, they have potential significance as beneficial supplements in the prevention and management of cancer.

Keywords- Flavonoids; Cancer prevention; Antioxidant activity; Anti-inflammatory effects; Oxidative stress; NF- κ B; COX; LOX; iNOS; Apoptosis; Angiogenesis; Chemoprevention; Bioavailability challenges; Natural compounds; Plant-derived polyphenols.

I. INTRODUCTION

Cancer develops through a complex series of steps that involve a mix of genetic, epigenetic, and environmental influences, all of which disrupt the natural balance between cell growth and cell death. A key non-genetic factor in this process is oxidative stress, which occurs when reactive oxygen species (ROS) and similar free radicals surpass the body's ability to defend itself with antioxidants [1,2].

Reactive oxygen species (ROS) are produced naturally in our bodies during regular activities such as energy generation by mitochondria, processing by peroxisomes, and through specific enzymes like NADPH oxidases. And they can originate from external factors like radiation, pollution, and various chemicals. When ROS accumulate excessively, they can damage important components of our cells which includes DNA, lipids, and proteins resulting in mutations, lipid peroxidation, abnormal protein aggregation, and ultimately disrupting the cell's balance and function [3].

At the molecular level, oxidative stress-induced damage to DNA can result in alterations to the DNA bases, strand breaks, and issues with repair mechanisms. These important processes can contribute to the onset of cancer. Simultaneously, the continuous generation of reactive oxygen species (ROS) can improperly activate specific signaling pathways such as NF- κ B, MAPK, and PI3K/Akt, which assist cells in surviving, proliferating, forming new blood vessels, and evading programmed cell death [4]. Also, tumors frequently undergo elevated oxidative stress and cancer cells responds by enhancing their antioxidant mechanisms, which includes increasing the production of enzymes such as superoxide dismutase, catalase,

and glutathione peroxidase. They also boost NADPH synthesis via the pentose phosphate pathway and activate redox-sensitive transcription factors like Nrf2, all to survive the challenges posed by reactive oxygen species (ROS) [5].

Getting to know the interplay between ROS production, cellular damage, and the body's defense mechanisms is very important for grasping how antioxidants such as flavonoids could potentially inhibit or delay the initial stages of cancer progression.

1.1. Role of Inflammation in Cancer Progression

Inflammation is a very important factor in the development of cancer as it modifies the tumor environment, enabling cancer cells to survive, proliferate, create new blood vessels, invade adjacent tissues, and metastasize. When inflammation becomes chronic triggered by persistent infections, obesity, exposure to harmful substances, or autoimmune diseases it establishes an environment rich in reactive oxygen and nitrogen species (ROS/RNS), inflammatory signals such as IL-6, TNF- α , and IL-1 β , along with immune cells [6,7]. These components can cause DNA damage, induce genetic instability, and compromise the body's inherent defenses against tumors. When inflammation is detected by the body, specific pathways become activated. Key among these are NF- κ B, STAT3, and MAPK, the primary components that transmit signals from cytokines or internal stress within cells. These signals subsequently activate genes that assist cells in surviving, proliferating, and evading programmed cell death [8].

Inflammation is not a random occurrence; it actively modifies the surrounding tissue by triggering enzymes like matrix metalloproteinases (MMPs), which facilitate invasion. Not only that, but inflammation also promotes the development of new blood vessels through factors such as VEGF, providing tumors with the necessary blood supply for increased growth and making them harder to control. It also contributes to suppressing the immune response: prolonged inflammation typically draws in or produces cells that inhibit immunity, including regulatory T cells, myeloid-derived suppressor cells, and M2 macrophages. These cells diminish the body's capacity to combat the tumor and may even aid in its metastasis [9,10].

1.2. Importance of Natural Compounds in Cancer Prevention

Natural compounds, particularly those derived from plants like flavonoids, are gaining recognition as important factors in cancer prevention. These substances, which can be found in fruits, vegetables, herbs, and whole grains, offer numerous health benefits such as combating oxidative stress, lowering inflammation, and affecting gene expression that may contribute to halting or slowing cancer progression. Research and studies based on population studies, animal research, and laboratory experiments indicate that a higher intake of foods rich in flavonoids is associated with a reduced risk of various cancers, including colorectal, lung, breast, and prostate cancers [11,12].

Natural compounds can help prevent cancer by neutralizing dangerous molecules known as reactive oxygen species (ROS), which diminishes DNA damage caused by oxidation. This decreases the likelihood of mutations and prevents the activation of pathways that promote cancer. Numerous flavonoids also assist in regulating inflammation by reducing specific inflammatory signals such as NF- κ B, COX-2, and cytokines, while enhancing the body's antioxidant defenses [13,14].

Also, natural compounds can contribute to lowering cancer risk by affecting how cells interact and function, they may help inhibit rapid cell division, promote the death of damaged cells, block the formation of new blood vessels that supply tumors, impede cancer's progression, and in some cases, even reverse alterations in gene regulation. Due to these various effects, they are considered promising candidates for cancer prevention, either on their own or in combination with other therapies. But, challenges remain such as ensuring proper absorption in the body, determining the appropriate dosages, verifying their safety, and understanding how laboratory findings relate to actual human cases [15].

II. OVERVIEW OF FLAVONOIDS

2.1. Definition and Classification of Flavonoids

Flavonoids constitute a large group of naturally occurring substances that can be found in various plants. They all possess a similar structure consisting of two aromatic rings, referred to as A and B, which are connected by a three-carbon chain that often forms a ring, known as the C ring [16]. These compounds are synthesized in plants via the phenylpropanoid pathway, which begins with an amino acid called phenylalanine, as well as through the polyketide pathway, which includes molecules like malonyl-CoA [17]. In the plant kingdom, flavonoids typically exist in various forms, sometimes linked to sugars (glycosides), or modified with methyl or acyl groups, or simply as pure aglycones [18].

Flavonoids are primarily categorized based on their structure, such as the presence of double bonds or ketone groups in the C ring, and the positioning of various groups like hydroxyl or methoxyl on the aromatic rings [19]. The major categories include flavones, flavonols, flavanones, flavanols (commonly referred to as flavan-3-ols), anthocyanidins, isoflavones, chalcones, and flavanonols (Table 1). Each category varies according to factors like the saturation of the rings, whether there is a double bond between C2 and C3, the point of attachment of the B-ring, and the types of substitutions found on the rings [20,21].

Table 1: Classification of flavonoids with their structures, dietary sources, & biological activities

Subclass	Structural Features	Common Dietary Sources	Biological Activities	References
Flavones	Characterized by a C2=C3 double bond and a carbonyl group at C4 on the C ring; hydroxyl substitutions on A/B rings	Parsley, celery, chamomile	Anti-inflammatory, anti-proliferative, antioxidant	[22]
Flavonols	Similar to flavones but contain a hydroxyl group at C3	Onions, kale, apples, broccoli	Strong antioxidant activity, metal ion chelation	[23]
Flavanones	Saturated C ring (absence of C2=C3 double bond)	Citrus fruits (oranges, grapefruit)	Anti-inflammatory, vasoprotective	[24]
Flavanols (Catechins)	Saturated C ring, hydroxylation at C3, absence of carbonyl group	Green tea, cocoa, grapes	Potent antioxidant, cardioprotective, chemopreventive	[25]
Anthocyanidins	Possess a cationic flavylium ion core, responsible for red/blue/purple pigmentation	Berries, red cabbage, cherries	Anti-angiogenic, anti-metastatic properties	[26]
Isoflavones	Unique B-ring attachment at C3 position (unlike other flavonoids)	Soybeans, legumes	Phytoestrogenic, protective in hormone-dependent cancers	[27]
Chalcones	Open-chain flavonoids with no heterocyclic C ring	Tomatoes, pears, hops	Anti-inflammatory, antimicrobial effects	[28]
Flavanonols	Similar to flavanones but with hydroxyl group at C3	Milk thistle (silymarin), citrus fruits	Hepatoprotective, antioxidant	[29]

2.2. Dietary Sources of Flavonoids

Flavonoids are present in a wide variety of plant-based foods and beverages, making it easy to incorporate them into a balanced diet. It can primarily be found in fruits like berries, apples, grapes, and citrus varieties, as well as in vegetables such as onions, kale, broccoli, leafy greens, and peppers. Legumes, particularly soybeans and various beans, are also excellent sources. Both green and black teas, along with cocoa, chocolate, and even wine, include flavonoids as well [30,31]. For instance, flavonols such as quercetin and kaempferol are commonly found in onions, apples, tea, garlic, and red wine. In contrast, flavanones like naringin and hesperidin are particularly rich in citrus fruits such as oranges and grapefruits [32, 33].

Anthocyanidins are what provide fruits with their vibrant red, blue, and purple hues, and they are commonly found in berries, cherries, and grapes [34,35]. On the other hand, isoflavones such as genistein and daidzein are particularly prevalent in soybeans, soy products and various legumes [36].

The amount of flavonoids present in foods can differ significantly based on the plant species, its ripeness, and the methods used for processing or cooking. For instance, green tea contains a high concentration of flavan-3-ols, commonly referred to as catechins, which are important for the total flavonoid intake in people's diets [37].

2.3. Bioavailability and Metabolism of Flavonoids

The health advantages of flavonoids rely not only on their functionality in laboratory settings but also on the efficiency with which our bodies can take them in and utilize them. Typically, we ingest flavonoids as glycosides, meaning they are linked to sugar molecules and are not readily absorbable by themselves. Once they reach the small intestine, specific enzymes or gut bacteria convert these glycosides into simpler forms known as aglycones, which our bodies can more easily absorb [38,39]. After absorption, flavonoid aglycones experience extensive processing within our cells and liver. They undergo transformations such as glucuronidation, sulfation, and methylation, which increase their water solubility and facilitate transport. Nonetheless, these modifications often diminish their antioxidant capacity in comparison to the original compound [40].

Numerous flavonoids are rapidly removed from the body via urine and bile. For instance, substances like anthocyanins and catechins are typically eliminated more quickly, whereas metabolites of quercetin tend to linger for a longer time [41]. The gut microbiome is very important in this process it assists in converting non-absorbable forms into metabolites that the body can utilize, as well as generating distinctive bioactive compounds that were not found in the original food [42].

III. FLAVONOIDS AS ANTIOXIDANTS

3.1 Mechanisms of Antioxidant Activity

Flavonoids serve as antioxidants by functioning in various ways that frequently occur simultaneously. They contribute to reducing reactive oxygen and nitrogen species (ROS and RNS) levels, which can be detrimental to our body's molecules. A primary mechanism behind this is known as radical scavenging, during this mechanism phenolic –OH groups, particularly those on the B-ring like 4'-OH or catechol groups, donate hydrogen atoms, either by directly transferring H (through hydrogen atom transfer, HAT) or by sequentially transferring electrons and protons (via single-electron transfer-proton transfer, SET-PT, or sequential proton loss electron transfer, SPLET). This process helps to neutralize free radicals and safeguard cells against damage [43,44].

Flavonoids also function through metal chelation, wherein they attach to transition metals like Fe^{2+} and Cu^{2+} . This inhibits reactions like Fenton or Haber-Weiss that generate harmful hydroxyl radicals [45,46].

3.2. Scavenging of Reactive Oxygen and Nitrogen Species

Flavonoids function as antioxidants by neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby assisting in the prevention of cellular damage that can contribute to cancer development. For example, in studies involving ischemia-reperfusion injury, quercetin has demonstrated its ability to decrease superoxide ($\text{O}_2^{\bullet-}$) levels and maintain the availability of nitric oxide (NO), lessening tissue injury caused by oxidative stress [47]. In experiments with liver cells subjected to inflammatory signals, flavonoids such as quercetin, kaempferol, taxifolin, and apigenin significantly reduced the generation of peroxide, superoxide, and nitric oxide, even when the cells faced oxidative and inflammatory stress [48].

Isoflavones, including biochanin A and coumestrol, are proficient at neutralizing reactive oxygen species (ROS) in human skin cells like fibroblasts and keratinocytes, particularly under stress from hydrogen peroxide. They aid in lowering indicators of lipid peroxidation, shielding the skin from harm [49].

So essentially, this scavenging mechanism occurs when the phenolic hydroxyl groups of flavonoids neutralize free radicals by donating either a hydrogen atom or an electron. This is particularly effective when the B-ring contains ortho- or para-positioned di- or tri-hydroxyl groups, enhancing the efficacy of the process [50,51].

3.3. Modulation of Cellular Antioxidant Enzymes

Flavonoids reinforce cellular antioxidant defenses by two principal ways, first by enhancing the activity of enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase) and second by up-regulating their expression through transcriptional pathways.

Initially, they enhance the function of enzymes that combat free radicals, such as superoxide dismutase, catalase, and glutathione peroxidase and they stimulate the body to produce more of these enzymes by activating specific genes via a pathway known as Nrf2–ARE. Various common dietary flavonoids, including quercetin, apigenin, and kaempferol, facilitate the movement of Nrf2 into the cell nucleus, where it activates the expression of antioxidant genes like HO-1, NQO1, and enzymes that maintain glutathione levels for optimal performance [52,53].

3.4. Evidence from In Vitro and In Vivo Studies

Increasing amounts of research, both in laboratory settings and within living organisms, have found the ability of flavonoids to function as antioxidants and contribute to cancer prevention. In an experiment that looked at various conditions with mice treated with d-galactose, six flavonoids such as epicatechin, epigallocatechin, procyanidin B2, quercetin, taxifolin, and rutin has demonstrated efficacy in neutralizing free radicals like DPPH and ABTS in vitro. When these compounds were administered to live mice, they reduced harmful agents such as serum malondialdehyde (MDA) and nitric oxide, while enhancing the body's overall antioxidant capacity, including activities of SOD, CAT, and glutathione peroxidase [54].

In another instance, a benzene fraction abundant in flavonoids derived from *Selaginella bryopteris* demonstrated protective effects at the cellular level across various studies involving both human and mouse cells. It assisted in preventing DNA fragmentation, maintained the balance of proteins that regulate the cell cycle, and enhanced the function of important antioxidant enzymes within cells. When examined in living organisms, this fraction significantly reduced the likelihood of tumor formation in lung cancer models induced by benzopyrene and delayed the onset of skin tumors in papillomagenesis trials [55].

Also, through in vitro studies of medicinal plants in Nepal it was found that it demonstrated significant antioxidant properties in assays such as DPPH and ABTS, contained a high concentration of flavonoids, and also suppressed the proliferation of specific cancer cell lines including HeLa, Hep3B, and HCT116 [56].

All these in vitro and in vivo studies showed that flavonoids can directly neutralize free radicals in laboratory settings and also aid in preventing oxidative damage, decreasing lipid peroxidation, and combating cancer in living organisms. This shows their potential in cancer prevention.

IV. FLAVONOIDS AS ANTI-INFLAMMATORY AGENTS

4.1 Molecular Mechanisms of Anti-Inflammatory Action

Flavonoids help regulate inflammation by influencing several key molecular pathways involved in the start and progression of cancer. One primary mechanism by which they achieve this is by inhibiting the NF-κB transcription factor: numerous flavonoids prevent the phosphorylation and degradation of IκBα. As a result, NF-κB cannot enter the nucleus and activate genes that encourage inflammation, such as TNF-α, IL-1β, COX-2, and iNOS [57,58,59].

In addition to inhibiting NF-κB, flavonoids also reduce the activity of MAPK pathways such as ERK, JNK, and p38. This leads to decreased phosphorylation of these kinases, resulting in diminished activation of AP-1 and a reduction in the production of inflammatory cytokines [60,61].

Also, flavonoids have the ability to inhibit STAT3 signaling, thereby reducing inflammation triggered by cytokines and diminishing the expression of genes that facilitate cell growth and survival. They affect important sensors and proteins (such as TLR4/MyD88 and TAK1) that initiate inflammatory responses when the body detects threats or within a tumor environment [62].

Certain flavonoids enhance human body's anti-inflammatory defense by stimulating Nrf2. When Nrf2 is activated, it enters the nucleus and triggers the expression of genes such as HO-1 that generate antioxidants and safeguard cells. This mechanism aids in diminishing inflammation induced by reactive oxygen species (ROS) and establishes a natural feedback loop that regulates inflammation and oxidative signals [63,64].

4.2. Regulation of NF-κB and Pro-Inflammatory Cytokines

Flavonoids combats inflammation by disrupting NF-κB signaling, which regulates various genes associated with inflammatory responses. They inhibit the activation of IKK, preventing the degradation of IκBα. As a result, NF-κB is unable to enter the nucleus and activate inflammation-related genes, such as TNF-α, IL-6, COX-2, and Inos [65]. Substances like quercetin, apigenin, and luteolin have demonstrated a reduction in cytokine production induced by LPS in immune cells, primarily through the inhibition of NF-κB. By diminishing these inflammatory signals, flavonoids can lessen chronic inflammation [66].

4.3. Inhibition of COX, LOX, and iNOS Pathways

Flavonoids aid in reducing inflammation by inhibiting key enzymes such as COX, LOX, and iNOS that are involved in the creation of inflammatory agents. Certain flavonoids, including quercetin, apigenin, and luteolin, primarily focus on COX-2, leading to a decrease in prostaglandin E₂ (PGE₂) levels, a substance associated with tumor development and the formation of new blood vessels [67]. Similarly, flavonoids have the ability to inhibit LOX enzymes, leading to a decrease in leukotriene production and a reduction in neutrophil recruitment, ultimately safeguarding tissues from injury during active inflammation [68].

Table 2: Flavonoids targeting COX, LOX, and iNOS pathways. Summary of key flavonoids and their inhibitory effects on major pro-inflammatory enzymes involved in cancer-related inflammation.

Flavonoid	Primary Targets	Effect	References
Quercetin	COX-2, iNOS	↓ PGE ₂ production, ↓ NO levels	[70]
Apigenin	COX-2, LOX	Inhibition of prostaglandins and leukotrienes	[71]
Luteolin	COX-2, iNOS	↓ NF-κB activation, ↓ pro-inflammatory cytokines	[72]
Kaempferol	iNOS	↓ NO production, anti-nitrosative stress	[73]
EGCG (Green Tea Catechin)	COX-2, iNOS	↓ COX-2 expression, ↓ NO release	[74]
Baicalein	5-LOX	↓ Leukotriene B ₄ synthesis	[75]

Flavonoids such as kaempferol and EGCG (epigallocatechin gallate) contribute to reducing inflammation by inhibiting the expression of iNOS. They achieve this by disrupting the NF-κB and MAPK signaling pathways, leading to decreased levels of nitric oxide (NO) and reduced nitrosative stress in inflamed tissues [69]. In summary, by inhibiting the COX, LOX, and iNOS pathways, flavonoids can combat chronic inflammation and mitigate the inflammatory environment that often encourages tumor development.

4.4. Preclinical and Clinical Evidence

In preclinical studies, substances such as quercetin, kaempferol, luteolin, and EGCG have demonstrated significant anti-inflammatory properties. For example, in animal studies involving colitis, administering these flavonoids decreases concentrations of inflammatory substances like TNF-α and IL-6. Also, they inhibit pathways such as NF-κB and the activation of the NLRP3 inflammasome, which aids in alleviating damage observed in colon tissues [76,77,78].

From a clinical standpoint, research and trials indicate that flavonoids could affect inflammatory markers in individuals, although the evidence is not extensive. One review examined flavonoids as possible cancer therapies and observed modest improvements in certain blood cancers, particularly with compounds such as flavopiridol, which generally have quite low side effects [79].

Dietary intake research has shown that increased consumption of flavonoids may be associated with a reduced risk of various cancers, including colon, breast, lung, and prostate, likely due to their anti-inflammatory properties [80,81].

V. FLAVONOIDS IN CANCER PREVENTION

5.1 Role in Initiation, Promotion, and Progression Stages of Cancer

Flavonoids contribute to cancer prevention throughout the three primary stages by interacting with various molecular mechanisms. In the initiation stage, their antioxidant properties help counteract reactive oxygen species and minimize DNA damage resulting from oxidative stress (Figure 1). Also, numerous flavonoids affect enzymes that metabolize toxins; they can suppress some Phase I enzymes while enhancing Phase II detoxifying enzymes, thereby decreasing the likelihood of detrimental DNA alterations that could result in cancer [82,83].

During the promotion phase, flavonoids assist in diminishing persistent inflammation that encourages tumor development and cell growth. They inhibit key signaling molecules such as NF- κ B, AP-1, and MAPKs, while also reducing the concentration of pro-inflammatory cytokines and enzymes like cyclooxygenase and lipoxygenase. This collective effect contributes to hindering the growth of cells that have begun to transform and halts signals that sustain premalignant lesions [84,85].

During tumor progression, flavonoids help slow down cancer growth and spread. They do this by causing cancer cells to stop dividing and to self-destruct. Flavonoids also block new blood vessel formation by reducing VEGF signals and the growth of blood vessel cells. Plus, they prevent cancer from invading other tissues or spreading to distant parts by lowering levels of enzymes like matrix metalloproteinases and interfering with pathways like PI3K/AKT and STAT3. All these effects work together to slow down tumor growth and reduce the chances of metastasis, as seen in many lab studies [86,87].

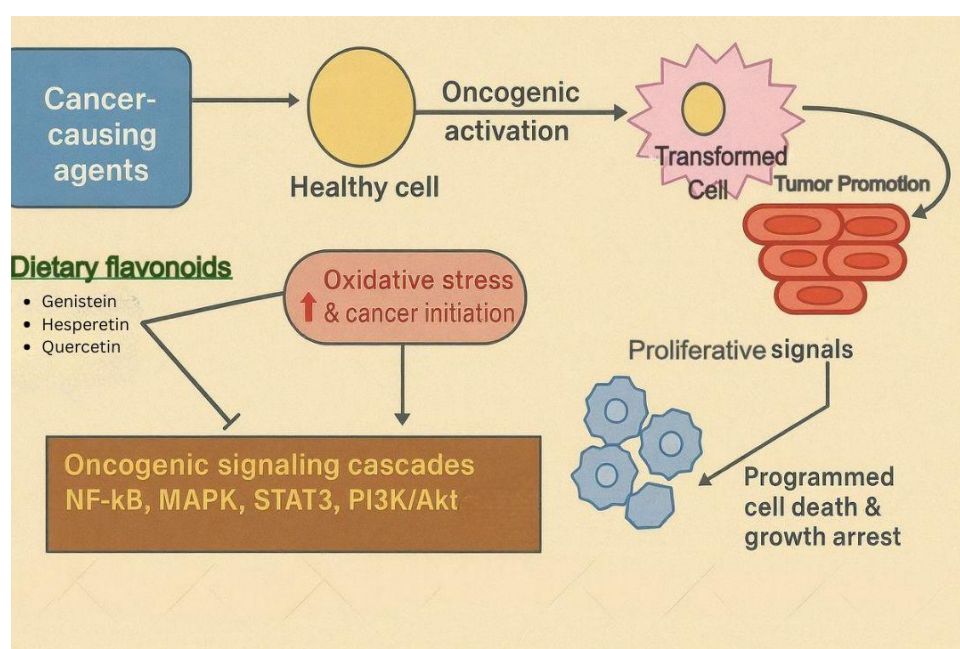


Figure 1: Diagrammatic representation of how dietary flavonoids, including genistein, hesperetin, and quercetin, can impact oxidative stress as well as important cell signaling pathways (such as NF- κ B, MAPK, STAT3, PI3K/Akt) that play a role in the initiation and progression of cancer.

This schematic diagram shows how cancer-causing agents initiate the transformation of normal cells into cancer cells. When individuals are exposed to these agents, healthy cells may undergo changes. If the environment fosters tumor development, these altered cells can eventually progress to cancer. Natural substances found in various foods, such as genistein, hesperetin, and quercetin (known as flavonoids), are represented here as agents that can hinder or diminish the initial stress on cells that could lead to cancer. The diagram also shows how these flavonoids may decelerate cancer-related signals, including pathways such as NF- κ B, MAPK, STAT3, and PI3K/Akt. Consequently, these compounds can assist in

regulating cell growth signals, promote cellular programmed death, and inhibit abnormal growth, all of which can slow cancer progression.

5.2. Modulation of Cell Cycle, Apoptosis, and Angiogenesis

Flavonoids play a significant role in combating cancer. They achieve this by regulating the cell cycle, inducing apoptosis, and inhibiting the formation of new blood vessels (Figure 2). Regarding the cell cycle, compounds such as quercetin, genistein, apigenin, luteolin, and EGCG can halt cancer cells at specific phases, such as G1/S or G2/M. For example, quercetin lowers the levels of cyclin D1 and CDK2 in colon cancer cells, thereby stopping the cells from advancing beyond the G2/M phase [88,89].

Flavonoids can induce apoptosis in cancer cells via both the mitochondrial (intrinsic) and the external (extrinsic) pathways. They enhance the expression of proteins that facilitate cell death, such as Bax and Bad, while also promoting the release of cytochrome c. This mechanism further activates caspases-3, -7, and -9, which are essential components of the apoptosis pathway. Concurrently, flavonoids reduce the amounts of proteins that safeguard cells from dying, including Bcl-2, Bcl-xL, and survivin. Example, compounds like genistein, hesperetin, and quercetin have consistently demonstrated the ability to alter the ratio of Bax to Bcl-2—and to stimulate caspases-9 and -3 resulting in the apoptosis of cancer cells in the breast, colon, stomach, and lung [90].

Angiogenesis is a notable factor in tumor growth and metastasis, flavonoids have the ability to target this process. These compounds inhibit factors such as VEGF, bFGF, HIF-1 α , and MMPs (-2 and -9), while also interfering with crucial signaling pathways, including PI3K/Akt/mTOR, ERK, and NF- κ B in both endothelial and cancer cells. Example, EGCG has been shown to reduce microvessel density (MVD) in breast cancer models, which correlates with lower VEGF levels and diminished HIF-1 α activity [91,92].

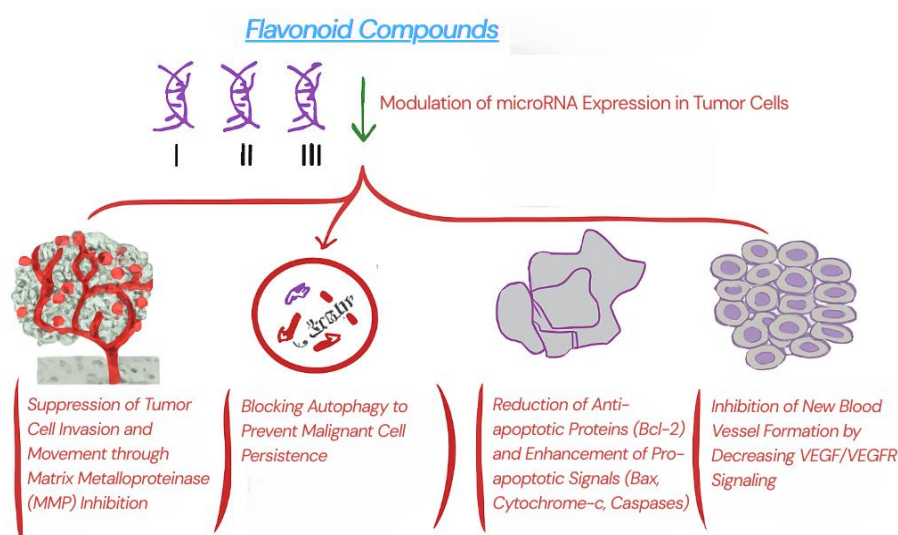


Fig 2 Overview of flavonoid compounds regulating microRNA expression to inhibit tumor progression, promote apoptosis, block autophagy, and suppress angiogenesis.

This schematic diagram shows how flavonoid compounds can aid in cancer prevention and treatment by affecting microRNA levels in tumor cells. The illustration shows that flavonoids can modulate microRNAs, leading to four primary anti-cancer effects: (1) inhibiting the invasion and spread of tumor cells by hindering enzymes known as matrix metalloproteinases (MMPs), (2) blocking the survival of cancer cells via autophagy, (3) reducing levels of proteins that promote cell survival, such as Bcl-2, while promoting cell death pathways associated with Bax, cytochrome-c, and caspases, and (4) inhibiting the formation of new blood vessels by decreasing signals like VEGF and VEGFR that encourage angiogenesis.

5.3. Synergistic Effects with Conventional Therapies

Flavonoids such as EGCG, silibinin, quercetin, chrysin, and formononetin have been found to have the ability to enhance the effectiveness of conventional cancer treatments like chemotherapy and radiation. They contribute to the improved efficacy of these therapies and also aid in preventing resistance. In glioblastoma models, these natural compounds amplify the effects of drugs like temozolomide by affecting processes such as cell death, growth, autophagy, movement, and mechanisms of resistance [93].

In experiments with breast cancer cell lines, the combination of carvacrol and 5-fluorouracil (5-FU) have shown to significantly enhance cell death and lower P-glycoprotein levels compared to using 5-FU by itself. This indicates that flavonoids might improve the effectiveness of chemotherapy by decreasing drug resistance that results from drug efflux [94].

Studies have also shown that flavonoids can enhance the effectiveness of medications like paclitaxel. When used together, they promote apoptosis, decelerate the cell cycle, and diminish survival signals in cancer cells. This combination proves to be more effective in eliminating cancer cells in laboratory tests and animal research compared to using either treatment by itself [95,96].

5.4. Population-Based Studies and Clinical Trials

Numerous extensive observational studies and reviews have shown that individuals who consume a greater quantity of flavonoid-rich foods generally have a decreased likelihood of developing certain cancers, particularly colorectal and some hormone-related cancers. However, the findings may vary based on the specific variety of flavonoid and the demographic group being analyzed [97,98]. When examining more comprehensive population data, increased overall flavonoid consumption is also associated with a lower risk of mortality from all causes and a reduction in deaths due to heart disease. However, the evidence regarding whether a higher intake of flavonoids directly leads to reduced cancer mortality rates is not uniform [99,100].

There is a limited number of randomized clinical trials available. The majority of human research has focused on green tea catechins, such as EGCG, or on green tea extract. One of the research projects examined the impact of green tea extract supplements on mammographic density in postmenopausal women at high risk. The findings were inconclusive, indicating some biological effects but insufficient evidence to definitively establish that it prevents cancer [101,102].

In general, population research found out that specific kinds of flavonoids may offer a protective effect. At the same time, clinical trials reveal that the underlying mechanisms are logical, but the outcomes differ significantly primarily due to variations in dosages, formulations, the parameters being measured, and the duration of follow-up. This highlights the necessity for larger, more rigorously structured randomized trials to gain a clearer understanding of their advantages.

VI. CHALLENGES AND LIMITATIONS

6.1 Issues of Bioavailability and Stability

One of the major challenges in utilizing flavonoids as antioxidants and anti-inflammatory agents for cancer prevention is their low bioavailability. Many dietary flavonoids have poor solubility in water, struggle to pass through intestinal walls, and are rapidly altered by the liver through processes such as glucuronidation and sulfation [103,104]. As a result, only small quantities of the active compounds actually reach the bloodstream. So, converting flavonoids into their permethylated form can prevent these chemical modifications, enhancing their stability in the body and improving intestinal absorption, which can help maintain or even amplify their health benefits [105].

Aside from their limited absorption, flavonoids also tend to be quite unstable under bodily conditions and in various environments. They can easily decompose when subjected to alterations in pH, exposure to light, heat, or enzymes, and they may even be modified by gut bacteria [106, 107]. This instability can result in the loss of their antioxidant capacity, alter their functioning in the body, or create breakdown products that may be less effective or unpredictable. These combined challenges of stability and absorption complicate the translation of encouraging lab findings into real health benefits within the body [108].

6.2. Potential Adverse Effects and Toxicity Concerns

While flavonoids are typically safe when consumed in food, their possible side effects and toxicity present significant challenges when considering their use for cancer prevention. At regular dietary amounts, they are generally harmless, but at higher, drug-like doses, certain flavonoids may lead to issues such as liver damage, kidney problems, and hormonal disruptions [109,110]. Essentially, flavonoids can behave as pro-oxidants, particularly when they come into contact with transition metals or are found in high concentrations within cells. This can result in the creation of reactive oxygen species, which might damage DNA and other cellular components rather than providing protective benefits [111,112].

Flavonoids also have the potential to affect the function of enzymes involved in drug metabolism, such as CYPs and UGTs, as well as drug transporters. This shows that there is a legitimate chance of interactions between drugs and nutrients occurring within the body, which could influence the effectiveness and processing of chemotherapeutic drugs or other medications [113,114]. Initial research into the development of these compounds in laboratory settings and their ability to induce genetic harm has revealed some troubling effects associated with certain flavonoids. This underscores the necessity of rigorously assessing their safety, particularly when consuming high doses or experimenting with new supplement formulations [115,116].

6.3. Standardization and Dosage Challenges

A major obstacle in transforming flavonoids from research studies into effective cancer prevention therapies is the variability in their content and composition across different sources. The flavonoid content in natural plant materials can vary considerably based on factors such as the plant species, cultivation methods, harvest timing, processing techniques, and storage conditions. This variability complicates the comparison of findings from different research and the establishment of consistent dosages. Accurately measuring flavonoids becomes even more challenging due to the limited availability of reliable reference standards for many of these compounds. While some flavonoids, like quercetin, have been extensively researched, numerous others lack authentic standards, which hinders precise measurement [117,118].

When it comes to dosage, flavonoids present a complicated issue. Some research has shown that both insufficient and excessive amounts can diminish their advantages or even lead to negative effects. Determining the optimal and safest dosage is challenging since individuals metabolize these compounds in diverse ways, the processes of absorption, metabolism, and distribution in the body differ from one person to another. To establish clear guidelines, well-structured clinical studies using standardized flavonoid formulations and accurate dosing are very important. This research and studies is needed to be done to understand the safe and effective use of flavonoids [119,120].

VII. FUTURE PERSPECTIVES

7.1 Novel Drug Delivery Approaches for Flavonoids

To utilize flavonoids in cancer prevention development of novel drug delivery systems is done so that we can tackle the issues with solubility, stability, and bioavailability. Researchers are investigating nanoparticle carriers which include solid lipid nanoparticles, polymeric nanoparticles, mesoporous silica, and metal-based nano systems that exhibit significant potential to increase drug efficacy and targeted drug delivery [121]. These minuscule delivery mechanisms can enhance the efficacy of compounds like quercetin, EGCG, and apigenin by facilitating slow release, targeted delivery to cancer cells, and minimizing side effects throughout the body [122,123].

Lipid-based formulations such as liposomes, nano emulsions, and solid lipid nanoparticles are being optimized to better safeguard flavonoids from degradation, enhance their absorption, and amplify their antioxidant and anti-inflammatory effects within the body [124,125]. Also, researchers are investigating ‘smart’ delivery systems that can react to the tumor microenvironment, including variations in pH, levels of reactive oxygen species, or specific receptors to release therapies precisely where needed, while minimizing adverse effects in other areas [126]. Continuous preclinical and translational studies are necessary for transforming these promising approaches into practical treatments.

7.2. Development of Flavonoid-Based Nutraceuticals

Transforming flavonoids into effective supplements depends on addressing challenges such as low solubility, stability, and the body's absorption efficiency. Researchers have been using strategies like phytosomes, inclusion complexes, and nano-encapsulation to enhance the oral bioavailability of compounds such as quercetin and EGCG. Thereby, increasing their biological impact [127,128].

For future development, it is important to emphasize the standardization of dosing, perform comprehensive stability assessments, and create robust clinical trials to demonstrate both safety and preventive advantages. Also, collaborating with regulatory bodies on quality guidelines, claims, and labeling is necessary. Providing formats that are convenient for consumers, such as sustained-release tablets, functional foods, or ready-to-drink products, will aid in making these offerings accessible to a broader audience [129,130].

7.3. Personalized Nutrition and Precision Medicine Applications

Recent research suggests that personalizing flavonoid intake based on a person's genetics, metabolism, and lifestyle might be more effective at preventing cancer than generic dietary advice. Researchers in ‘dietary oncoparmacognosy’ are exploring how bioactive foods like flavonoids can be combined with precision medicine approaches to better predict which individuals and tumor types will respond best [131].

Research on the absorption of flavonoids has revealed significant individual variability. This variability arises from differences in metabolic processes, gut bacteria composition, and genetic factors that influence enzyme functions related to flavonoid processing. It shows the importance of personalized dosing for effective prevention strategies [132].

As we continue to advance in precision medicine, leveraging tools such as genomics, metabolomics, and microbiome assessments, along with computational models, can help in predicting the efficacy of flavonoids, determining optimal dosages, and pinpointing the best food sources for various individuals or populations [133,134].

VIII. CONCLUSION

In conclusion, research and clinical studies have provided compelling evidence that flavonoids may play a role in cancer prevention. These compounds function as antioxidants by neutralizing reactive oxygen species (ROS) and also possess anti-inflammatory properties [135]. They enhance the body's natural defenses by increasing levels of enzymes like heme oxygenase-1, which contributes to combating oxidative stress that can cause damage to DNA and other important molecules [136,137]. This kind of damage is often a important factor in the onset of cancer. Also, flavonoids affect significant inflammatory pathways such as NF- κ B, AP-1, COX-2, and cytokines like IL-6 and TNF- α . By doing so, they help alleviate chronic inflammation, which numerous studies now associate with the initiation, progression, and metastasis of tumors [138,139].

Transforming the potential advantages of flavonoids into tangible clinical benefits is not an easy task. The primary challenges include their bioavailability, the way they are metabolized, and their stability within the body [140]. Also, their effects can differ significantly based on the specific type of flavonoid, the dosage, the particular cells involved, and the timing

of consumption. Moreover, there is a lack of sufficient high-quality clinical trials to assert with confidence their effectiveness in cancer prevention among humans [141,142].

Looking forward to future research should focus on developing standardized formulations of flavonoids, improving delivery methods such as utilizing nanotechnology or glycosylation and identifying their specific molecular targets and responses to varying doses. Long-term epidemiological studies, along with in-depth research, are necessary to transform promising laboratory findings into tangible health benefits for communities. If these obstacles are overcome, flavonoids could play a very important role in both dietary and therapeutic approaches to prevent cancer.

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