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Phenolic compounds and their potential in cancer management

Danik Martirosyan[1,2], Ananni Monet Hayes[1,3], and Nicholas Shen[1,4]

[1]Functional Food Center Inc. 5050 Quorum Drive, Suite 700, Dallas, Texas, 75254, USA; [2]Functional Food Institute, 4659 Texas Street, Unit 15, San Diego, CA, USA; [3]Kent State University, 800 E Summit St, Kent, OH 44240 Kent, Ohio, USA; [4]Santa Clara University, 500 El Camino Real, Santa Clara, 95050 CA, USA

***Corresponding author:** Danik Martirosyan, PhD, Functional Food Institute, 4659 Texas Street, Unit 15, San Diego, CA-92116, USA

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ABSTRACT:

Flavonoids are a diverse group of polyphenolic compounds produced by plants, playing multiple roles in plant defense and human health. In plants, flavonoids mitigate oxidative stress caused by reactive oxygen species (ROS), enhance resilience to abiotic stresses (e.g., drought, salinity, UV), and defend against biotic stresses (e.g., antimicrobial signaling). Food bioactive compounds (FBCs) are found in small doses of flavonoids. FBCs are used to formally identify functional foods and promote health in the human body, as high intake has been shown to decrease the risk of cancer, metabolic syndrome, type II diabetes and other cardiovascular diseases. Phenolic compounds, characterized by one or more hydroxyl groups attached to an aromatic ring, are significant bioactive compounds due to their antioxidant, anti-inflammatory, and neuroprotective properties, making them essential in health-related applications and disease prevention.

Flavonoid phytochemicals such as quercetin, myricetin, and kaempferol exhibit significant therapeutic potential in human health. These phytochemicals have shown the ability to regulate glucose metabolism and immune responses, reduce cancer risk, and manage cancer symptoms.

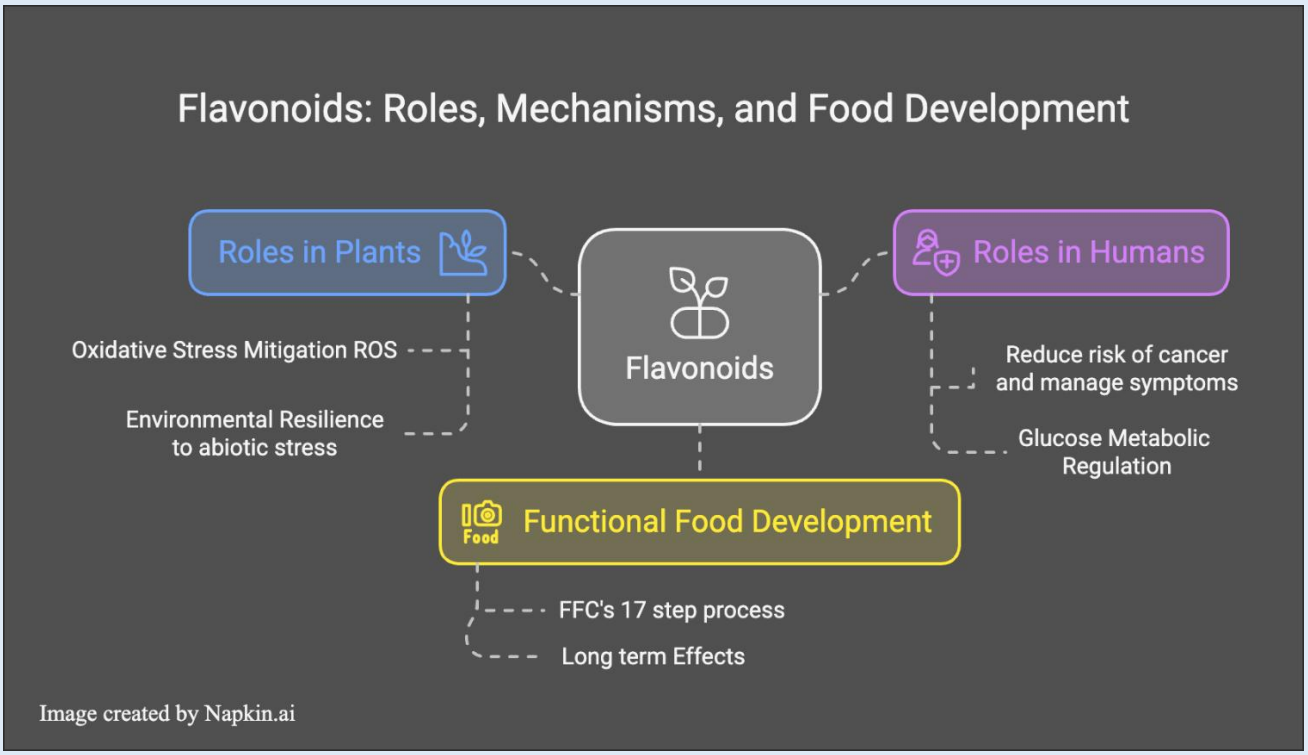
In this review, we will review studies showing the flavonoids' ability to:

- Induce cancer cell apoptosis
- Reduce cell proliferation
- Inhibit cell viability

Biomarkers such as cell proliferation and angiogenesis will be used to track the flavonoids' cancer-preventative metrics for patients in remission.

This review's novelty is its comprehensive evaluation of flavonoids in plant stress resilience and cancer treatment. It identifies key bioactive compounds, biomarkers, and mechanisms of action while applying the **17-step framework** to propose future studies for advancing functional food products.

Keywords: Flavonoids, oxidative stress, anti-cancer, apoptosis, breast cancer, colon cancer, biotic stress, abiotic stress, foods, health benefits



Graphical Abstract (Summary): Flavonoids in Plants, Humans, and Functional Food Development

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Introduction

Flavonoids are phenolic compounds in plants, characterized by benzene rings with one or more hydroxyl groups, and synthesized in response to microbial infections [1]. In plant biology, they serve as compounds that protect plants from environmental stressors and infections. These microbial infections and stressors may be caused by pruning, hail, blowing sand, insects, viruses, or bacteria spread through the natural openings of a plant [2]. Researchers have been conducting more studies on their possible health advantages, recognizing the potential health benefits of these phenolic substances. These studies have identified the hydroxyl groups in flavonoids as the cause of their ability to prevent damage to target biomolecules, which can cause malfunction of cellular processes, mutations in

genetic control, and contributions to disease development [3-5]. Flavonoids do this by neutralizing ROS by donating electrons or hydrogen atoms from their hydroxyl groups, thereby preventing oxidative damage to lipids, proteins, and DNA.

Cancer is a complex disease that can grow uncontrollably and spread to other human body parts [6]. It is one of the leading causes of death globally caused by genetic mutations and other factors like chronic inflammation, poor diet, or exposure to harmful substances [7-8]. While treatments like chemotherapy are common, they often have severe side effects and little effectiveness, leading to interest in flavonoids. They help fight cancer by reducing oxidative stress, which can damage cells and lead to cancer. Some flavonoids in food like tea, soy, and citrus fruits can slow tumor growth, kill cancer cells, and stop cancer cell migration [9-10]. These compounds work especially well in colon, breast, and lung cancers, targeting cancer cells without harming healthy ones [6,23-25,33]. With more research, flavonoids could become an important, natural part of cancer treatment.

This paper aims to review the beneficial roles of flavonoids in plant stress and various cancer treatments, highlighting their significance in protecting human health and plant systems.

Retrieval of Published Studies: A literature review of published studies regarding the role of flavonoids in assisting plants with oxidative stress was conducted electronically using PubMed®, ScienceDirect, and relevant journals from the Functional Food Center's database. These databases were chosen based on the large number of items housed within them which are of relevance to our literature review. A total of 47 review and research articles were included, spanning publications from 2000 to 2024, to reflect two decades of advancements in flavonoid-related research. Articles were selected for their objective, scientific insights on the biochemical mechanisms by which flavonoids mitigate oxidative stress in plants and their potential effects on biotic and abiotic stress tolerance. Inclusion criteria emphasize works demonstrating the pathways and mechanisms by which flavonoids interact with ROS and studies exploring their effects on plant resilience under stress. Articles not available in English and those diverging from the focus on oxidative stress and plant defense were excluded to ensure clarity in the findings presented. Keywords for the search included “flavonoids,” “oxidative stress,” “reactive oxygen species,” “plant defense mechanisms,” “biotic stress,” “abiotic stress,” and “functional foods development.”

Chemistry of Flavonoids: Flavonoids have a fifteen-carbon skeleton with two benzene rings. They can be divided into flavones and flavonols, flavanones, and more [11]. Over 9,000 flavonoids have been classified into seven subgroups depending on the modification of their basic structure [12].

Phenolic compounds are bioactive substances derived from the secondary metabolic pathways of plants, which play a key role in plant defense and offer significant health benefits to humans due to their antioxidant, anti-inflammatory, and anti-cancer properties [13]. Flavones possess the C2’-C3’ double bond and C-ring with a hydroxyl group on the A ring, making them anti-inflammatory agents [14]. Flavonols process a hydroxyl group at position C3’ of the C ring, which enhances its antioxidant effects [10]. Flavanones have a saturated C’ ring, offering anti-inflammatory benefits [12]. Isoflavones contain a C-ring with a B-ring at position 3 and are known for their hormone-balancing effects [15]. Neoflavonoids contain a 4-phenyl coumarin backbone and are rarely found in food plants, but they provide antimicrobial and anti-cancer properties [16]. Lastly, flavanols are the 3-hydroxy derivatives of flavanones, which support cognitive health [17]. The structural diversity of flavonoids contributes to their

wide range of health benefits. Their variations influence their reactivity and bioavailability, critical factors in plant defense mechanisms and their therapeutic potential in humans. The molecular difference can be recognized with the review (Figure 1).

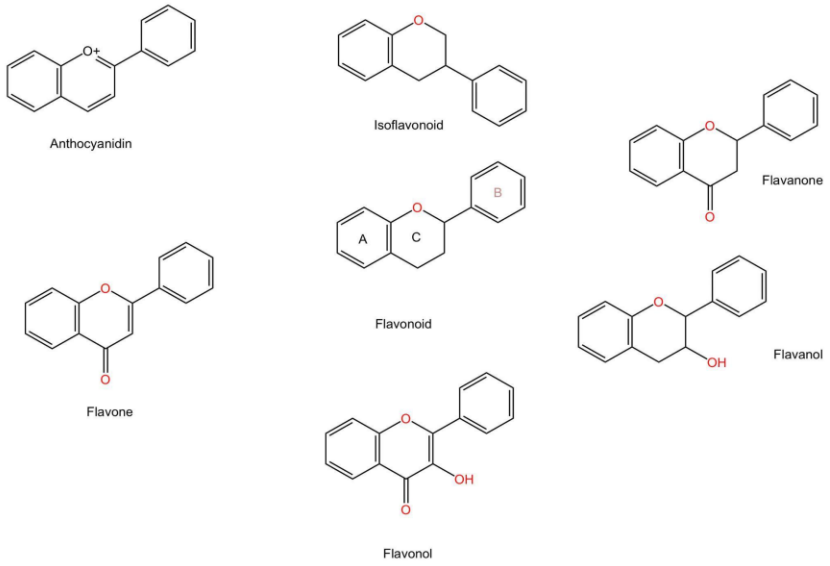

Figure 1. Basic molecular structures of flavonoids and subgroups

Flavonoid Food and Medicinal Herbs: As flavonoids are phytochemicals and cannot be synthesized in plants and humans, the flavonoids found in animals are of plant origin. They are responsible for color, taste, prevention of fat oxidation, and protection of vitamins and enzymes [18]. Some food sources of flavonoids include tea, fruit skins, onion, red pepper, red wine, olive oil, lemons, oranges, soybeans, cherries, strawberries, and more [17]. Each flavonoid subgroup plays a role in certain foods (Table 1).

Table 1. Representation of Flavonoids in Food.

Class	Flavonoids	Food	Study
Flavanols	Catechin, Epicatechin, Epigallocatechin	Tea	[40]
Flavones	Chrysin, Rutin, luteolin, and luteolin glucosides	Buckwheat, red pepper, red wine, fruit skins, celery, parsley, chamomile	[6, 19]
Flavonols	Kaempferol, quercetin, myricetin	Onion, red wine, olive oil, berries, lettuce, apples, grapes	[42, 40]
Flavanone	Naringin, Hesperidin	Citrus Fruits	[6]
Isoflavone	Genistin, daidzin	Soyabean	[6]

Each flavonoid can be represented by the color of the foods eaten. Red, blue, and purple foods contain anthocyanins, which play a significant role in plant defense mechanisms by absorbing harmful UV lights and deterring herbivores and pathogens [20]. Yellow and orange foods contain flavanones, and flavones play a role in modulating signaling pathways and aiding in the production of plants' antimicrobial properties. Finally,

green foods contain flavonols, which act as antioxidants and help regulate plant auxin transport to promote growth [42].

Solubility, the ability of a substance to dissolve in a solvent to form a homogeneous solution, also plays a major role in the therapeutic efficacy of flavonoids [21]. The low solubility of flavonoid aglycones (the non-sugar components left after the sugar portion of a glycoside is removed) in water, along with their limited absorption, prevents humans from experiencing acute toxic effects from flavonoid intake, except in the case of rare allergies [21]. This low solubility can present an issue for medicinal applications, which has resulted in the development of semisynthetic water-soluble flavonoids [19]. Semisynthetic flavonoids are modified versions of naturally occurring flavonoids, designed to address challenges like poor water solubility, low bioavailability, and rapid metabolism. Many different methods are used to create these synthetic flavonoids including sulfation, which shows improved aqueous solubility and better therapeutic outcomes in oxidative stress-related diseases, phosphorylation, which enhances both solubility and stability, allowing for improved delivery in therapeutic applications, and glycosylation, which improves water solubility and intestinal absorption [43].

Flavonoid Anti-Cancer Benefits: Cancer is a health problem that causes abnormal cell growth. It is a global burden and one of the leading causes of death (Table 2). It is a heterogenous disease triggered by impairment of cellular homeostasis [6]. Cellular homeostasis refers to the process in which a cell maintains a stable internal environment despite external changes, including temperature, pH, ion concentrations, and more. This ensures optimal conditions for cellular functions. Flavonoids induce ROS, highly reactive molecules that are regulated by flavonoids to induce apoptosis (cell death) and suppress abnormal cancer cell growth and invasiveness [6].

T**able 2.** Global impact of cancer in 2022.

Cancer site	No. of New Cases	No. of Deaths
Lung	2,480,301	1,817,172
Breast	2,308,897	665,684
Prostate	1,466,680	396,792
Colon	1,926,118	903,859
Stomach	968,350	659,853
Liver	865,269	757,948
Esophagus	510,716	445,129
Thyroid	821,173	47,485

Many flavonoids play a role in reducing the risk of specific cancers and can be used in a holistic approach. The most prevalent cancers in men are lung, liver, and colorectal cancers, and in women, the most prevalent cancers are breast and lung cancer [22]. Flavonoids are known to inhibit cell growth and act as anticancer agents [23]. Each flavonoid can have different anti-cancer effects, as this research is still being tested through preclinical trials.

Anti-Breast Cancer Activity: Many flavonoids play a role in anti-breast cancer activity. Most breast cancer deaths are caused by triple-negative breast cancer (TNBC), which is treated with extremely aggressive and non-target treatment strategies [24-25]. TNBC is a breast cancer that doesn't have HER2 protein (which promotes the growth of cancer cells in other breast cancers), progesterone receptor (another hormone that can influence cancer growth), and estrogen receptors (another hormone that can influence cancer growth). This makes treatment for TNBC a lot harder as they don't

respond to target or hormonal therapies for breast cancer [24]. The treatment for TNBC is rising as the drugs being introduced to the market have unforeseen side effects or only moderate efficacy [25]. TNBC frequently spreads to the lungs, brain, and liver.

Several pre-clinical trials with the TNBC breast cancer cells– MDA-MB-435, MDA-MB-231– and the effect of flavonoids were studied [24-27] (Figure 4). Many flavonoid phytochemicals (luteolin, myricetin, quercetin, hesperetin) showed potential for TNBC treatment by targeting the dysregulated signaling pathways in TNBCs [25]. These signaling pathways are communication pathways that tell cells how to grow and divide. In TNBC, these pathways are often not working properly which can cause cancer cells to grow uncontrollably. By targeting these pathways, flavonoids can stop or slow cancer cell growth [25].

The first procedure included the treatment of luteolin (10 µM and 25 µM) dissolved in dimethyl sulfoxide on MDA-MB-435 and MDA-MB-231 cultures at 37 degrees Celsius [24]. Dimethyl sulfoxide ensures that myricetin can be used in precise concentrations as it is poorly soluble in water. The results showed luteolin inhibited cell migration and viability in breast cancer cells, showing that luteolin has anti-cancer effects by limiting cancer's ability to spread and reducing its survival rate.

The second procedure included the treatment of quercetin (10-50 µM) on MDA-MB-231 TNBC cancer cells incubated at 37 degrees Celsius with 5% CO_2 to mimic the conditions of the human body for 24 hours [28]. Results found that quercetin inhibits the activations of IGF1R, a specific signaling pathway in the breast cancer cell line MDA-MB-231 that is often overactive in cancer [28]. This essentially proves quercetin interferes with a key mechanism that cancer uses to grow and avoid cell death. By shutting down IGF1R, quercetin reduces the ability of these cells to thrive.

The third procedure included myricetin treatment on MDA-MB-468 and MDA-MB-231 breast cancer cell culture with 50 µM myricetin maintained in a 10% CO2 atmosphere at 37 °C to mimic human conditions and incubated for twenty-four hours [26]. Results found that myricetin inhibits cancer cell growth in MDA-MB-231 and MDA-MB-468 cells [26]. Myricetin also exhibited cytotoxicity–the ability of a substance to kill or damage cells– in these cells, proving the flavonoid has the potential to be applied therapeutically to limit cancer cell growth [26].

These procedures studied the effects of flavonoids—luteolin, quercetin, and myricetin—on breast cancer cells and their anti-cancer properties (Table 3). Many other flavonoids also show anti-breast cancer effects and prove that new effective therapies can be developed to target the subset of disease developed. Many new developments have been made against the primary breast tumor, yet the major deaths come from TNBC.

Table 3. The anti-cancer effects of flavonoids on breast cancer cultures.

Flavonoid	*In Vitro*	Dosage	Results	Study
Luteolin	MDA-MB-231 and MDA-MB-468 TNBC cells treated at 37 degrees C incubated for 24 hours	10 µM and 25 µM	Lutenol inhibits cell migration for TNBC cells, slowing the cancer from moving to other parts of the body	Cook et al., 2016 [24]
Myricetin	MDA-MB-231 and MDA-MB-468 TNBC cells treated at 37 degrees C and 10% CO2 for 24 hours	50 µM	Myricetin inhibits the growth of TNBC cells	Knickle et al., 2018 [26]
Quercetin	MDA-MB-231 cells treated at 37 degrees C with 5% CO2 for 24 hours	10-50 µM	Quercetin suppresses TNBC movement by blocking cell glycolysis, stopping tumor cell migration to other areas of the body	Chen et al., 2021 [28]

To test the effect of flavonoids in real-world settings, a study was conducted on 572 female patients who underwent breast cancer surgery at Hanyang University Seoul Hospital [29]. Each factor of the patient–tumor size, weight, age, alcohol drinking, energy intake, etc– was taken into consideration. A trained dietician collected the patients' dietary data after a 24-hour recall period [29]. The foods consumed by the patients included green tea, castor aralia, red lettuce, butterbur, kale, mustard, onion, and seasoned cabbage, and flavone-rich foods included pepper leaf, mung bean, shepherd's purse, Chinese cabbage, green pepper, red pepper, red lettuce, and celery [29]. To assess the variables, the Kolmogorov-Smirnov test was implemented [29]. This test is a statistical test used to compare two distributions. It measures the maximum difference between the sample's empirical distribution function (distribution of the sample data) and the cumulative distribution function (the distribution being tested against).

Table 4. Flavonoid intake based on BMI and its association with cancer recurrence risk

Nutrient/Food Type	Dosage	With Recurrence (n=66)	Without Recurrence (n=506)	Does BMI Make a Difference?
		Lower BMI (<23)	Higher BMI (≥23)	
Flavonoids (mg/day)	10mg	60.84 ± 34.03	30.62 ± 20.99	Yes (p = 0.002)
Flavonols (mg/day)	10mg	37.97 ± 29.21	18.32 ± 14.07	Yes (p = 0.041)
Quercetin (mg/day)	10mg	26.78 ± 17.99	11.67 ± 13.43	Yes (p = 0.008)
Kaempferol (mg/day)	10mg	8.09 ± 6.83	4.17 ± 3.35	Yes (p = 0.030)
Isorhamnetin (mg/day)	10mg	3.10 ± 3.50	2.48 ± 2.22	No (p = 0.584)
Flavones (mg/day)	10mg	22.24 ± 12.51	12.29 ± 11.33	Yes (p = 0.007)
Apigenin (mg/day)	10mg	9.09 ± 4.50	4.61 ± 3.71	Yes (p = 0.005)
Luteolin (mg/day)	10mg	8.91 ± 6.43	7.68 ± 8.40	Yes (p = 0.020)

The results of this study found overweight and obese patients had a lower intake of flavonoids such as quercetin and kaempferol. They were negatively associated with the risk of cancer recurrence [29]. There was a significant correlation between dietary flavonoids and disease-free survival in overweight and obese patients. This study proved that the dietary intake of flavonoids is negatively associated with cancer recurrence in overweight and obese patients who underwent breast cancer surgery. People with lower BMI tend to consume more flavonoids and those with higher BMI consume fewer, which could increase recurrence risk (Table 4). If a p-value shows a numerical value greater than 0.05, there isn't a significant difference in the research. If a p-value is less than 0.05, there was a significant difference. There were multiple points of difference within the table.

Anti-Colon Cancer Activity: Colon cancer is usually associated with age and lifestyle and is the third and second most common cause of cancer death in men and women, respectively [30]. The study of colon cancer treatment has been widespread, and flavonoids such as myricetin have been proven to have anti-colon cancer

properties. Myricetin is found in berries, vegetables, herbs, and walnuts [30].

The first procedure included treatment of HCT-15 (human colon cancer cells) that were cultured at 37 degrees Celsius and 5% CO_2, which mimics the conditions of the human body [30]. The cultures were treated with myricetin after being dissolved in dimethyl sulfoxide [30]. It dissolves the hydrophobic compounds in myricetin. It was proven that myricetin treatment to HCT-15 human colon cancer cells reduced cell viability and induced apoptotic death after 24-hour incubation [30]. Cell viability is the ability of cells to survive and function.

The second procedure included a quercetin treatment of HCT16 colon cancer cells and COLO 320, the primary colon cancer cell line. These cells were cultured at 37 degrees Celsius. They were treated with 80 µM (micromolar, a unit to express the amount of solute dissolved in a solution) and 120 µM of quercetin dissolved in dimethyl sulfoxide and incubated for 72 hours [31]. The results revealed a lower proliferation potential in the HCT 116 and COLO 320 cancer cells [31]. This means that quercetin effectively kills the cancer cells or stops them from functioning.

The third procedure included the study of the anti-proliferation of kaempferol in HCT116 [32]. The HCT116 cultures were supplemented with 10% hyclone at 37 degrees Celsius at 95% air and 5% CO_2 to imitate the human body conditions [32]. The HCT116 cells were treated with kaempferol at 0.1, 0.3, 1, 3, 10, 30, 100, and 200µM for 24 hours [32]. It was revealed that Kaempferol inhibits the growth of human colon cancer, induces apoptosis, and has strong anti-proliferation effects.

The studies highlight the promising role of flavonoids such as myricetin, quercetin, and kaempferol in treating colon cancer by targeting cancer cell viability, proliferation, and survival. These findings suggest flavonoids possess potent anti-cancer properties (Table 5) and could serve as therapeutic agents against colon cancer.

Table 5. Flavonoid effects on colon cancer cells.

Flavonoid	Dosage	*In Vitro*	Results	Study
Myricetin	5 µM to 100 µM	HCT-15 treated at 37 degrees C and 5% CO2 for 24 hours	Myricetin reduced cell viability in the cancer cells.	Mi Eun et al., 2014 [14]
Kaempferol	0.1, 0.1, 1, 3, 10, 30, 100, and 200µM	HCT116 cultures supplemented at 37 degrees C at 5% CO2 for 24 hours	Kaempferol inhibits growth, induces apoptosis, and has strong anti-proliferation effects against colon cancer.	Wei et al., 2009 [17]
Quercetin	80 and 120µM	HCT116 and COLO 320 treated for 72 hours	Quercetin lowered proliferation in HCT 116 and COLO 320 cells	Meenu et al., 2023 [31]

A randomized, double-blind, placebo-controlled, phase II presurgical trial in patients with colon cancer was observed [33]. The patients were between 18 and 85, had at least one benign tumor in the colorectal tract that was at least 1 cm, and were given anthocyanin plus curcumin for 4-6 weeks [33]. Patients took 500mg of Meriva (curcumin) and 500 mg of Mitroselect (anthocyanin) daily before breakfast and dinner.

Table 6. Anthocyanin and curcumin effect on benign colon tumors.

Biomarker	Dosage	Group	Pre (Median, IQR)	Post (Median, IQR)	% Change	p-value
HOMA-index	500mg Anthocyanin and 500 mg Curcumin	Active	1.52 (1.21–2.45)	1.07 (0.77–1.31)	-28%	0
	Matching Placebo	Placebo	1.39 (1.03–1.66)	0.66 (0.48–0.97)	-53%	
hs-CRP (mg/dL)	500mg Anthocyanin and 500 mg Curcumin	Active	0.15 (0.10–0.25)	0.20 (0.10–0.60)	0%	1
	Matching Placebo	Placebo	0.10 (0.10–0.10)	0.15 (0.10–0.30)	0	
L/A Ratio	500mg Anthocyanin and 500 mg Curcumin	Active	0.70 (0.35–1.30)	0.40 (0.20–0.70)	-51%	0
	Matching Placebo	Placebo	0.80 (0.40–2.30)	0.30 (0.20–0.90)	-63%	
Adiponectin (µg/mL)	500mg Anthocyanin and 500 mg Curcumin	Active	12.80(7.60–20.80)	9.70 (6.00–18.20)	-12%	1
	Matching Placebo	Placebo	12.60 (7.10–19.20)	13.20 (7.60–20.30)	0	
Leptin (ng/mL)	500mg Anthocyanin and 500 mg Curcumin	Active	8.30 (3.75–11.00)	2.90 (1.30–7.20)	-65%	0.91
	Matching Placebo	Placebo	11.00 (5.00–22.00)	4.05 (2.00–16.20)	-51%	
IGFBP-3 (ng/mL)	500mg Anthocyanin and 500 mg Curcumin	Active	3262.15 (2680.80–3706.15)	3227.50 (2678.70–3545.30)	-6%	0.91
	Matching Placebo	Placebo	3150.80 (2402.80–3546.20)	2891.25 (2698.90–3731.90)	-6%	
IGF-1 (ng/mL)	500mg Anthocyanin and 500 mg Curcumin	Active	112.65 (96.95–146.15)	110.20 (79.30–137.90)	-12%	0.92
	Matching Placebo	Placebo	109.69 (79.70–124.50)	98.85 (73.70–140.70)	-10%	
25OHD (ng/mL)	500mg Anthocyanin and 500 mg Curcumin	Active	16.80 (7.55–22.35)	15.10 (9.20–22.90)	-10%	0.92
	Matching Placebo	Placebo	15.20 (7.80–17.95)	16.55 (11.00–26.60)	0.09	
IL-10 (pg/mL)	500mg Anthocyanin and 500 mg Curcumin	Active	3.15 (2.70–4.20)	4.10 (2.70–6.20)	0.21	0.29
	Matching Placebo	Placebo	3.20 (2.30–3.70)	3.20 (2.30–3.90)	0%	

The clinical study results found that curcumin and anthocyanin didn't result in the expected changes in the biomarker (Table 6). The baseline measurement before treatment did not have a drastic change post-treatment. Yet, the study revealed that insulin sensitivity and metabolic regulation improved due to the treatments. The IL-10 (an anti-inflammatory) increased by 21%, showing a potential anti-inflammatory effect in the treatment [33]. With more studies and treatment, there can be further progress in flavonoid treatment in cancer for therapeutic relief.

Roles of Flavonoids in Various Plant Stresses

Oxidative Stress: Various abiotic and biotic factors– high light intensity, extreme temperatures, drought, pathogens, and pollutants– can lead to oxidative stress [34]. Oxidative stress is caused due to an excess of excitation energy in the chloroplast [34]. Excitation energy is the minimum energy required to move an electron in an atom or molecule from its ground state to a higher energy level. Excess excitation in the chloroplast, especially under high light conditions, results in the overproduction of reactive oxygen species like superoxide radicals, hydrogen peroxide, and hydroxyl radicals [21]. These molecules can damage vital cellular

components like lipids, proteins, and DNA. The reducing functions of flavonoids are important to plants under severe stress conditions. Flavonoids act as antioxidants that help plants mitigate oxidative stress, and they can neutralize reactive oxygen species before they cause damage [35]. Quercetin and kaempferol effectively protect plant cells from oxidative damage [36].

In addition, flavonoids contribute to regulating the plant's antioxidant defense system. They can regulate antioxidant enzymes to enhance the plant's ability to convert harmful ROS into less reactive molecules like water and oxygen, which reduces oxidative stress [21].

Biotic Stress: When plants are infected with pathogens and pests and suffer from biotic stress (bacteria, viruses, nematodes, fungi, and insects), they need hypersensitive responses (HR). Hypersensitive responses are an element of plant disease resistance through the production of phytoalexins [3]. Phytoalexins form and act against pathogenic bacteria, fungi, and nematodes.

Invasion of Nematodes: Plant parasitic nematodes are harmful to plants. They can destroy the host plant by causing wounds and microbial diseases, which can be indicated through brown spots, galls, spots, cysts, rotting, or swelling formed on the roots [5]. Flavonoids can reduce the yield loss caused by nematodes [4]. For example, phytoalexin glyceollin can significantly reduce the invasion of cyst nematodes [38]. More research needs to be conducted on the defense mechanism of flavonoids against parasitic nematodes.

Abiotic Stress: Abiotic stress can be inflicted on plants by UV stress, cold stress, salt stress, drought stress, and heavy metal stress [34]. Under UV induction, plants can produce flavonoids in their epidermal cells [9]. Compared with low-altitude plants, high-altitude plants are subjected to high UV-B exposure. Genes associated with flavonoid biosynthesis play an important role in plants under excessive light and UV stress as they accumulate photo-protectant flavonoids [11]. These photo-protectant flavonoids absorb harmful solar wavelengths to mitigate oxidative damage to cells or DNA [12]. Cold stresses are common during the process of growth and development [34]. This can affect plant growth from germination to maturity. Under low-temperature conditions, plants can experience changes in photosynthesis, metabolism, and membrane structure [39]. Flavonoids play an important role in coping with cold stress by providing plants with natural defense mechanisms that strongly resist cold stress [40].

Salt stress greatly threatens food production by inhibiting plant growth and development through osmotic stress [41]. The limiting effect of excess salts in the soil on plant growth is mainly osmotic stress and ion toxicity [42]. Flavonoid glycosides play a positive role in enhancing salt tolerance [42].

Drought stress is a major factor affecting plants' biochemical processes [43]. Plants can induce cellular protection against drought stress through flavonoids, including anthocyanins, that help protect plants against excessive sunlight and water loss by reducing stomatal transpiration and density [11].

In recent years, industrialization and the use of pesticides have caused heavy metal contamination in the soil. Heavy metal stress causes the inactivation of enzymes and destroys membrane integrity, altering basic plant reactions such as photosynthesis, respiration, and homeostasis [44]. Heavy metal stress also generates ROS, leading to lipid peroxidation, damaging the plant's biomolecules and destroying DNA strands [33, 45].

Flavonoids and Modern Agricultural Practices: The growing demand for food, unsustainable farming practices, and the use of pesticides and chemicals deplete essential soil nutrients, leading to declining nutritional value in crops and the animals that consume them. As plants struggle to obtain the nutrients they need, the food we rely on becomes less nutritious, contributing to widespread nutrient deficiencies [46].

Additionally, agricultural methods like soil tilling and chemical fertilization significantly reduce the production of vital compounds such as flavonoids. This loss, combined with synthetic farming techniques, not only diminishes the health benefits of modern foods but also weakens their natural flavor, making organically grown foods a healthier and more flavorful alternative [46].

The use of pesticides and unsustainable agricultural practices makes it even harder for humans to consume flavonoids. To make matters worse, flavonoids are considered to have relatively low bioavailability in foods consumed by humans [47]. Therefore, it is vital that more research is done on agricultural practices that increase plant production efficiency without depleting the plants' flavonoid levels.

Evaluation of Phenolic Compounds Role in Cancer: Functional Food Product Creation and Assessment Using FFC's Guidelines: Through robust randomized control trials, the phytochemicals kaempferol, quercetin, and myricetin have demonstrated the ability to treat and prevent cancer. Despite the research being largely done on in vitro cells, the impact of flavonoid treatments all yielded significant results. Therefore, we propose that these flavonoid phytochemicals be considered potential functional food components. The Functional Food Center defines Functional Foods as "natural or processed foods that contain biologically active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [44].

The Functional Food Center's 17-step process, which will be described below, explains how to develop functional food products for the consumer market [44-45]. Steps 1 and 2 require establishing a goal for our functional food and determining a relevant bioactive compound. The phytochemicals found in flavonoids can be used to prevent or even treat cancer; this is a potential goal for the product. Step 3 requires the establishment of an appropriate dosage [44-45]. This review found that dosages for each phytochemical varied from study to study [24-33]. Therefore, more research must be conducted on specific dosages to properly use flavonoids as a functional food ingredient. Step 4 requires an appropriate time of consumption for the bioactive compound. In the previously mentioned studies, supplement administration varied in frequency and time of day. Future research exploring the optimal timing and frequency of supplementation would be beneficial. Step 5 asks for the specific pathways and mechanisms of action regarding the flavonoid's anti-cancer properties [44-45]. The mechanisms of action for the flavonoid intervention of cancer proliferation have already been documented. However, further research and larger sample sizes are needed. Step 6 is the establishment of relevant biomarkers [44]. The research mentioned in this review found that cancer-specific biomarkers were proliferation and angiogenesis markers [14-17]. These measurements were to examine the flavonoid's ability to treat cancerous cells. However, further research into their preventative properties may be necessary. As for step 7, an appropriate food vehicle will be chosen for the bioactive compound. Flavonoids are naturally occurring and have many options for appropriate food vehicles. Step 8 involves conducting preclinical studies to evaluate efficacy and safety, while Step 9 focuses on clinical trials to determine appropriate dosage, timing of consumption, efficacy, and safety [44]. Step 10 requires creating a consumer label to provide information on the most effective consumption methods, including the product's benefits and the appropriate dosage [44].

Step 11 involves publishing research on functional food in peer-reviewed journals, preferably open access, to ensure consumer transparency and provide an educational resource for the public [44]. Following this, step 12 focuses on educating the public about the functional food product, emphasizing the importance of

keeping consumers well-informed [44]. For step 13, information will be sent to the appropriate governmental agencies for approval. Additional requirements for scientific support may vary from country to country. Step 14 involves the development of a functional food product. Once the product reaches the market for consumer use (Step 15), it is classified as a Level C functional food. With additional studies and after-market research, the product may be reclassified as a level B or A functional food based on its demonstrated efficacy and benefits [44].

The Novelty of this work: This article examined the flavonoids in mitigating oxidative stress in plants and their potential therapeutic applications in human health, particularly in cancer prevention and treatment. We have identified biomarkers and mechanisms of action through which flavonoids exert their effects by evaluating various preclinical trials utilizing flavonoids. For flavonoid-containing foods to advance through the process of becoming functional food products, additional clinical trials are necessary, along with the development of consumer labels, approval by a reliable government agency, and the release of these products to the public, followed by epidemiological studies and after-market research. In this article, we evaluated data on the effectiveness of flavonoids in plant and human health by applying the steps for developing functional food products proposed by the Functional Food Center [44-45].

CONCLUSION

Flavonoids, a diverse class of naturally occurring compounds, offer a wide range of benefits to both humans and plants, making them crucial in health, agriculture, and medicine. In humans, flavonoids help combat chronic conditions like diabetes by regulating glucose metabolism and improving insulin sensitivity.

They also exhibit antiviral properties by inhibiting virus replication and strengthening the immune response. For example, against malaria, flavonoids disrupt the life cycle of parasites, showcasing their potential in tropical medicine. In various pre-clinical trials examined in this review, consistent findings were made regarding the role of flavonoids in tumor prevention. Our studies have shown that flavonoid phytochemicals such as kaempferol, quercetin, and myricetin all demonstrate anti-cancer properties. These properties are found in several different pathways leading to or caused by tumors.

While there has been a lot of evidence supporting the efficacy of flavonoids as a cancer treatment, it is important to acknowledge studies that do not show significant outcomes. This implies that more research with larger sample sizes is necessary in this field. It is also important to understand that multiple studies conducted in this review are in vitro. In the realm of cancer research, in vitro studies have many limitations that have real-world implications. For instance, in vitro studies are conducted in controlled environments and cannot replicate a living organism's complexity. This may create issues as factors, such as how the cancer cells interact with their surrounding microenvironment, may be unforeseen in the research. Another limitation is the inability to model systemic effects, meaning the immune system's role in cancer development and treatment is lost in in vitro studies.

Flavonoids have a multifunctional nature that makes them a cornerstone of natural defense and therapeutic strategies. Flavonoids hold the potential to be further developed into powerful tools for fighting diseases like cancer and for improving agricultural resilience, cementing their role as essential compounds in both human health and environmental sustainability. In order to continue furthering our knowledge of flavonoids as a functional food and investigate their effectiveness as a cancer therapy, we must conduct more studies on the direct effect of flavonoids on cancer patients. We must also examine longitudinal studies to

assess their consumption's long-term effects and potential risks. Such research will enable a deeper understanding of the full range of benefits and any limitations associated with flavonoids

List of abbreviations: Central nervous system, CNS; Green tea extracts, GTE; Hypersensitive responses, HR; Central nervous system, CNS; Reactive oxygen species, ROS; Homeostatic Model Assessment, HOMA; High-Sensitivity C-Reactive Protein, hs-CRP; Lupus Anticoagulant Ratio, L/A ratio; Insulin-like growth factor binding protein, IGFBP; Human colorectal carcinoma, HCT; Colon, COLO

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Authors Contribution: The original idea (role of flavonoids in plant oxidative stress and clinical treatment) was conceived by DM and discussed with AH and NS. AH collected data, wrote and edited the manuscript. NS participated in writing and editing the manuscript. DM advised, participating in writing and editing the manuscript. All authors read and approved the final version of the manuscript

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