# "Unlocking The Potential: Dietary Flavonoids As Cytotoxic Agents In Human Cancer Therapy"

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## ABSTRACT

Flavonoids, which are widely present in nature and our food, play a critical role in how our diet can help protect against diseases like cancer. The ability of these polyphenols to fight cancer hang on on variousParameters, such as their concentration, chemical structure with the specific type of cancer involved. Different types of cancer cells react differently to flavonoids, depending on the tissue they originate from. This study focuses on the most commonly consumed dietary flavonoids and their potential effects on various human cancers.

For instance, apigenin, chrysin, and luteolin show promising potential as powerful anti-cancer agents for cervical cancer. When it comes to cancers originating from the liver and colon, where flavonoids are primarily metabolized, there are notable variations in their effectiveness against cancer cells. In the case of gastric cancer, kaempferol emerges as a hopeful candidate, while luteolin shows promise for treating ovarian cancer. These findings shed light on how specific flavonoids in our diets could have significant impacts on different forms of cancer.

**Keywords;** Flavonids,Cancer, Thearpy, Flavonoids Biosynthesis , Anti Cancer activity , Oxidative Stress , Cancer stem call.

**Introduction**

Because of research and prevention efforts, the death rate from cancer has decreased throughout time; nonetheless, the incidence of the disease has increased. A plant-based food has been linked to a minor risk of diseases associated with tumor initiation, according to several studies [1]. Vegetables contain phenolic compounds, carotenoids, and flavonoids, among other bioactive components that may contribute to the health advantages of a plant-based diet. The latter are thought to be essential and are used in a wide range of pharmaceutical, cosmetic, therapeutic, and nutraceutical applications. These uses have led to a significant rise in flavonoid research in the past years.

Flavonoids is partial subgroup of secondary herbal metabolites, originate from a diverse category which is obtained from phenolic compounds produced by plants. They are commonly circulated between photosynthetic organisms having rich in several plant-based diet and beverages (see Table 1). These foods can vary greatly in the types and amounts of flavonoids they contain. The chemical structure of flavonoids consists of di benzene rings fused with each other by a 15-carbon skeleton joined to a heterocyclic pyran ring (labeled as C) as a rings A and B [2]. Flavonoids come in several subclasses, such as chalcones, anthocyanins, flavones, flavonols, flavanones, and flavanonols [3]. The distinguishing features among these subclasses stem from the flavone ring, which forms the core structure of most flavonoids (refer to Figure 1). Differences in the mark of unsaturation with oxidation of carbon ring also contribute by this variety. In plants, the basic form of flavonoids is the aglycone. However, flavonoids can also take on other forms, such as glycosides formed by bonding with carbohydrates like galactose, arabinose, D-glucose, or L-rhamnose.

Additionally, they can exist as CH3ethers or acetyl esters of the -OH group. These various structures contribute to the diversity of flavonoids found in nature. [4].
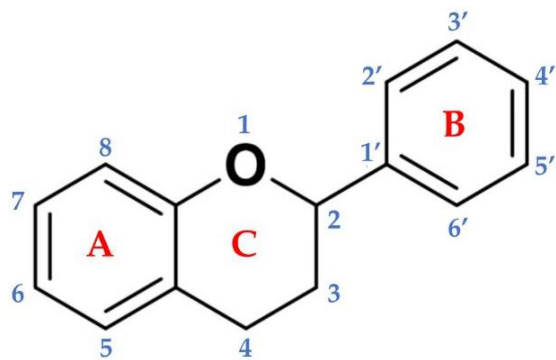


**Figure 1.** Basic backbone of flavonoids. The chemical structure is composed of two benzene rings (**A** and **B**) linked to the heterocyclic pyranic ring (**C**).

| Food Sources | Functions | Food Sources | Functions | Food Sources | |
|---|---|---|---|---|---|
| 3-Deoxyanthocyanidins | Apigeninidin, luteolinidin | 3-Deoxyanthocyanidins | Apigeninidin, luteolinidin | 3-Deoxyanthocyanidins | [5] |
| Sorghum, Purplecorn | Pigmentation, antioxidant | Sorghum, Purplecorn | Pigmentation, antioxidant | Sorghum, Purplecorn | [6] |
| Anthocyanins | Cyanidin-3- O-glucoside, Peonidin-3-O-glucoside | Anthocyanins | Cyanidin-3- O-glucoside, Peonidin-3-O-glucoside | Anthocyanins | [7] |

| Blackberry, Blueberry, Cherry, Strawberry | UV protection, attraction for pollinators and seed dispersers | Blackberry, Blueberry, Cherry, Strawberry | UV protection, attraction for pollinators and seed dispersers | Blackberry, Blueberry, Cherry, Strawberry | [8] |
|---|---|---|---|---|---|
| Flavones | Apigenin, luteolin | Flavones | Apigenin, luteolin | Flavones | [9] |
| Celery, Green peppers, Parsley, Peppermint, Thyme | Natural pesticides in plants, nodulation, UV protection | Celery, Green peppers, Parsley, Peppermint, Thyme | Natural pesticides in plants, nodulation, UV protection | Celery, Green peppers, Parsley, Peppermint, Thyme | [10,11] |

Within the broad class of flavonoids, there are well over 10,000 compounds [12,13]. If we take into account all the metabolites with their conjugates that body produces after ingesting the flavonoids, in addition to the products that are made during food processing and storage, this amount rises significantly. As a result, depending on the source and matrix, flavonoid concentrations, structural complexity, and physicochemical properties can differ significantly [14]. Because of their quantitative and qualitative variety in fruits and vegetables, flavonoids are exceedingly difficult to quantify dietary intake of. This makes it difficult to develop epidemiologic connections about because their effect on people wellness and sickness. Several authors have evaluated the research it's on the absorption and BA wich are available in the data [15–17]. There is some degree of confusion regarding the true conc. of flavonoids' BA and absorption in the body due to a several parameters which can affect their BA, including molecular weights, glycosylation, and esterification [17].

Bacteria and fungi with herbs all use the shikimate path production of aromatic amino acids. This pathway consists of seven steps carried out by enzymes, with chorismite synthase catalyzing the final step to produce chorismate, the pathway's end product by using phosphoenolpyruvate with erythrose-4-phosphate. Chorismate is converted to prephenate by the enzyme chorismate mutase, leading to the synthesis of phenylalanine from prephenate. Which is serves as the precursor for phenylalanine with 4-coumaroyl-CoA after enduring activity by phenylalanine ammonia-lyase (PAL) and 4-coumarate-CoA ligase. This step initiate the production of flavonoids (refer to Figure 2). Studies on enzyme localization suggest that these enzymes are found on the cytosolic part of endoplasmic reticulum are present in the soluble segment of cell extracts.Furthermore, the enzymes in this pathway work together in a connected manner, each step leading tothe next to successful synthesis of aromatic amino acids which is a flavonoids.

Furthermore, the molecules that the gut is unable to absorb will move on to the colon, where colonic bacteria will structurally alter them. Urine is the final excretion of the generated catabolite after being absorbed into the bloodstream. Furthermore, by promoting the populace of good microbes like Bifidobacterium with Lactobacillus having a role of preventing the development of various bacteria, flavonoids can change the contain of the gut microbiota [19]. Flavonoids' capacity to do this offers a crucial anticlastic mechanism.

"Building Blocks of Plant Health: Understanding Flavonoid BiosynthesisPathways"

Genes found in liverworts, mosses, and the earliest terrestrial plants are implemented in the breakdown of flavonoids [20]. Through the investigation of mutants exhibiting a changed synthesis of flavonoids found in different plant species, the biochemical route was defined [21]. Phenylalanine and malonyl-CoA are crucial components needed for creating flavonoids, and they are produced through two main pathways: TCA cycle with its shikimate pathway. In bacteria, fungi, and plants, aromatic amino acids are formed by this pathway. This pathway consists of 7 phases having enzymes like chorismate synthase. It ultimately leads to the production of chorismate, the final product of this process. Chorismate is then transformed into prephenate by chorismate mutase, and prephenate serves as the starting material for synthesizing phenylalanine. [22].

Phenylalanine is the starting material of 4-coumaroyl-CoA in plants produced by 4-coumarate-CoA ligase and phenylalanine ammonia-lyase activity (PAL). 4-coumaroyl-CoA combines with malonyl-CoA to start the synthesis of flavonoids [23] (Figure 2).

Immune localization tests suggest that these enzymes localize to the cytosolic side of the endoplasmic reticulum (ER), and they are retrieved inexcerpts. Moreover, on the surface of the endoplasmic reticulum (ER), enzymes interact with one another through protein–protein interactions to create complexes [21, 24, 25].

Information about certain enzymes' co-localization at the nucleus and tonoplast has hinted at the biosynthetic complex's dynamic behavior. In order to satisfy the physiological requirements of the cells, this would encourage both the channeling and the displacement of the final products [24].

The substances—which include anthocyanins, flavonol, and flavone glycosides—are aimed towards either cell walls or vacuoles as storage organelles [21]. It's worth mentioning that the movement of flavonoids across the tonoplast isn't a one-way street.

This means that plant cells can actually retrieve and reuse flavonoids from their storage in vacuoles, especially when specific physiological conditions call for it. [25]. Apart from cell walls and vacuoles, flavonoids

## Flavonoid biosynthetic pathway
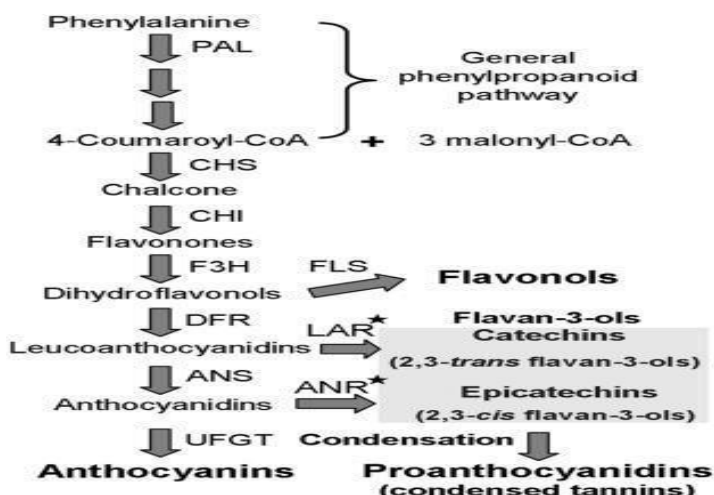


## Application of Flavonoids in Herbs

A strong indicator of flavonoids' important significance in plant physiology is the persistence of genes related to their metabolism throughout terrestrial plant evolution [15]. Flowers' color and scent are attributed to flavonoids, which also play a part in reproductive strategies, shield cells from UV radiation—a radiation that is vital to terrestrial plants—and contribute to disease resistance and symbiotic association, acting as

signal molecules in the symbiotic relationship between plants and microorganisms. They shield the plant from adverse environmental conditions by taking part in stress responses [26–28]. The fact that flavonoids are widely distributed indicates that their antioxidant activity is a strong characteristic essential to terrestrial plants' survival and fitness. Because of their potent antioxidant activity, which has harmful effects of reactive oxygen species (ROS), their synthesis is actually increased after the plant has been subjected to extreme stress [29, 30].

## Flavonoids and Biotechnology

Plant biotechnology is working toward the critical objective of metabolically engineering flavonoids because they have been linked to numerous advantageous agronomic features and health benefits for people [25]. Plants have different levels of flavonoids which lays on the species, growth environment with developmental step. In actuality, farm-grown herbs may not every time be a reliable supplier metabolite, despite the fact that aromatic and medicinal plants are highly effective at creating these compounds. This is because of challenges with plant culture, seasonal fluctuations in productivity, production that is particular to tissues or organs, and issues with cleansing. For these reasons, if field-grown plants were the primary source of raw materials, it would be difficult to maintain the industrial production of polyphenols.

However, due to the stereospecificity and extremely complicated structures of flavonoids, chemical production is frequently not economically viable [31]. To address these challenges, using in vitro methods could be a valuable strategy to increase the production and availability of flavonoids throughout the year. Researchers have turned to a range of plant in vitro cultivation, such as nodule, cell suspension cultivation, cultures of organ, and bushy root cultures, along with alteration methods, to delve deeper into it with progress the synthesis of these significant composites. [31–35]. Numerous strategies have been considered, including the use of elicitors, precursor feeding, and the selection of high-yielding lines [36]. In the latter scenario, substances from either biological or chemical sources are introduced into the culture media. These substances have the capability to trigger the build-up of secondary metabolites in plants. This accumulation turns as a resistance mechanism in reply to tension. [28], which is activated and triggered by pathogen attacks [31–33,36]. Confident outcomes given by this species [37], and from this anglethe defense system of pathogens are taken to study .Furthermore, advancements in the understanding of miRNAs' function in controlling the flavonoid biosynthesis pathway will facilitate modifications to the molecules' metabolism. The synthesis of desirable combinations of metabolites as well as improved yield may be achieved by the manipulation of miRNA levels [38].

## Exploring the Cancer Preventive Properties of Flavonoids

Flavonoids have a wide range of biological activity because its potent anti-inflammatory with antioxidant properties that effectively combat free radicals, an essential mechanism having progressive growth of many long-lasting degenerative diseases (Figure 3). Increases in able radicals under uncontrolled circumstances damage lipids, proteins, and nucleic acids, causing aging and death of cells as well as promoting the development of cancer [39].
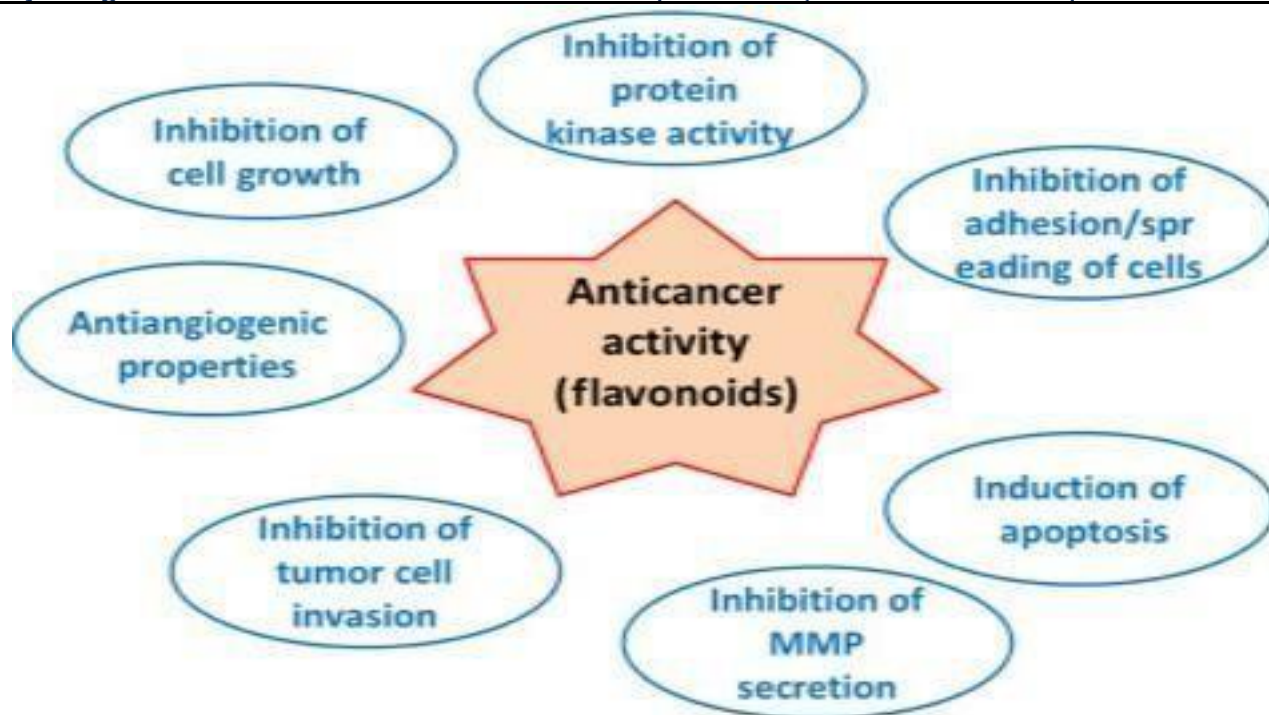
**Figure 2.** Anticancer potential of flavonoids (from [40] with modifications

## *Flavonoids and Their Impact on Oxidative Stress*

Because the antioxidant system in tumour cells is ineffective, the intracellular milieu of these cells contains raised states by reactive oxygen species (ROS) than regular cells, primarily hydrogen peroxide. A sufficient glutathione (GSH/GSSG) ratio in normal cells is what turns hydrogen peroxide into water. A crucial first step towards carcinogenesis is the conversion of hydrogen peroxide to (OH•) radical a highly damages DNA and mu- stations with a tumor suppressor gene when the glutathione ratio falls [60]. There are three steps involve in cancer progress: 1. Start 2. Promotion and 3. Progression. Every stage of this process involves oxidative stress (Figure 4). ROS can cause damage to DNA during the beginning phase by introducing structural changes and gene mutations in the DNA

As a result of changes in genetic factor appearance with intercellular communication, and intracellular signaling paths, ROS play a critical role in either promoting or decreasing cell death during the promotion phase [61]. Lastly, additional mutagenesis in the ongoing cell populace is one way that oxidative stress advances the tumor process [62]. Increasing the existing high concentration by ROS in cancer cells in order to start the apoptotic cascade is the therapeutic aim of many anticancer medications [63]. Despite being known for their antioxidant properties, flavonoids can also operate as pro-oxidants, which can cause cancer cells to undergo apoptosis.
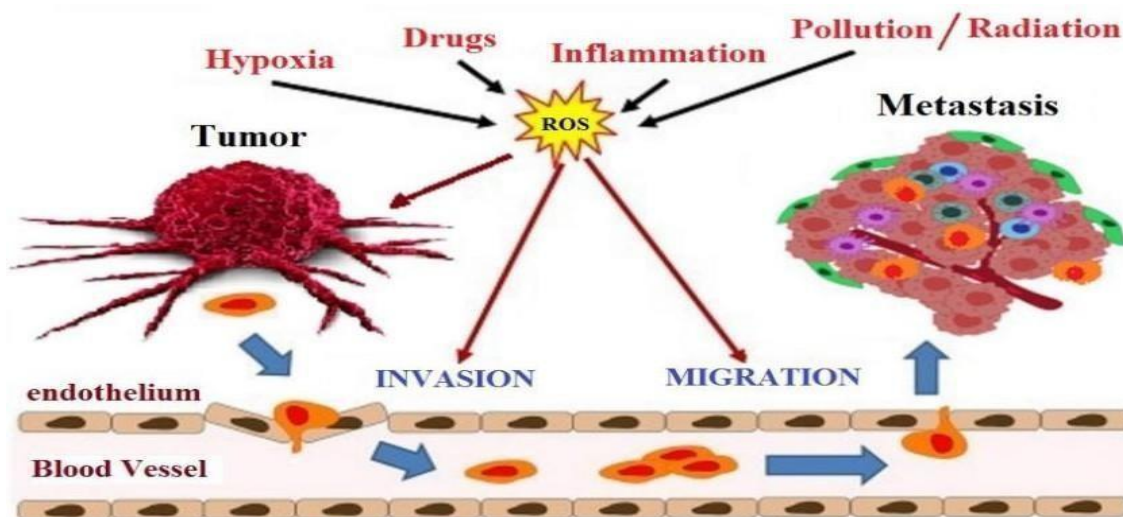
**Figure 3.** Involvement of oxidative stress in cancer progression.

Naringenin, a flavanone plentiful in Citrus paradisi, tangerine tree, orangish, and the peels of raw lemon and lime, has shown promising effects. Studies indicate that it can hinder the invasiveness and ability to spread of intestinal malignance cells and liver carcinoma cells [66,67]. Additionally, it has been observed to break the cell series and persuade programmed cell death in various types of human cancer cells [64, 65]. Interestingly, naringenin exhibits a ultra-oxidant outcome by reducing the activities of glutathione reductase with glyoxalase within cancer cells [68]. This reduction in enzyme activity leads to a decreased mechanisms accountable to detoxifying $H_2O_2$, letting for the accumulation of hydrogen peroxide and enhancing lipid peroxidation. This, in turn, results in damage to cell membranes.A recent stage 1 clinical study had emphasized the security and pharmacokinetics of naringenin [69].

Following a solo dosage of Citrus sinensis extract, naringenin was detected in blood at a concentration as a 43 μM within four hours. These findings underscore the potential of naringenin as a valuable compound in cancer research and treatment.


**Flavonoids and Apoptosis/Autophagy**

Currently, the primary focus in the search for anticancer drugs is to stimulate the apoptosis (cell death) of malignance cells [70]. Regrettably, malignance cells have developed mechanisms to evade cellular demise by hindering the beginning of the apoptotic path. Also, the development of drug resistance promotes tumor growth [71]. Flavonoids, casticin since the Vitex agnus-castus plant, which is commonly used as an anti-inflammatory in traditional Chinese remedy, have shown the ability to induce apoptosis by altering various pro-survival proteins, including Bcl-2. This molecule works by downregulating the intrinsic apoptosis mechanism. Studies have demonstrated this effect in several types of cancers, including gallbladder, esophageal, colon, leukemia, and glioblastoma, by downregulating proteins [72].

Similarly, vitexin, another natural flavonoid found in the Chinese plant Crataegus pinnatifida gives to less the Bcl-2/Bax fraction, proclamation cytochrome c by mitochondria, and activate caspase-3 lung malignance cells [73].Quercetin, a widely having it in onions with broccoli, was found to stop the proliferation of a humanoid metastatic ovarian malignance cell mark (PA-1). This inhibition was mediated by quercetin's ability to downregulate the appearance of antiapoptotic particles like Bcl-2 and Bcl-xL, while upregulating the countenance of pro-apoptotic molecules like Caspases three with nine .

Autophagy, a catabolic mechanism activated under stress conditions, plays a positive role in cell demise

processes. Numerous antineoplastic drugs excite autophagy, making it a possible approach in malignance treatment [75]. An water extract of allspice high in flavonoids, induced cell death in breast malignance cells by constraining the Akt/mTOR trail with one more activating autophagy in both laboratory experiments and animal studies [76]. Similarly, kaempferol induced autophagy in SK-HEP-1 human liver malignance cells over Akt gesturing and AMPK, foremost to G2/M arrest by downregulating CDK1/cyclin B [77]. Additionally, genistein has been found to induce autophagy in several malignance kinds, including uterine, breast, and prostate cancer. This activation of autophagy appears to contribute to its anti-tumor effects [78]. These findings shed light on the potential of flavonoids as valuable tools in the fight against cancer.

**Flavonoids Targeting Cancer Stem Cells**

A minor subgroup of cells inside lumps, known as melanoma stem cells (MSCs), play a energetic part in starting and sustaining lump growth. These CSCs are essential for various aspects of cancer, including its development, maintenance, progression, resistance to treatment, recurrence which is transfer to further portions of the body [79]. Emerging research suggests that dietary phytochemicals, like flavonoids, could be effective against CSCs [80]. Like a naringenin has found that defeat breast melanoma stalk cells by increasing the activity of p53 and the estrogen receptor α, much like hesperidin [81].

The common flavone apigenin is commonly found in foods like celery, parsley, and chamomile giving antineoplastic properties, particularly against glioblastoma, the most aggressive primary brain tumor. Studies, such as one by Kim et al. [82], have demonstrated that apigenin with quercetin having delay the skill to glioblastoma stem-like cells to renew themselves and invade tissues by reducing action of c-Met signaling way. Apigenin has also been found to decrease stem cell-like characteristics with a tumor-forming possible of triple-negative breast melanoma cells [84]. Furthermore, it improves the effectiveness of cisplatin against CD44+ prostate melanoma cells [83].

In oral melanoma cells, luteolin—a flavone goted in various dietary sources—has been shown to reduce their ability to self- renew with another cons is to reinstate their compassion to radiation [85]. Another flavonoid of interest is quercetin, found in foods like carrots, oregano, rosemary, olive oil, and peppers. Quercetin targets multiple types of CSCs having breast, gastric with pancreatic cancers [87–89]. Due to their ability to combat cancer, flavonoids like quercetin are being explored for their potential in medical applications [86]. These studies suggest that flavonoids hold promise in the fight against cancer, particularly in targeting the critical CSC population within tumors.

**Unveiling the Anti-Angiogenic and Anti-Metastatic Potential of Flavonoids**

The role of flavonoids to stop the angiogenesis presents an intriguing avenue in cancer research. Angiogenesis which is important for tissue development, wound healing with embryonic development. However, in the presence of a tumor, this process can become harmful. Increased blood vessel formation provides cancer cells with more nutrients, aiding in their survival and proliferation. Angiogenesis is tightly regulated by various factors, including vascular endothelial growth factor (VEGF) having inhibitory action like angiostatin & thrombospondin.

Parameter's contributory to swelling and melanoma can also excite angiogenesis [90]. Due to its vital role in melanoma growth, assault, and metastasis having development of angiogenesis inhibitors has become a significant emphasis in antineoplastic investigate. The FDA has approved several anti-angiogenesis medications for melanoma action [91]. Ongoing research is investigating novel compounds that could hinder tumor angiogenesis.

Wogonin, a flavonoid type composition derived from Scutellarin baicalinase's, is an O-methylated flavone that has been found to suppress both in vivo and in vitro angiogenesis induced by LPS [92]. Genistein modifies the appearance of VEGF, metalloproteinases with the epidermal growth factor receptor to inhibit angiogenesis [93]. Kaempferol targets the VEGF receptor 2 to prevent blood cell formulation when stimulated by VEGF in human umbilical vein endothelial cells (HUVECs). This process also involves ERK having mitogen-activated protein kinase path [94].

A dietary flavonoid known as luteolin (8-C-β-D-glucopyranoside) with glycosylation stop the development of tumors in MCF-7 breast cancer cells exposed to 12-O-tetradecanoylphorbol-13-acetate (TPA) by reducing the production of MMP-9 metalloproteinase and interleukin-8
(IL-8). [95]. Quercetin gives the stoppage of development gastric melanoma cells by unsettling the function of urokinase-plasminogen activator modulation by various pathways like AMP etc. [96].

Recent research has demonstrated that luteolin effectively inhibits the proliferation, migration, and invasion of human melanoma cells (A375) by inducing apoptosis in a dose-dependent manner. This action is associated with the suppression of Akt and PI3K phosphorylation within the same cell model. Additionally, the study indicated that luteolin decreases the levels of MMP-2 and MMP-9 while enhancing the expression of tissue inhibitors of metalloproteinase (TIMP)-1 and TIMP-2 [97].
Further investigations have revealed that luteolin markedly suppresses the growth of A375 cell tumors in a mouse xenograft model. These results indicate that the anticancer properties of luteolin are likely mediated through the down-regulation of MMP- 2 and MMP-9 expression via the PI3K/Akt pathway [97].

## Flavonoids: Impact on Cancer Cell Differentiation and Potential Therapeutic Implications

The objective of distinction treatment is to prompt cancer cells to undergo differentiation, halting their proliferation [68]. A notable advantage of differentiation therapy compared to traditional chemotherapy is its lower toxicity, ensuing in reduced side actions for patients [98]. Transglutaminase type 2 contributes to the differentiation process triggered by quercetin and pelargonidin in highly metastatic B16-F10 melanoma murine cells. [99].

All-trans retinoic acid (ATRA) is a widely used therapeutic agent for inducing differentiation in affected role having a acute promyelocytic leukemia. In this way increased cure many time become a cause to drug tolerance, necessitating higher doses [100]. There is a need for novel drugs with stronger differentiation-inducing properties to counteract drug resistance. Flavonoids present intriguing characteristics in this regard. They have the ability to induce cellular differentiation in APL cells.
Interestingly, the flavone structure appears to be crucial for inducing cell differentiation. For instance, quercetin induces APL cells to differentiate into monocytes, while luteolin and apigenin prompt differentiation into granulocytes. Conversely, APL cells do not undergo differentiation in response to galanin, kaempferol, or naringenin [100].

## Flavonoids to Improve Sensitivity to Chemotherapy

Combination therapy involving multiple substances has been shown to enhance the overall clinical effectiveness of existing anticancer drugs [68,106]. Finding innovative approaches to increase sensitivity to chemotherapy and reduce adverse side effects remains crucial due to issues like multi-drug resistance and tumor recurrence. Flavonoids have emerged as promising candidates in this regard due to their anticancer properties (Figure 5). Yuan et al. demonstrated the antiproliferative efficacy of arsenite in combination with

delphinidin, an anthocyanin compound, on human NB4 and HL-60 APL cells [107]. Delphinidin was found to modulate glutathione levels and reduce NF-κB activity, thereby sensitizing arsenite-resistant leukemia cells to cell death. The combination treatment also demonstrated selectivity by increasing arsenite's cytotoxicity. Furthermore, various cell types derived from solid tumors have shown benefits from combined flavonoid therapy.

Quercetin has been shown to sensitize human glioblastoma U87 and U251 cells to temozolomide, an oral alkylating chemotherapy drug, in vitro, through the suppression of heat-shock protein 27 [108]. Notably, flavonoids have the ability to cross the blood-brain barrier, making them potential candidates for brain cancer treatment [109].The combination of isoflavone biochanin has also shown anticancer potential, emphasizing the promising role of flavonoids in enhancing the effectiveness of existing chemotherapy drugs.
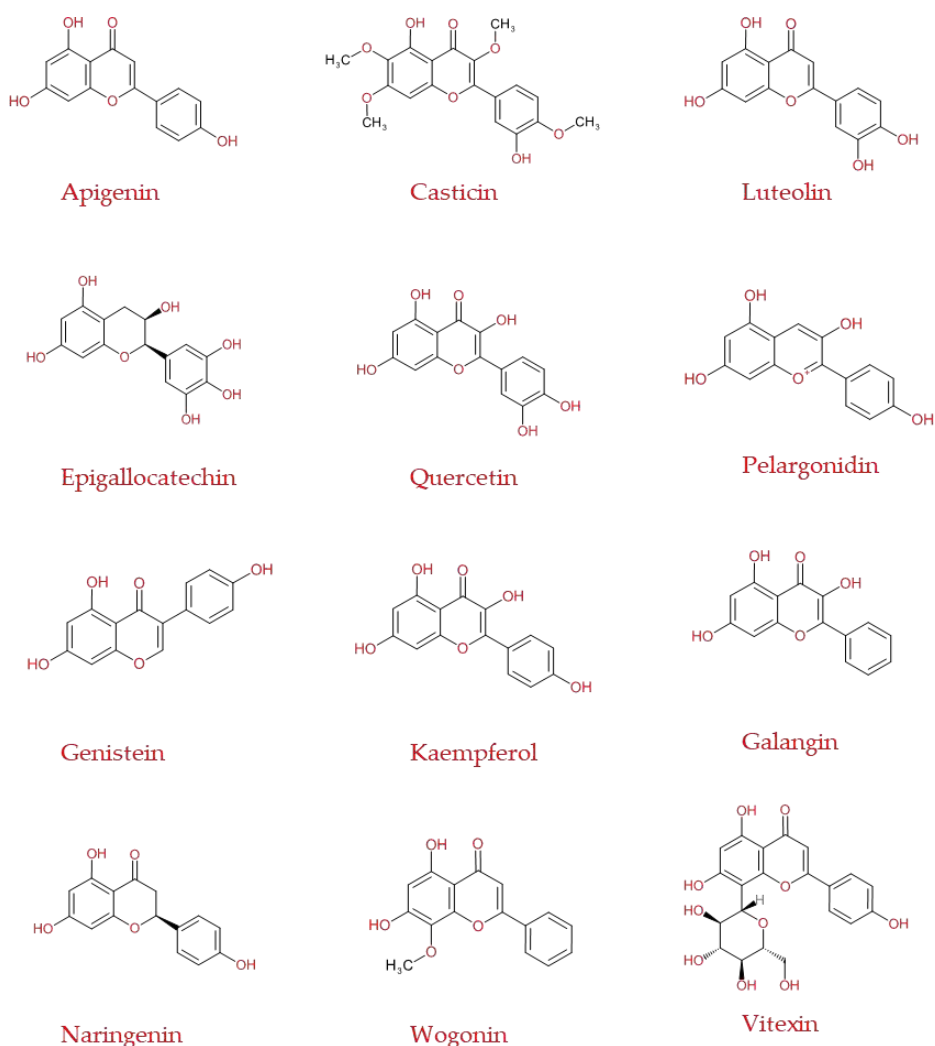


**Figure 4.** Chemical structure of the principal flavonoids discussed in the present review, also used in the experimental chemotherapy treatments.

## Conclusions

Flavonoids have demonstrated especially potent effects in stopping the development of tumors with inducing resistance in melanoma cells to standard treatments. An effort is complete to address the possible of flavonoids in malignancy treatments, whether used solo or in group, with the current compilation of material from the literature. with medicines used in chemotherapy. Finding the mechanisms of action for flavonoids will take time, despite their demonstrated potential usefulness in slowing the growth of tumors.

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