# Flavonoids Join the War on Cancer

By Uwe Wenzel, PhD


## ABSTRACT

*Are natural food ingredients able to aid cancer therapy? A huge body of in vitro and in vivo observations provides convincing evidence that various ingredients occurring naturally in plant foods possess potent anticancer activities. Among those compounds are the flavonoids, a class of more than 4,000 polyphenols occurring ubiquitously in plants. The mechanisms proposed for their action in cancer prevention encompass antioxidant activities, 17-β-estradiol-antagonizing properties, scavenging effects on activated mutagens and carcinogens, interactions with proteins that control cell cycle progression, and alterations of gene expression. It seems plausible that these biologic actions contribute to the cancer-preventive effects of diets rich in fruits and vegetables as seen in epidemiologic studies. However, once a cancer has developed, the goal is not chemoprevention but eradication of specifically transformed cells without affecting nontransformed cells. In this regard, selected flavonoids, such as epigallocatechin gallate or flavone, have shown promising results in their ability to kill transformed cells with only minor effects on nontransformed cells. The multifunctional activities of flavonoids might therefore be especially useful in cancer therapy. In-progress clinical trials should provide results on their in vivo efficacy soon.*


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## INTRODUCTION

Apart from food's necessity to support life, many food components can be regarded as health-promoting while others can be regarded as harmful. The importance of nutritional factors in the genesis of chronic diseases emerged about 100 years ago when cancer and cardiovascular diseases began to replace infectious diseases as the most important causes of early mortality. In a major treatise on cancer, W. R. Williams concluded in 1908 that "the incidence of cancer is largely conditioned by nutrition."[1] Analysis of cancer mortalities with respect to the prevalence of associated risk factors revealed that about 40% of cancers in the US and other industrialized countries may be due to diet.[2] "Food, Nutrition, and the Prevention of Cancer: A Global Perspective," a report and project issued and implemented by the American Institute of Cancer Research and the World Cancer Research Fund (UK) clearly demonstrated the high impact of diet on cancer prevention and development. As many as 375,000 cases of cancer, at current cancer rates, could be prevented each year in the US by choosing healthier diets. A simple change, such as eating the recommended five servings of fruits and vegetables each day, could reduce cancer rates by more than 20%.

Cancers of the colon and rectum appear to be especially associated with dietary habits and therefore the analysis of dietary components that can alter colon cancer risk has drawn much attention. Meta-analysis suggests that the consumption of red or processed meat may be positively, although weakly, associated with an increased colorectal cancer (CRC) risk.[3] More consistent but still weak evidence comes from case-control studies in which a higher consumption of vegetables is associated with a lower risk of colon cancer.[3] The association between high intake of dietary fiber and low risk of colon cancer is moderately consistent and may indicate protective effects of diets characterized by high consumption of plant foods, including cereals, vegetables, and fruits.[3]

## EFFECTS OF FRUITS AND VEGETABLES ON CANCER DEVELOPMENT

Results obtained in cell cultures or animal studies have demonstrated significant inhibitory effects of a number of ingredients in fruits and vegetables on cancer cell growth. Among these compounds are the antioxidative vitamins A, C, and E, the carotenoids, mineral elements such as calcium and selenium, fiber, and flavonoids.[4-11] However, outcomes from human intervention studies on the effects of such compounds in colon cancer patients have been more or less disappointing.[12-14]

Results were even more negative in the CARET[15] and the ATBC[16] studies. Both primary prevention trials were stopped because of higher lung cancer incidence and mortality in smokers who were given supplementary β-carotene. What we learned from this is that compounds that are effective growth inhibitors in cancer cells are not necessarily good chemopreventive agents in vivo and vice versa. In particular, antioxidants are generally regarded as effective

**TALKING POINTS** Physicians Pharmacy Formulary Cancer Nurses

*Due to their anticancer activities, selected flavonoids could prove to be effective therapeutics or adjuvants in cancer therapy.*

*Selected flavonoids are potent growth-inhibitors and apoptosis inducers.*

*Information about the bioavailability of flavonoids are needed in order to assess efficacies.*

*Antioxidants are not necessarily suitable as supportive agents in cancer therapy.*

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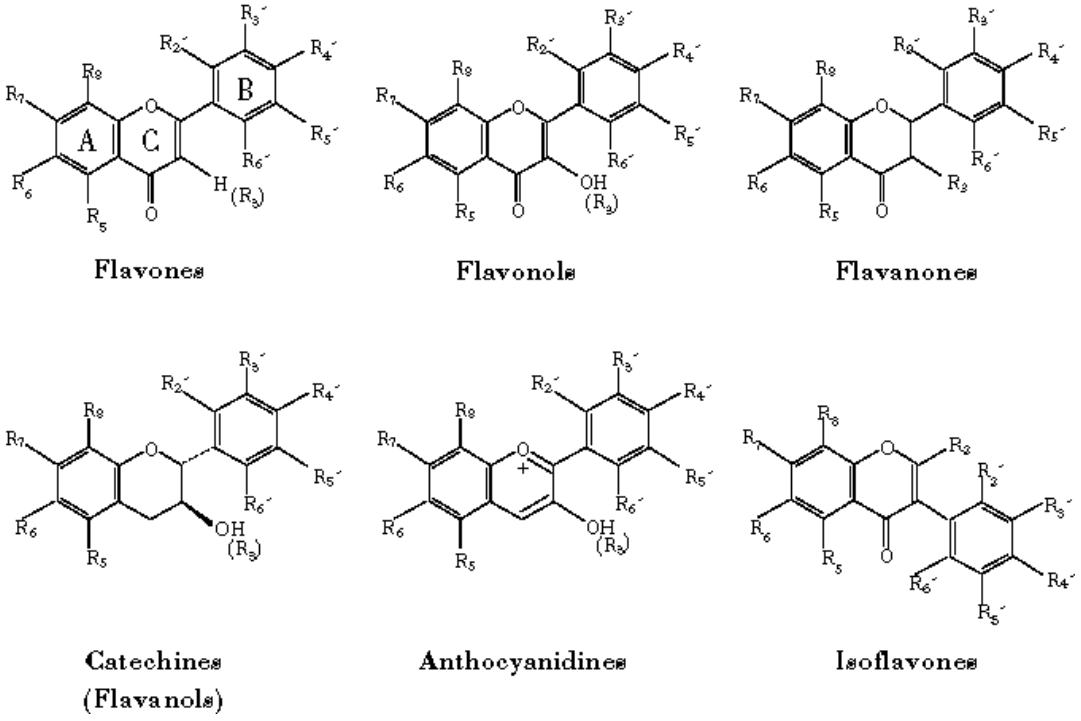
chemopreventive agents since they are potent scavengers of reactive oxygen species (ROS). ROS-mediated DNA damage contributes to spontaneous mutagenesis, and cells deficient in repair mechanisms and with low concentrations of protective compounds, including antioxidants, have elevated levels of spontaneous mutations, which might initiate cancer development.[17] On the other hand, ROS may be essential as activators of programmed cell death (apoptosis) to remove cells that have accumulated mutations. It was demonstrated recently that depletion of antioxidants inhibited tumor growth in a transgenic mouse brain tumor model.[18] Moreover, antiapoptotic proteins that act as antioxidants, such as bcl-2, are usually upregulated in cancer cells as a mechanism to escape apoptosis.[19,20] This supports the notion that a high level of antioxidants could be fatal in allowing transformed cells to resist cell death signals.

It is also important to remember that every compound displays a distinct dose-response relationship. It was shown for lycopene as well as β-carotene in human colonocytes that protection against DNA damage occurs only at relatively low concentrations, comparable to those found in the plasma of individuals consuming a carotenoid-rich diet. Such results have contributed to the tremendous popularity of dietary supplements. At higher concentrations, however, carotenoids may actually increase the extent of DNA damage.[21] In the United States alone, more than $12 billion was spent on them in 1998 without any clear indication of benefit. It should also be noted that side effects including immunoallergic acute hemolysis, thrombocytopenia, and acute renal failure have occurred in patients taking certain flavonoids.[22]

Therefore, for cancer prevention, isolated phytochemicals cannot be recommended per se. This also holds true for selected flavonoids, which might be especially suitable for chemoprevention due to their superior

**FIGURE 1. SUBCLASSES OF FLAVONOIDS**




The basic structure consists of an O-heterocyclic ring (C) fused to an aromatic ring (A) and by a carbon-carbon bond to a second aromatic ring (B). Classification is based on variations on the heterocyclic C ring.

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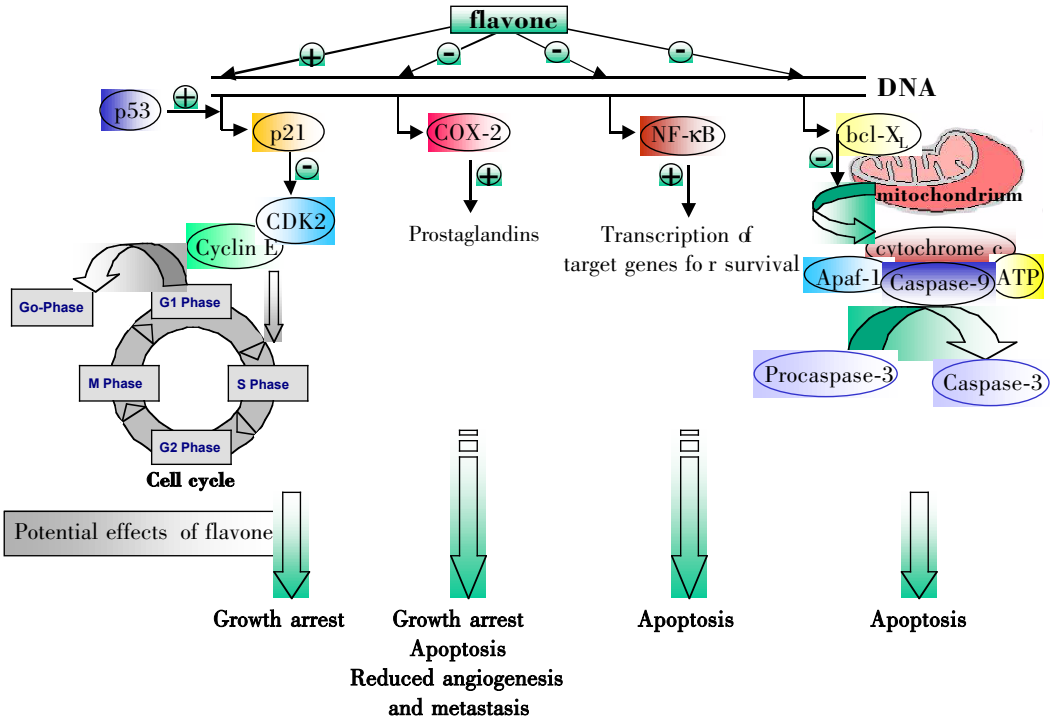
**FIGURE 2. OBSERVED EFFECTS OF FLAVONE IN CANCER CELLS AT THE MOLECULAR LEVEL**




Flavone increases the transcription of the cyclin-dependent-kinase (CDK)-inhibitor p21. The p21 protein is usually induced by the tumor suppressor p53, but induction of p21 by flavone occurs independent of p53 activity. Increased p21 levels inhibit the CDK2-cyclin E complex that is crucial for S-phase entry of the cell cycle. As a consequence of increased p21 expression and reduced expression of cyclins,[32] flavone leads to a cell-cycle arrest. Growth-inhibition may be exerted by flavone also through a diminished cyclooxygenase-2 (COX-2) expression. COX-2 is responsible for the synthesis of prostaglandins that have been shown to be involved in stimulation of cell growth and inhibition of apoptosis, but may also play a role in angiogenesis and metastasis. The reduced mRNA-levels of NF-κB by flavone exposure may inhibit the transcription of survival genes and thereby allow apoptotic signals to prevail. Flavone moreover reduces the transcript levels of bcl-$X_L$, a mitochondrial anti-apoptotic factor that inhibits the release of cytochrome c from mitochondria. Cytochrome c together with the apoptotic-protease-activating-factor-1 (Apaf-1), ATP and Caspase-9 forms the so-called apoptosome that triggers the activation of the executioner protease caspase-3. Therefore, the flavone-induced inhibition of bcl-$X_L$ expression causes increased apoptosis.

Note: The symbols + and - represent stimulation and inhibition, respectively.

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radical scavenging activities[23] but may also possess serious unwanted side effects. Until we learn more about the mechanisms and dose-response relationships of isolated phytochemicals, a diet rich in fruits and vegetables best meets the current requirements of preventive, healthy nutrition.

## *FLAVONOIDS AS CANCER THERAPEUTICS*

Flavonoids are categorized into the subclasses of flavones, flavonols, flavanones, catechines, anthocyanidines, and isoflavones (Figure 1). Their inhibitory potency in various stages of tumor development in animal studies has attracted much attention.[24-26] Apart from the strong antioxidative properties of most but not all flavonoids, they also display a multitude of other biologic functions that might be relevant in cancer therapy. Cancer cells differ from normal cells by their increased proliferation rate and reduced apoptosis and differentiation rates. Selected flavonoids have been shown to affect these parameters by different molecular mechanisms.

For instance, the flavonoid flavopiridol has been shown to inhibit various cyclin-dependent kinases (CDKs), which are crucial for transition of a cell through the cell cycle.[27] As a consequence, a growth arrest in human breast carcinoma cells was observed. The catechin epigallocatechin gallate (EGCG),[28] the isoflavone genistein,[29] the flavonol quercetin,[30] and flavone[31,32] were shown to induce gene expression of the CDK-inhibitor p21. Expression of p21 is usually associated

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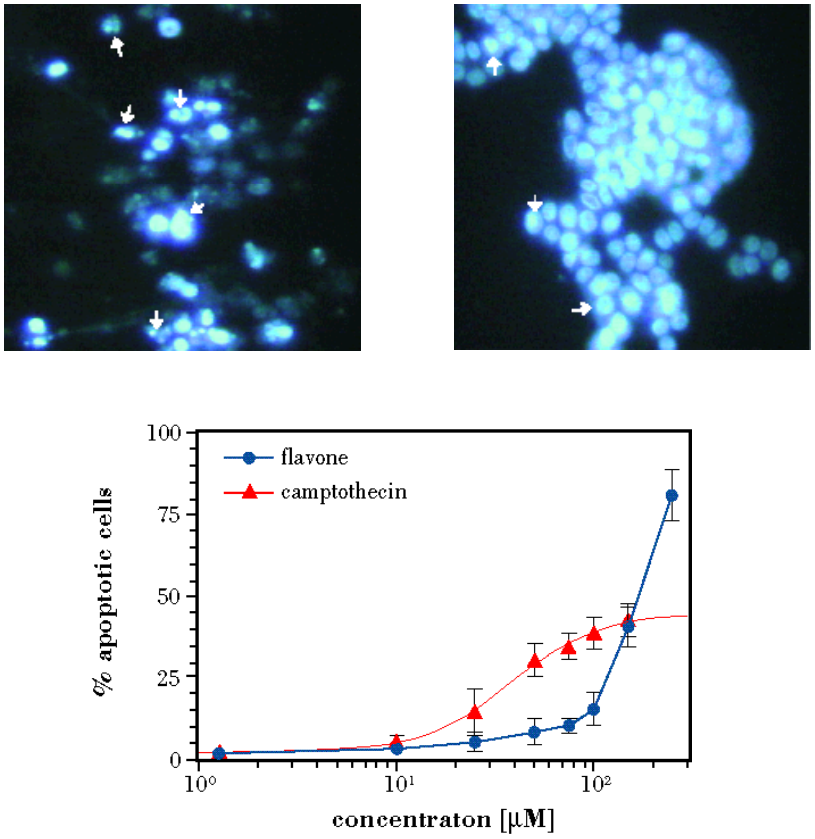
with a cell cycle arrest that allows other proteins to control and repair the replicated DNA. The p21 gene is also a major transcriptional target of the tumor suppressor protein p53.[33] P53 is mutated in almost 50% of all human cancers, and one consequence of its loss of function is inability to induce p21. This causes a key problem in cell cycle control since the development of sporadic tumors is generally associated with reduced expression of p21.[34] In contrast, enhanced expression of p21 has been shown to inhibit the proliferation of malignant cells in vitro and in vivo.[35] In p53-mutant tumors, selected flavonoids and in particular flavone might be useful as a therapeutic or as an adjuvant therapy. As shown by Bai et al[31] in human lung adenocarcinoma cells, and by our group in human colon carcinoma cells,[32] flavone induces the expression of p21 independent of the tumor suppressor p53.

Besides its effects on the expression of p21, a number of other genes involved in cancer development were shown to be affected by flavone treatment in colon cancer cells.[32] The mRNA levels of the antiapoptotic factors NF-κB and bcl-$X_L$ and of cyclooxygenase-2 (COX-2) were shown to be potently downregulated by flavone. The ability of the transcription factor NF-κB to inhibit apoptosis in cancer cells contributes significantly to their chemoresistance.[36] Therefore, flavone might be helpful as an adjuvant in cancer

**FIGURE 3. APOPTOSIS IN HUMAN COLON CANCER CELLS AS MEDIATED BY FLAVONE OR CAMPTOTHECIN**




**Top**: Staining of DNA with Hoechst 33258 for the detection of apoptosis (see arrows) after incubation of the cells with camptothecin or flavone. **Bottom**: Percentage of apoptotic cells as a function of camptothecin or flavone concentrations measured after 24 hours of incubation.

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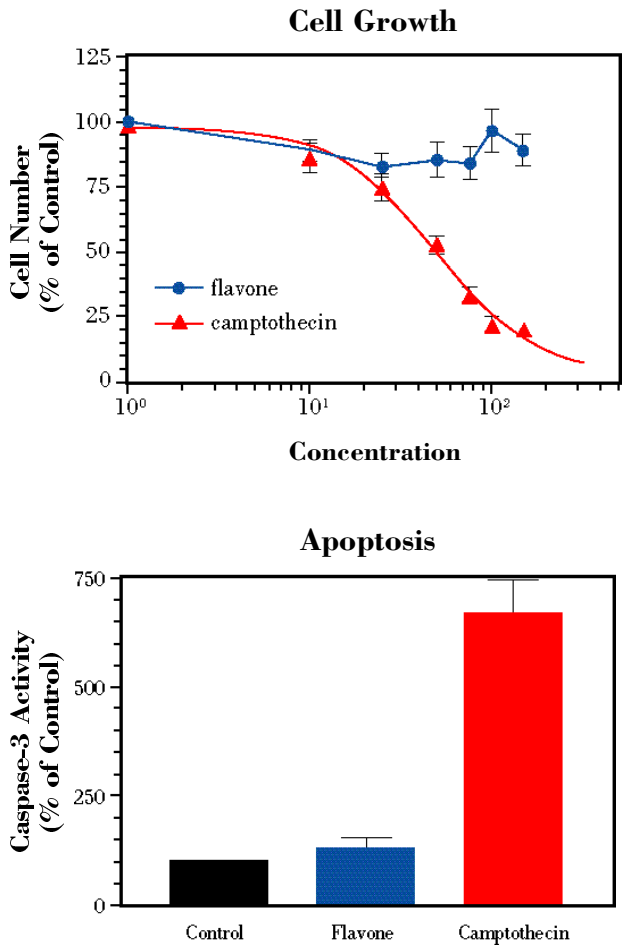
therapy. Also the downregulation of bcl-$X_L$ could provide a benefit in cancer therapy since bcl-$X_L$ seems to play a major role in colorectal tumorigenesis and disease progression.[37] Overexpression of the COX-2 gene is consistently found during neoplastic development in a variety of tissues, and prostaglandins formed along the dysregulated COX pathways have been shown to mediate tumor promotion in animal studies. However, prostaglandins may also play a role in other tumor growth processes, such as angiogenesis, metastasis, and immunosuppression.[38] Consequently, COX-2 has become a key target of pharmacotherapy, especially in prevention and therapy of CRCs.[39] Inhibition of COX-2 enzyme activity is achieved by nonsteroidal anti-inflammatory drugs including newly developed COX-2-specific inhibitors, whereas flavone prevents gene expression of the enzyme. Figure 2 summarizes the observed effects of flavone at the molecular level in cancer cells.

As we have shown, the effects of flavone on the gene transcription level are associated with growth inhibition, increased cellular differentiation, and elevated apoptosis rates in human colon cancer cells.[32] Whereas 30 other flavonoids tested in cancer cells displayed similar antiproliferative properties,[11] flavone differed from all other compounds in its very strong apoptosis-inducing capacity. Flavone enhanced the activity of caspase-3, an early marker for apoptosis induction, by 16-fold, whereas camptothecin, a classic antitumor drug, increased caspase-3 activity only six-fold.[32] When DNA-fragmentation and chromatin condensation were measured as a marker of the final stages of the apoptotic process, 80% of colon cancer cells were killed by flavone whereas only 40% were killed by camptothecin treatment for 24 hours (Figure 3).

Besides effective induction of apoptosis by cancer therapeutics, another major goal is to achieve a high selectivity toward transformed cells to reduce the number and severity of side effects. The limited selectivity of classic apoptosis-inducing antitumor drugs in the treatment of CRCs frequently leads to mucosal damage. Moreover, increased apoptosis rates in nontransformed cells can be accompanied by neoplastic transformation.[40,41]

We compared the effects of flavone with those of camptothecin in normal colonic cells isolated and cultivated from colonic crypts of healthy mice.[32] Whereas camptothecin proved to be a strong growth inhibitor in the nontransformed colonocytes, flavone did not affect proliferation rates of normal murine cells (Figure 4). The apparent growth inhibition caused by camptothecin seemed to be mediated by enhanced apoptosis since caspase-3 activity was increased about sevenfold at 24 hours of exposure (Figure 4). As flavone did not show any significant effects on apoptosis and no cytotoxicity in the murine nontransformed cells (Figure 4), it could be beneficial in terms of a low side-effect profile.

**FIGURE 4. EFFECTS OF FLAVONE AND CAMPTOTHECIN ON GROWTH (TOP) AND APOPTOSIS (BOTTOM) IN PRIMARY MURINE COLONOCYTES**




Cell counts were estimated after 72-hour incubation and caspase-3 activity (as a marker for apoptosis) was determined after 24-hour incubation.

Adapted from Wenzel et al.[32]

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Similar selective growth-inhibiting activity and significant apoptosis-inducing effect in cancer cells have also been demonstrated for the green tea polyphenol EGCG.[42] The constitutive expression of NF-κB and the binding of NF-κB to DNA-cis-regulatory elements was inhibited by EGCG at much lower concentrations in cancer cells than in nontransformed cells.[43] Moreover, the activation of NF-κB by stress stimuli, such as tumor necrosis factor-α (TNF-α) or lipopolysaccharide (LPS), was also inhibited by EGCG more prominently in cancer cells than in normal cells.[43]

## *CONCLUSIONS*

In conclusion, various compounds occurring naturally in food plants could be valuable in improving current cancer treatment as well as in prevention strategies. Similar to other dietary constituents, some flavonoids could be very effective chemopreventive agents due to their high antioxidative capacity. Flavonoids, including those that do not possess any antioxidant activity, have been shown to be potent inhibitors of cancer cell growth and therefore might support cancer therapy. Their multifunctional activity could make them especially beneficial in prevention and in combination antitumor therapies. The strength of such a combination therapy was shown by the prevention of colorectal adenomas in mice using inhibitors of the epidermal growth factor and of COX signaling pathways.[44] This synergistic action needs to be exploited systematically in cancer therapy, in particular in modulating the "threshold" for apoptosis.[45] Clinical trials with flavonoids are currently underway and should show whether these agents are effective in humans.[46-48]

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