

Cytotoxicity of dietary flavonoids on different human cancer types

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ABSTRACT

Flavonoids are ubiquitous in nature. They are also in food, providing an essential link between diet and prevention of chronic diseases including cancer. Anticancer effects of these polyphenols depend on several factors: Their chemical structure and concentration, and also on the type of cancer. Malignant cells from different tissues reveal somewhat different sensitivity toward flavonoids and, therefore, the preferences of the most common dietary flavonoids to various human cancer types are analyzed in this review. While luteolin and kaempferol can be considered as promising candidate agents for treatment of gastric and ovarian cancers, respectively, apigenin, chrysin, and luteolin have good perspectives as potent antitumor agents for cervical cancer; cells from main sites of flavonoid metabolism (colon and liver) reveal rather large fluctuations in anticancer activity probably due to exposure to various metabolites with different activities. Anticancer effect of flavonoids toward blood cancer cells depend on their myeloid, lymphoid, or erythroid origin; cytotoxic effects of flavonoids on breast and prostate cancer cells are highly related to the expression of hormone receptors. Different flavonoids are often preferentially present in certain food items, and knowledge about the malignant tissue-specific anticancer effects of flavonoids could be purposely applied both in chemoprevention as well as in cancer treatment.

Key words: Diet, flavonoids, human cancers, prevention, treatment

INTRODUCTION

Numerous edible plant-derived compounds have been linked to the chemoprevention and treatment of cancer.^[1-9] For the past decades, much research has been developed in order to discover natural compounds with potential anticancer activity^[6,10-12] and several plant-derived agents (e.g., paclitaxel, docetaxel; vinblastine, vincristine; topotecan, irinotecan, etoposide, etc.) have been successfully used for cancer treatments.^[13-15] Among the anticancer medications, 69% of drugs approved between 1940 and 2002 are either natural products or developed based on knowledge gained from natural products,^[16,17] a rate which is much higher than in other areas of drug development.^[18] Natural

products offer an untold diversity of chemical structures, and it is very likely that phytochemicals will continue to be important in cancer therapeutics.^[19-21] Application of plants in the treatment of cancer seems to be inevitable, constituting the basis for modern medical science and providing a great source for new drugs.^[22,23]

Medicine and one's daily food are equally important in making a sick body well.^[24] Diet is intimately linked to both the incidence and avoidance of many types of cancer^[25] and dietary behavior has been identified as one of the most important modifiable determinants of cancer risk.^[26] Strong and consistent epidemiological evidences suggest that a diet enriched with naturally occurring substances significantly reduces the risk for many cancers.^[27-31] Indeed, the adoption of diets rich in vegetables and fruits, together with the maintenance of physical activity and appropriate body mass, could reduce the cancer incidence by 30-40%.^[32-34] Moreover, several studies suggest that there is a decreased risk for different types of cancer among vegetarians.^[35] Numerous classes of compounds present in fruits and vegetables are assumed to take the role of cancer-preventive agents. Among these compounds, flavonoids have been proven to be particularly important.^[27,29,36]

FLAVONOIDS AS POTENT ANTICANCER AGENTS

Flavonoids are naturally occurring polyphenolic metabolites distributed throughout the plant kingdom and found in

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substantial amounts in fruits, vegetables, grains, nuts, seeds, tea, and traditional medicinal herbs.^[37-39] Within individual plants, flavonoids occur in every part but are usually concentrated in the leaves and flowers.^[40] Flavonoids are edible plant pigments responsible for much of the coloring in nature.^[41,42]

Many of the different flavonoids are part of the regular human diet. Although they are nonessential dietary factors,^[9] flavonoids are thought to be nutritionally valuable compounds,^[43] being the key natural products that provide the most essential link between the diet and prevention of chronic disorders. One of the most investigated activities of flavonoids is their contribution to cancer prevention and treatment.^[6]

Several thousand flavonoids are known to occur in nature, defined chemically as compounds containing a phenylchromanone structure (C6-C3-C6) with at least one hydroxyl substituent.^[44-47] Flavonoids can be further divided into flavonols, flavones, flavanols, flavanones, anthocyanidins, and isoflavonoids based on the saturation level and opening of the central pyran ring^[15,45,48] [Figure 1].

The daily human intake of flavonoids is quite different in amounts and classes due to various feeding habits of people from different regions and cultures.^[25,49] Reports of estimated daily consumption of flavonoids range from 20 mg/day to 1 g/day.^[50] As the total flavonoid intake in Western countries is estimated at 23 mg/day,^[51] humans consuming high fruit and vegetable diets may ingest up to 1 g of these compounds daily.^[52,53] No information is available about the content of flavonoids in the diet of vegetarians.^[54,55] The main food sources of major dietary flavonoids are presented in Table 1.

As natural products, flavonoids are regarded as safe and easily obtainable, making them ideal candidates for cancer chemoprevention or associated agents in clinical treatment.^[3,43,56]

Almost all artificial agents currently being used in cancer therapy are highly toxic and produce severe damage to normal cells.^[57,58] The ideal anticancer agent would exert minimal adverse effects on normal tissues with maximal capacity to kill tumor cells and/or inhibit tumor growth.^[12,34] The lack of substantial toxic effects for long-term therapies and inherent biological activity of flavonoids make them ideal candidates for new therapeutics.^[16,59] Indeed, flavonoids have been shown to reveal cytotoxic activity toward various human cancer cells with little or no effect on normal cells, and this fact has stimulated large interest in developing of potential flavonoid-based chemotherapeutics for anticancer treatment.^[60,61]

Several observations have suggested that natural flavonoids have growth inhibitory effects on various kinds of cancer cells mediated by different molecular targets and acting through diverse metabolic pathways.^[62-64] However, the precise mechanisms responsible for the antitumor effect of flavonoids are still not thoroughly understood.^[64,65] Flavonoids can easily bind to the cell membrane, penetrate *in vitro* cultured cells, and modulate the cellular metabolic activities.^[66,67] Mitigation of oxidative damage, inactivation of carcinogen, inhibition of proliferation, promotion of differentiation, induction of cell cycle arrest and apoptosis, impairment of tumor angiogenesis, and suppression of metastasis contribute to the anticarcinogenic activities of flavonoids.^[24,25,30,32,49,68] These polyphenolic compounds can interact with xenobiotics metabolizing enzymes, inhibit several kinases involved in signal transduction, interact with estrogen type II binding sites, and alter gene expression patterns.^[61,69-71]

Normal cell growth is maintained by the balance between cell proliferation and cell death, and apoptosis is a central regulator of tissue homeostasis.^[72,73] Cells from a variety of human malignancies have a decreased ability to undergo apoptosis in response to some physiological stimuli. Induction of apoptosis in malignant cells may therefore represent a promising approach

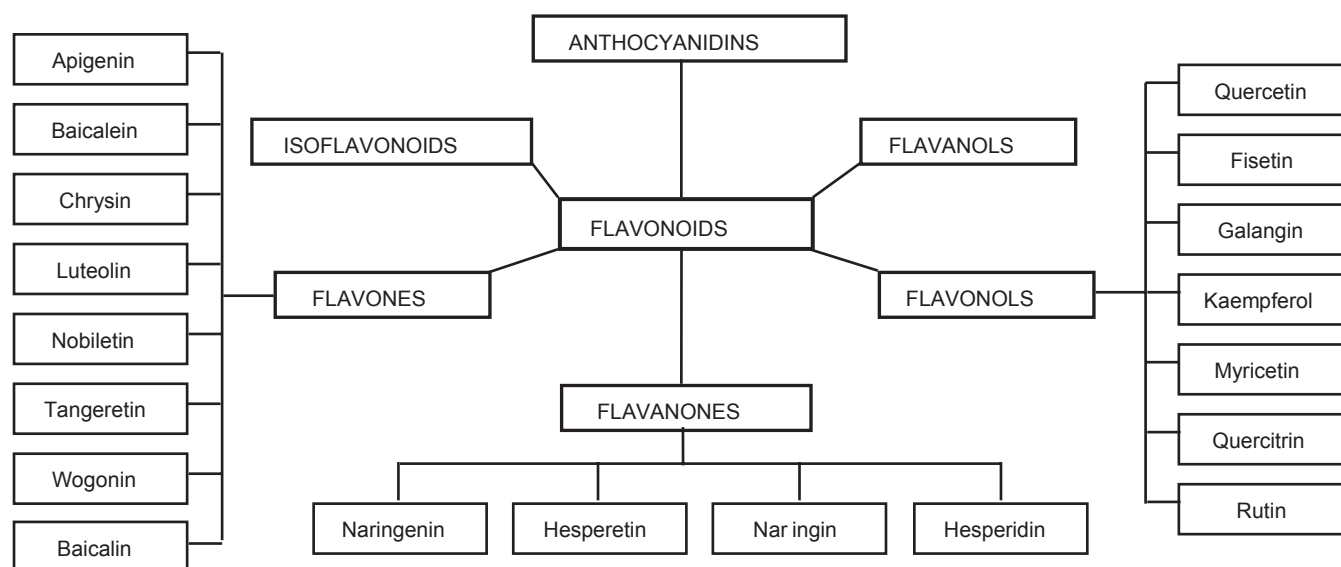
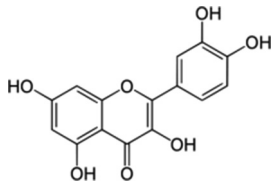
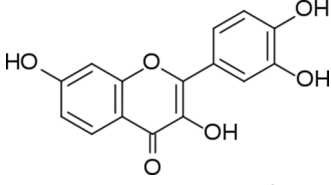
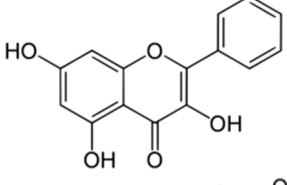
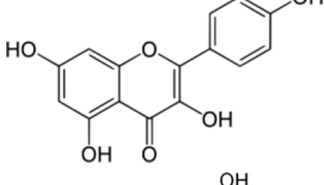
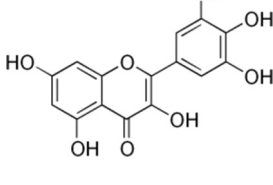
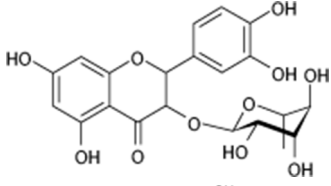
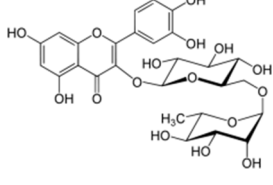
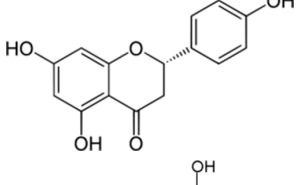
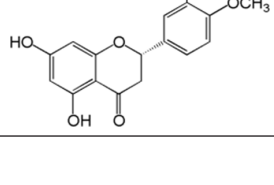
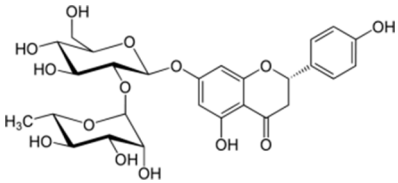
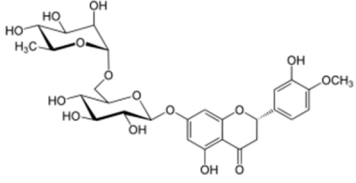
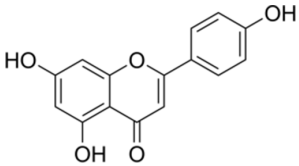
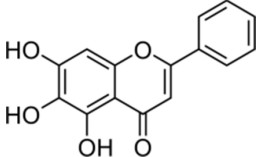
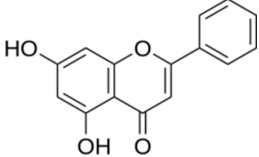
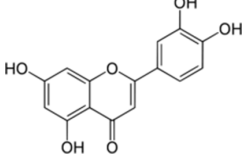
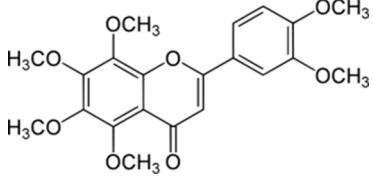
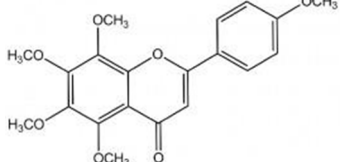
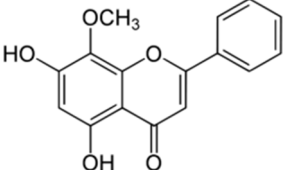


Figure 1: Scheme of major flavonoid aglycones and their glycosides

Table 1: Structures and main food sources of major flavonoid aglycones and their glycosides

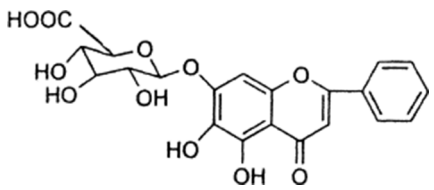
Flavonoids	Structure	Major food sources	References
<i>Flavonols</i> Quercetin		Various fruits and vegetables, such as apples, citrus, and red grapes, Italian cabbage, broccoli, onions, tomato; especially abundant in capers and lovage leaves	[152]
Fisetin		Various fruits and vegetables, such as cucumber, onion, persimmon, strawberry, apple, kiwi, and grape	[2,3,27,82,140-142,153-158]
Galangin		Medicinal herbs, including <i>Alpinia officinarum</i> (Hance), <i>Alnus pendula</i> Matsum., <i>Plantago major</i> L., and <i>Scutellaria galericulata</i> L.; a major component of propolis	[6,7,25,159-161]
Kaempferol		Berries, tea, many commonly consumed fruits and vegetables, such as broccoli, kale, and endive; active constituent of <i>Ginkgo biloba</i> L.	[72,86,162,163]
Myricetin		Tea, berries (especially grapes), fruits, and medicinal plants	[26,42]
<i>Glycosides</i> Quercitrin		Tartary buckwheat, some oaks species, some medicinal plants, such as <i>Bauhinia malabarica</i> Roxb. and <i>Hypericum perforatum</i> L.	[164-166]
Rutin		Abundant in various plants, such as buckwheat and apples as well as many plant-based beverages, such as lime juice and noni	[124,129,167]
<i>Flavanones</i> Naringenin		Citrus fruits, such as grapefruits and orange fruits and juice, also in tomato; isolated from <i>Salvia leriifolia</i> Benth.	[18,32,46,75,102, 103,168,169]
Hesperetin		Citrus fruits, such as orange and grapefruit fruits and juices	[104,170,171]

Contd...

Table 1: Contd....			
Flavonoids	Structure	Major food sources	References
<i>Glycosides</i> Naringin		Citrus plants, most abundant in grapefruits being responsible for the bitter taste	[11,172-175]
Hesperidin		Citrus fruits, such as lemon, orange, and lime juices and peels	[8,124,176,177]
<i>Flavones</i> Apigenin		Widely distributed in fruits and vegetables, including onions, artichoke, orange, tea, wheat sprouts, and some seasonings; the most abundant sources are the leafy herb parsley and dried flowers of chamomile (<i>Matricaria chamomilla</i> L.)	[45,47,57,127,130, 178-182]
Baicalein		The root of Chinese herb <i>Scutellaria baicalensis</i> Georgi (also known as Baikal Skullcap or Huang Qin)	[20,183-186]
Chrysin		High levels in honey and propolis; found also in many plant extracts, including <i>Passiflora caerulea</i> L. flower	[187-189]
Luteolin		Various fruits and vegetables; abundant in onion, celery, spinach, green pepper, broccoli, beet, cabbage, cauliflower, artichoke, olive oil, tea, perilla leaf, parsley, peppermint, thyme, sage, rosemary, and oregano	[15,49,68,71,122, 190]
Nobiletin		Citrus flavonoid extracted from citrus fruits and peel	[53,107,191]
Tangeretin		Abundant in the peel of various citrus species, such as sweet orange and mandarin; the Dancy tangerine contains the highest total amount	[62,145,172]
Wogonin		The root of Chinese herb <i>Scutellaria baicalensis</i> Georgi (also known as Baikal Skullcap or Huang Qin)	[20,131,135,184, 192]

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Table 1: Contd...

Flavonoids	Structure	Major food sources	References
Glycosides Baicalin		The root of Chinese herb <i>Scutellaria baicalensis</i> Georgi (also known as Baikal Skullcap or Huang Qin)	[20,66,73,184,193, 194]

to both chemoprevention and chemotherapy, and searching for agents that can specifically trigger apoptosis in tumor cells has become an attractive strategy in anticancer drug discovery.^[38,74-77] The anticancer efficacy of flavonoids is due, at least in part to their ability to induce apoptosis of tumor cells.^[37,78-81]

One of the most common incidents required for human cancer development known as a hallmark of malignant cells is deregulation of the cell cycle.^[35,82,83] Agents that can inhibit cell-cycle progression and lead to cell-growth arrest are very important in cancer prevention and therapy studies,^[35] and considerable attention has been paid to the ability of dietary flavonoids to inhibit cell-cycle progression.^[82] Flavonoids have been found to arrest cell-cycle progression at either G₁/S or G₂/M boundaries by modulating of multiple cell cycle regulatory proteins.^[69] Somewhat conflicting results have been reported with regard to the stage-specific arrest caused by one and the same compound,^[59,84] and several studies have indicated the ability of flavonoids to block the cell growth at more than one stage of the cell cycle.^[85]

Due to the polyphenolic structure, flavonoids have been found to possess both anti- and prooxidant action.^[86] While antioxidant effect and ability to scavenge reactive oxygen species (ROS) have been shown to account for most of the reported biological effects of phenolic compounds, several recent studies have revealed that anticancer activities of flavonoids may be mediated through prooxidant action.^[49,87] Cancer cells exhibit a higher and more persistent oxidative stress level compared to normal cells, rendering malignant cells more vulnerable to being killed by drugs that boost increased ROS levels, such as some flavonoids.^[88-91] Whether a flavonoid acts as anti- or prooxidant depends on its dose, cell type, and also culture conditions.^[37,90,92]

The specific activity of flavonoids on cell function can also depend on their chemical structure.^[93-95] The structures of the most common dietary flavonoids are presented in Table 1. Important factors affecting cytotoxic and/or antiproliferative activities of polyphenols include the saturation of the C₂-C₃ bond and the position as well as the number and substitution of hydroxyl groups in the A and B rings.^[69,96,97] However, even the minor modifications in the molecules can be responsible for strong variations in their activity, and flavonoids with very similar structures could not produce identical biological

responses.^[40,97-99] Indeed, some authors have suggested that the anticancer capability of flavonoids cannot be predicted based on their chemical composition and structure,^[61] and it is the reason why no structure activity relationships are analyzed in the present work.

OBSCURITIES LIMITING THE USE OF FLAVONOIDS IN CANCER CHEMOPREVENTION AND TREATMENT

Flavonoids have been found to exert cytotoxic activities only at relatively high doses, within the micromolar concentration range.^[26,82,100] The amount of dietary flavonoids in plasma varies according to several parameters such as functional groups and daily intake.^[101] However, achieving the plasma levels sufficient to reveal antiproliferative and cytotoxic effects may not be possible via oral administration.^[9,100] For example, results from human data have shown that a full glass of orange juice supplies about enough naringenin to achieve a plasma concentration of 0.5 μM;^[102] a one-time consumption of approximately 550 g of grapefruit juice results in a mean peak plasma concentration of 6 μM naringenin;^[103] the physiological dose of hesperetin attainable from drinking orange juice is in the range of 0.5-6 μM;^[104] human plasma concentration of hesperidin reaches to 0.5 μM at 5-7 hours after ingestion of 0.5 liter of commercial orange juice providing 400 mg hesperidin;^[8] typical plasma concentration of apigenin is within 10 nM range;^[45] the concentration of chrysin in plasma after a single dose of 400 mg remains below 0.1 μM;^[101] and maximal plasma levels of luteolin reaches to about 0.2 μM at 1-2 hours after oral administration.^[31] In contrast, methoxylated flavonoids display up to 100-fold higher plasma concentrations on account of the reduced phase II conjugation reactions.^[101] Higher plasma levels can be achieved through intravenous injection,^[9,100] and the plasma concentration of flavonoids may also be significantly increased by regular intake for a prolonged period.^[45,101,105]

Despite encouraging preclinical results, the usability of flavonoids for chemoprevention has encountered only limited success, largely because of inefficient systemic delivery and bioavailability.^[106-108] Flavonoids are most often found in plant materials in the form of glycosides (bound to sugars), which are better soluble in water than the respective aglycones.^[47,68,109] Most of the glycosides

resist acid hydrolysis in the stomach^[45] and are deglycosylated by β -glucosidases in the small intestine.^[69] The aglycones are further glucuronidated and sulphated by the intestinal mucosa and liver before release into the blood serum.^[47,68,69] It is therefore likely that phytochemicals can accumulate in the small intestine and colon at levels greater than in plasma.^[110] Bioavailability of flavonoids is determined by different factors, including the sugar moiety of the polyphenolic compound and its further metabolism by the gut microflora,^[11] showing that different groups of flavonoids may have different pharmacokinetic properties.^[111,112] Moreover, considerable interindividual variation between humans can also influence the flavonoid metabolism, thus affecting the therapeutic action of polyphenolic compounds.^[103] Furthermore, the anticancer activity would be related not only to the parent flavonoid ingested but also to its metabolites; therefore, identification and measurement of the physiological flavonoid conjugates are important to thoroughly understand the role of dietary polyphenols in human health.^[31,52,69]

COMPREHENSIVE ANALYSIS OF CYTOTOXICITY OF FLAVONOIDS ON HUMAN CANCER LINES FROM DIFFERENT ORIGINS

Flavonoids have been demonstrated to suppress proliferation of various cancerous cells.^[69] However, not all polyphenolic compounds share the same antiproliferative activity,^[113] and depending on their structure, flavonoids display differences in the sensitivity and selectivity toward tumor cells.^[26,97,114] The sensitivities of cancer cells against flavonoids can be different depending on their derived tissues,^[16,115] indicating that the cytotoxicity induced by flavonoids might be related to selected cancer types.^[30,116] Even in the case of flavonoids with quite similar structures, there are compound-specific effects which are relevant to modulate particular biochemical processes so that the development of certain neoplasms could be differentially influential pointing to the tissue-specific cytotoxic action.^[117,118] The effectiveness of flavonoids may vary also because of the different disease etiologies.^[119]

It is of interest of the current review article to determine whether the most common dietary flavonoids can exert some clear-cut preferences to certain tumor tissue types. In nature, different members of the flavonoid family are often preferentially present in some food items;^[120] and knowledge about the malignant tissue-specific cytotoxic effects of flavonoids could be purposely applied both in the chemoprevention based on the genetic cancer risks and familiar anamnesis as well as in the cancer treatment. For this purpose, quantitative data characterizing the cytotoxic effects of different flavonoids on different human tumor cell lines were compiled from the literature sources, and statistical analysis to calculate the respective mean parameters was performed. IC_{50} values as the flavonoid concentrations required to inhibit 50% of cell growth are the most common representative indexes of the dose-response curve,^[121] and these parameters were also used in the current work. The mean cytotoxic constants of the most common dietary flavonoids on cancer cell lines derived from

various organ sites are presented in Table 2. Cultured human malignant cell lines used for evaluating the cytotoxicity of these compounds are listed in Table 3.

Paucity of data complicates the analysis

Despite the extensive investigation carried out with flavonoids in the past decades, there are still quite a few parameters available, characterizing quantitatively the efficacy of polyphenolic compounds on certain cancer types. In this way, the IC_{50} values of flavonoids measured using the cells derived from malignant esophageal tissues are too scarce to reveal any certain specificity patterns. At the same time, data measured on bone cancer lines show only very low or even no cytotoxic activity of different flavonoids [Table 2].

Rather, few half-maximal cytotoxic parameters are available also for cell lines derived from human tumors of bladder, mouth, stomach, pancreas, and ovary. However, some activity patterns and tissue specificities of flavonoids can still be brought forth for these organ sites. In the case of bladder, cancer flavones apigenin and luteolin seem to be cytotoxically most active. Besides these two flavones, chrysin and flavonol kaempferol have also been reported to have antiproliferative activity and induce apoptosis in oral cavity cancer cells. Epithelium of the oral cavity can absorb the flavonoids directly, and should benefit for high levels of exposure to these dietary phytochemicals.^[122]

Flavones apigenin, baicalein, luteolin, nobiletin, and tangeretin have shown to be the most effective flavonoids against carcinomas of stomach, whereas luteolin has even proposed to be a promising candidate agent for treatment of gastric cancer.^[123]

In addition to some flavonols, such as quercetin, fisetin, and galangin, flavanone glycoside hesperidin also inhibits human pancreatic cancer cells, explaining why lime juice rich in hesperidin has been suggested to possess potential in the prevention of pancreatic cancer.^[124]

The growth of human ovarian cancer cells cannot only be suppressed by several flavones including apigenin, baicalein, luteolin, and wogonin but also by flavonols quercetin and kaempferol. Kaempferol is a good candidate compound for chemoprevention of ovarian cancer; as in human studies, a significant 40% decrease in incidence of ovarian cancer was detected for individuals with the highest quintile of kaempferol consumption compared to those in the lowest quintile.^[106,125] The intake of this nontoxic and inexpensive phytochemical can be easily adopted into the lifestyle of most women.^[126]

Metabolic sites reveal large fluctuations toward flavonoid cytotoxicity

Present in dietary sources mostly as glycosides, flavonoids are cleaved in intestine by microbial enzymes and further metabolized in colon and liver to release into the blood as different conjugates. In this way, the epithelium of intestine is exposed to higher concentrations of flavonoids and their different metabolites than

Table 2: Cytotoxicity of flavonoids on human cancer cell lines derived from various organ sites (mean IC₅₀ ±SE, μM (n)). Cell lines used for assays are presented in Table 3

Flavonoids	Assay time	Bladder	Blood			Bone	
			Altogether	Myeloid	Lymphoid		Erythroid
<i>Flavonols</i>							
Quercetin	24 h	876.9±13.1 (4)	125.7±44.7 (7)	73.7±53.5 (3)	354.7 (1)	101.5±27.5 (3)	136.6±55.5 (4)
	48 h		42.6±8.3 (8)	41.2±6.0 (6)	83.3 (1)	10±2 (1)	91.5±39.6 (4)
	72 h		29.4±5.8 (19)	14.9±7.2 (2)	33.5±9.5 (10)	27.5±7.8 (7)	68.2 (1)
Fisetin	24 h		23.0±7.0 (2)	23.0±7.0 (2)			152.8±4.9 (1)
	48 h		23.5±8.5 (2)	32 (1)		15±2 (1)	127.2±3.7 (1)
	72 h						
Galangin	24 h						
	48 h		21.8±9.8 (2)	31.5 (1)		12±0.8 (1)	
	72 h						
Kaempferol	24 h		99.8±28.8 (4)	78.7±27.8 (3)	163.1 (1)		148.4 (1)
	48 h		42.4±2.3 (3)	40.4±1.8 (2)	46.4 (1)		
	72 h		36.9±9.0 (5)	30 (1)	48.2±2.4 (1)	35.4±15.4 (3)	
Myricetin	24 h	85 (1)	270.7±78.7 (2)	192 (1)	349.3 (1)		
	48 h		101.7±51.0 (3)	51.5±16.0 (2)	202 (1)		
	72 h		29.3 (1)	29.3 (1)			
<i>Glycosides</i>							
Quercitrin	24 h						
	48 h						
	72 h						
Rutin	24 h	>80 (2)	>200 (1)			>200 (1)	
	48 h		>100 (2)	>200 (1)	>100 (1)		
	72 h		420.8±233.8 (2)	187 (1)		654.7 (1)	
<i>Flavanones</i>							
Naringenin	24 h		658.9±41.2 (2)	700±100 (1)	617.7 (1)		
	48 h		152.1±18.9 (6)	171.5±18.5 (2)	164.9±21.8 (3)	75±6 (1)	>100 (1)
	72 h		22.0±1.5 (1)			22.0±1.5 (1)	>100 (1)
Hesperetin	24 h		545.8±45.8 (2)	500±100 (1)	591.6 (1)		
	48 h		274.5 (1)		274.5 (1)		
	72 h		>40 (1)		>40 (1)		
<i>Glycosides</i>							
Naringin	24 h		>100 (2)	>500 (1)	>100 (1)		
	48 h						
	72 h		>40 (1)		>40 (1)		
Hesperidin	24 h						
	48 h						
	72 h		>40 (1)		>40 (1)		
<i>Flavones</i>							
Apigenin	24 h	36 (1)	69.4±19.4 (8)	48.5±6.5 (5)	56.3±16.4 (2)	200 (1)	
	48 h	28 (1)	55.6±12.7 (11)	33.6±4.8 (6)	31.4±4.4 (2)	115.6±18.7 (3)	
	72 h		29.0±5.1 (10)	28.6±5.0 (6)	18.8±5.2 (3)	62.0±2.5 (1)	106.7±4.1 (1)
Baicalein	24 h		106.9±55.3 (3)	53.8±26.3 (2)	213.3 (1)		
	48 h		33.5±8.0 (4)	28.6±8.9 (3)	48.2 (1)		
	72 h		287.0 (1)	21.7±3.3 (6)	22.2±7.8 (2)	21.5±4.1 (4)	>1435 (1)
Chrysin	24 h		84.3 (1)		84.3 (1)		
	48 h		35.0±9.9 (3)	16 (1)	49.1 (1)	40±6 (1)	
	72 h		79.3±0.6 (2)		79.3±0.6 (2)		
Luteolin	24 h	33 (1)	69.4±10.8 (4)	54.8±15.2 (2)	78.1 (1)	90 (1)	
	48 h	25 (1)	45.9±14.0 (5)	26.8±8.4 (2)	18.6 (1)	78.7±8.7 (2)	
	72 h	68.2 (1)	39.1±16.3 (4)	21.7±2.5 (1)	34.2±32.2 (2)	66.3 (1)	70.2±14.3 (3)
Nobiletin	24 h						
	48 h						
	72 h		11.1±1.7 (3)	12.6 (1)	10.3±2.7 (2)		
Tangeretin	24 h						
	48 h						
	72 h		17.9±8.3 (4)		9.7±2.2 (3)	42.4±13.6 (1)	
Wogonin	24 h		96.6±46.6 (2)	96.6±46.6 (2)			
	48 h		17.4 (1)	17.4 (1)			
	72 h		30.2±0.6 (2)		30.2±0.6 (2)		

Contd...

Table 2: Contd....

Table 2: Contd....							
<i>Glycosides</i>							
Baicalin	24 h		>100 (1)		>100 (1)		
	48 h		64 (1)		64 (1)		
	72 h	156.2 (1)	35.1±6.1 (3)	36.8±1.1 (1)	34.2±10.4 (2)		>215 (1)
<i>Flavonoids</i>	Assay time	Breast			Colon	Liver	Lung
		Altogether	ER+	ER-			
<i>Flavonols</i>							
Quercetin	24 h	125.8±52.6 (7)	>100 (4)	138.3±72.2 (3)	44.5±3.5 (2)	147.5±34.3 (9)	113.0±35.8 (7)
	48 h	71.6±27.1 (8)	44.7±11.0 (7)	44.3±21.7 (1)	34.9±7.3 (23)	93.1±12.9 (11)	41.3±13.0 (18)
	72 h	50.6±11.7 (17)	70.4±22.2 (8)	33.1±7.3 (9)	65.2±11.7 (8)	39.7±6.0 (6)	34.8±7.7 (11)
Fisetin	24 h	78.4±3.4 (1)		78.4±3.4 (1)	306.7±121.0 (3)	66.7±6.7 (2)	36.2±16.2 (3)
	48 h	68.5±3.5 (1)		68.5±3.5 (1)	119.7±14.7 (4)	60.8±1.3 (1)	29.4±14.4 (3)
	72 h				50.9±19.8 (6)		
Galangin	24 h					100.4±17.0 (3)	>200 (1)
	48 h				>100 (1)		91.8±1.3 (1)
	72 h						78 (1)
Kaempferol	24 h	52.7±8.3 (3)	69 (1)	44.6±2.4 (2)	83.2±29.6 (2)	>200 (3)	29.7±20.3 (2)
	48 h	53.3±6.5 (2)		53.3±6.5 (2)	61.7±12.7 (8)	84.7±8.5 (1)	46.5±23.5 (4)
	72 h	47.0±2.9 (1)		47.0±2.9 (1)	107.4±43.3 (3)	>200 (1)	18.0 (1)
Myricetin	24 h				>100 (2)	>200 (4)	
	48 h				>100 (6)	>200 (1)	8.1±6.5 (2)
	72 h	62.1±3.5 (1)	62.1±3.5 (1)		68.0±20.4 (2)	>200 (1)	
<i>Glycosides</i>							
Quercitrin	24 h					>400 (1)	
	48 h	>200 (1)	>200 (1)		>200 (1)		>200 (1)
	72 h	>200 (1)	>200 (1)		>100 (1)		
Rutin	24 h	>100 (1)		>100 (1)	>100 (2)	>200 (3)	>200 (1)
	48 h	>100 (3)	>100 (3)		>100 (2)	>200 (3)	>100 (3)
	72 h	>100 (3)	>100 (2)	>100 (1)	>100 (7)	>200 (3)	>100 (2)
<i>Flavanones</i>							
Naringenin	24 h				>200 (3)	>100 (2)	>100 (3)
	48 h	123.4±33.4 (8)	117.5±42.0 (5)	133.1±66.9 (3)	>100 (6)	306.7±38.4 (3)	140.0±38.0 (2)
	72 h	63.1±3.1 (3)	61.6±4.6 (2)	66.2 (1)	134.2±8.8 (1)		>40 (1)
Hesperetin	24 h	>100 (1)	>100 (1)		51.1±19.1 (2)	~100 (1)	
	48 h	75.9±26.6 (5)	86.8±47.1 (3)	59.6±0.0 (2)	95.4±53.6 (2)		>100 (2)
	72 h	49.7±10.0 (2)	39.7 (1)	59.6 (1)	69.4±19.2 (3)		
<i>Glycosides</i>							
Naringin	24 h				>200 (3)	>100 (2)	100 (1)
	48 h	>200 (1)	>200 (1)		>200 (1)		>200 (1)
	72 h				143.6±2.3 (2)		>40 (1)
Hesperidin	24 h						
	48 h	51 (1)	51 (1)		77 (1)		106 (1)
	72 h				60.2±5.0 (2)		>40 (1)
<i>Flavones</i>							
Apigenin	24 h	47.7±12.9 (6)	22.5±5.2 (2)	60.4±15.8 (4)	53.3±8.8 (3)	64.6±5.7 (1)	121.7±88.8 (2)
	48 h	22.8±5.9 (9)	12.6±2.8 (5)	35.5±9.9 (4)	41.0±8.8 (6)	54.8±13.2 (6)	56.6±15.6 (2)
	72 h	20.5±3.7 (10)	16.8±2.5 (6)	26.1±8.3 (4)	51.6±20.6 (7)	38.9±1.1 (1)	32.3±12.3 (3)
Baicalein	24 h	>100 (1)	100 (1)				43 (1)
	48 h	51.2±18.4 (2)	51.2±18.4 (2)		6 (1)	117.5±48.0 (4)	14.7±12.0 (2)
	72 h	24.9±4.2 (3)	26.4±6.8 (2)	21.9 (1)	52.9±3.5 (2)	185.2 (1)	135.4 (1)
Chrysin	24 h	21.3±1.6 (3)	21.2±1.6 (3)			14.0±1.1 (1)	
	48 h	82.5 (1)	82.5 (1)		97.5±39.0 (4)		>100 (1)
	72 h				86.1±35.1 (3)	88.5 (1)	79.8 (1)
Luteolin	24 h	45.5±15.9 (4)	54.9±18.1 (3)	17.2 (1)	73.8±26.2 (2)	63.3±8.8 (3)	49.2±11.4 (4)
	48 h	43.6±16.1 (3)	43.6±16.1 (3)		53.4±13.0 (6)	64.1±11.0 (8)	24.4±9.6 (4)
	72 h	29.9±4.8 (9)	29.7±6.3 (7)	30.4±4.7 (2)	68.7±14.6 (7)	38.4±5.0 (4)	35.9±9.3 (8)
Nobiletin	24 h				66.2±1.3 (1)		>50 (2)
	48 h	1.8±0.4 (4)	2.5±0.5 (2)	1.2±0.0 (2)	148.9±74.4 (4)		31.4±27.9 (2)
	72 h						22 (1)
Tangeretin	24 h				37.5±0.1 (1)		>100 (1)
	48 h	1.0±0.2 (4)	0.7±0.4 (2)	1.3±0.0 (2)	1.6 (1)		3.2 (1)
	72 h				54.6±10.6 (4)		12 (1)

Contd...

Table 2: Contd....

Wogonin	24 h			187.5±32.7 (6)	307.0±2.1 (1)		
	48 h	96.1±3.9 (2)	96.1±3.9 (2)		43.8±7.3 (3)		
	72 h	71.3±2.7 (1)	71.3±2.7 (1)		24.6±0.6 (1)		
<i>Glycosides</i>							
Baicalin	24 h	206 (1)	206 (1)			46.9±4.3 (2)	
	48 h	78.8 (1)	78.8 (1)				
	72 h	44.7±18.7 (2)	44.7±18.7 (2)		44.8 (1)	87.4 (1)	
Flavonoids	Assay time	Melanoma	Mouth	Esophagus	Ovary	Pancreas	Stomach
<i>Flavonols</i>							
Quercetin	24 h	2.0±0.3 (2)	87.5±54.6 (4)	63.0±15.0 (2)			
	48 h	7.3±5.3 (3)	94 (1)	100.0±0.0 (2)	20.7±0.7 (1)		59.0±20.4 (6)
	72 h	24.7±13.3 (2)	36.0±7.0 (3)		44.6±9.2 (7)	13.0±2.5 (4)	52.0±42.0 (4)
Fisetin	24 h	80 (1)	200.7±97.2 (3)			48 (1)	
	48 h	37.2 (1)				38 (1)	
	72 h	17.5 (1)					
Galangin	24 h					22.1 (1)	100 (1)
	48 h						
	72 h		50 (1)				
Kaempferol	24 h	137.2±8.6 (2)	743 (1)	91.5±19.5 (2)			
	48 h	97.8±39.7 (3)	35 (2)		28.7±1.1 (1)		
	72 h	21.1 (1)			20 (1)		>40 (1)
Myricetin	24 h			219.0±14.0 (2)			
	48 h	5.7±3.8 (2)					
	72 h	>50 (3)					
<i>Glycosides</i>							
Quercitrin	24 h						
	48 h	>200 (1)					
	72 h		>200 (1)				
Rutin	24 h					306.4±9.1 (1)	
	48 h	>200 (1)				81.0±11.0 (1)	
	72 h					68.3±5.3 (1)	>40 (2)
<i>Flavanones</i>							
Naringenin	24 h						>100 (1)
	48 h	43.3±21.9 (3)				237±43 (1)	363.5±43.5 (2)
	72 h			452±24 (1)			>180 (1)
Hesperetin	24 h	>50 (1)					
	48 h	60 (1)					>125 (1)
	72 h	>50 (4)					>40 (1)
<i>Glycosides</i>							
Naringin	24 h						>100 (1)
	48 h	>200 (1)					
	72 h						>40 (1)
Hesperidin	24 h					241.1±9.4 (1)	
	48 h	>200 (1)				43.0±0.8 (1)	
	72 h					27.3±1.3 (1)	>40 (1)
<i>Flavones</i>							
Apigenin	24 h	71.0±52.1 (3)	40 (1)	131.5±19.5 (2)		87.8±10.2 (6)	
	48 h	27.5±13.5 (2)					22 (1)
	72 h	28.7±21.7 (2)	30.7±17.0 (3)		7.9 (1)		16.1±2.9 (2)
Baicalein	24 h		>200 (1)				
	48 h	7.7±0.5 (1)	>100 (1)				26 (1)
	72 h	>50 (3)	>1435 (1)		32±2.6 (1)		37.9±21.6 (2)
Chrysin	24 h	>50 (1)	64.3±28.8 (3)	85.0±22.0 (2)		88.7 (1)	
	48 h						51.8±11.2 (2)
	72 h	30.0±20.0 (2)	13±2 (1)		Not active (1)		
Luteolin	24 h	13.3±4.9 (2)		63.2±14.6 (3)			50 (1)
	48 h	17.1±7.5 (3)				75 (1)	30.3±0.7 (2)
	72 h	6.9 (1)	55.0±22.3 (3)		7.1 (1)		20.3±5.2 (5)
Nobiletin	24 h						
	48 h	0.5 (1)					174.3±21.0 (4)
	72 h						8.3 (1)
Tangeretin	24 h		19.3 (1)				
	48 h	0.3 (1)					
	72 h	>50 (3)					6.5 (1)

Contd...

Table 2: Contd....

Flavonoids	Assay time	PROSTATE		UTERINE	References	
		AR+	AR-			
Wogonin	24 h 48 h 72 h				19.9±1.2 (1)	
Glycosides Baicalin	24 h 48 h 72 h		>215 (1)		64.3 (1)	
FLAVONOLS						
Quercetin	24 h 48 h 72 h	72.2±11.5 (6) 71.8±23.7 (4) 62.8±28.8 (6)	75 (1) 1.3±0.0 (1) 22.2±2.8 (2)	78.9±14.0 (5) 95.3±4.7 (3) 83.1±40.8 (4)	80 (1) 34.1 (1) 5 (1)	[152]
Fisetin	24 h 48 h 72 h	~50 (3) 48.0±3.7 (5) 27.6±4.9 (2)	~50 (2) 45.0±2.9 (4) 22.7 (1)	~50 (1) ~60 (1) 32.5 (1)	60.6±8.6 (2) 47.7±11.7 (2)	[2,5,141,142,153,154,156,157,195-203]
Galangin	24 h 48 h 72 h					[5,7,39,161,196,197,203-206]
Kaempferol	24 h 48 h 72 h	94.9 (1) 52.6±42.5 (2) 37.6±10.0 (3)	94.9 (1) 10.1±0.3 (1) 52.5 (1)	>100 (1) 95 (1) 30.2±11.7 (2)		[23,46,49,60,86,125,195,196,198,199,203,205,207-228]
Myricetin	24 h 48 h 72 h	67.0±30.3 (3) >100 (2)	6.6±0.1 (1) >100 (1)	94.2±2.8 (2) >100 (1)		[26,46,51,60,69,96,111,145,196,198,199,203,209,210,218,221,226,227,229-233]
Glycosides Quercitrin	24 h 48 h 72 h					[217,221,233-236]
Rutin	24 h 48 h 72 h	>200 (2) >200 (1)		>200 (2) >200 (1)		[49,124,129,145,161,167,196,199,214,217,228,230,237-247]
FLAVANONES						
Naringenin	24 h 48 h 72 h		150 (1)	~100 (1) 233.0±10.0 (2) 23.9±1.5 (1)		[5,8,10,18,24,46,60,136,161,168,208,212,217,228,238,248-256]
Hesperetin	24 h 48 h 72 h	181 (1)		650 (1) >100 (2)		[60,65,69,96,97,128,136,161,171,199,208,217,224,228,232,244,251,252,254,257]
Glycosides Naringin	24 h 48 h 72 h	>200 (1)		>200 (1)	750 (1)	[8,10,11,102,199,217,228,238]
Hesperidin	24 h 48 h 72 h	101 (1) >100 (2)		101 (1) >100 (2)		[124,199,217,228,258]
FLAVONES						
Apigenin	24 h 48 h 72 h	35 (1) 28.5±8.5 (2) 30.9±5.1 (5)	20 (1) 25.0±5.0 (2)	37 (1) 34.8±7.7 (3)	33.3±4.3 (1) 12.8±2.2 (2) 8.8±0.8 (7)	[30,35,49,57,60,61,99,108,114,127,130,136,149,150,180,196-201,206,209,212,214,217,220,222,224-227,247,249,259-282]
Baicalein	24 h 48 h 72 h	~25 (2) 36.3±6.7 (10)	35.3±11.2 (5)	~25 (2) 37.2±8.6 (5)	30 (1) 36.2 (1)	[60,69,85,96,98,114,117,144,185,199,203,232,247,252,254,261,281-296]
Chrysin	24 h 48 h 72 h	24.5±0.1 (1) 32.7±24.2 (2)	56.8 (1)	24.5±0.1 (1) 8.5±0.0 (1)	22.8±3.8 (1) 15.2±7.2 (2) 13.6±0.6 (2)	[5,17,46,60,99,108,110,114,161,188,197,199,203,206,214,226,227,270,282,297-299]
Luteolin	24 h 48 h 72 h	32 (1) 23.5±5.3 (2)	18.2 (1)	32 (1) 28.8 (1)	10 (1) 13.4±6.7 (3)	[15,30,46,49,60,64,71,93,100,114,123,145,196,199,203,207,214,217,220,222,224-228,242,249,261,272,276,283,294,300-315]

Contd...

Table 2: Contd...

Nobiletin	24 h					[53,107,118,136,145,191,217,228,287,316]
	48 h	1 (1)		1 (1)		
	72 h					
Tangeretin	24 h					[69,96,108,136,145,175,191,199,217,228,232,287,317]
	48 h	0.5 (1)		0.5 (1)		
	72 h					
Wogonin	24 h	58.5±1.5 (2)	58.5±1.5 (2)			[117,192,261,282,287,312,318-324]
	48 h			17.0±2.4 (1)		
	72 h	53.0±13.0 (4)	36.0±6.1 (2)	70.0±20.0 (2)		
<i>Glycosides</i> Baicalin	24 h					[98,144,194,203,283,286,292,326]
	48 h					
	72 h	53.0±2.9 (4)	56.8±4.0 (2)	49.2±2.4 (2)	39.8 (1)	

Table 3: Human cancer cell lines used for cytotoxicity assays of flavonoids

Organ sites	Model cancer cell lines used for cytotoxicity assays
Bladder	BFTC905, EJ, J82, RT112, T24, TSGH8301
Blood	
Myeloid	Primary CD38+/MPC-1- immature myeloma cells, HL-60, RAW264.7, RPMI8226, THP-1, U937
Lymphoid	232B4, CCRF-CEM, CCRF-HSB-2, CEM, Daudi, Jurkat, MOLT-4, P3HR1, Raji
Erythroid	K562
Bone	6647, HOS-1, MG-63, PDE02, SaOs-2, SW872, TC106, U2OS, U2OS/MTX300
Breast	
ER+	Bcap-37, MCF-7, T47D, ZR-75-1
ER-	AS-B145, AS-B244, HCC1937, MDA-MB-231, MDA-MB-235, MDA-MB-435, MDA-MB-453, MDA-MB-468
Colon	Caco-2, COL-2, COLO201, COLO205, COLO320, COLO320HSR, HCT15, HCT116, HT-29, LoVo, LS180, LT97, MS-174T, NCOL-1, RKO, SNU-C4, SW480, T84, VACO235, WiDr
Liver	BEL-7402, HA22T, HA22T/VGH, Hep3B, HepG2, HLF, HuCC-T1, Huh-7, KIM-1, PLC/PRF/5, QGY7701, SK-Hep1, SMMC7721
Lung	A549, ChaGo-K1, COR-L23, DMS-114, GLC4, H441, H460, H461, H520, H661, H1299, H1792, LNM35, Lu-1, NCI-ADR/RES, SK-LU1, SW900
Melanoma	451Lu, A375, A375-C5, C32, MEL-2, OCM-1, SK-MEL1, SK-MEL5, SKMEL-28, UACC-62
Mouth	Ca9-22, Hep2, HSC-2, HSC-3, HSG, KB, OSCC-1/KMC, SCC-9, SCC-25, SCC B56
Esophagus	EC9706, Eca-109, KYSE-510, OE33, SNO
Ovary	A2780, OVCAR-5, SK-OV3
Pancreas	AsPC-1, CD18, EPP85-181P, EPP85-181RDB, MiaPaca-2, PANC-1, Panc-28, PK-1, S2-013
Prostate	
AR+	22Rv1, CWR22v1, LNCaP
AR-	DU-145, JCA-1, PC-3
Stomach	AGC, BON, EPG85-257P, EPG85-257RDB, HGC-27, KATO III, MGC-803, MK-1, MKN-7, MKN-28, MKN-45, MKN-74, NUGC-2, SGC-7901, SNU-484, TGBC11TKB, TMK-1,
Uterine	HeLa, RL95-2, SiHa

ER=Estrogen receptor, AR=Androgen receptor

the tissues at other locations; and this would also be true for the colonic tumor cells, showing that colorectal cancer appears most relevant to dietary factors.^[45,127] At the same time, the exposure

to different metabolites can explain the large fluctuations in cytotoxic constants of flavonoids measured using colorectal and liver cancer cell lines. It is possible that some metabolites could be more cytotoxic than parent compounds, giving a selective anticancer activity advantage *in vivo*.

The other aspect important to take into consideration by analyzing the cytotoxic data of flavonoids includes their differential effect against tumors with specific mutational spectra. The differential effectiveness of inhibition of cell growth and arresting cell cycle in response to flavonoids in various colorectal cancer cell lines may be associated with the functional status of p53 and/or ras genes. While apigenin has been indicated to have stronger effect on tumors with mutations in genes which are critical to colon cancer development, thus being more effective in controlling the growth of tumors with certain mutational spectra and less effective in wild-type normal cells,^[29,46,127] kaempferol and hesperetin seem to exhibit higher resistance toward mutant p53 human colon cancer cell lines.^[125,128]

Some other flavonoids including quercetin and baicalein have also been shown to be useful agents for prevention and treatment of colon cancer [Table 2]. However, compared to quercetin and baicalein, their glycosides rutin and baicalin, respectively showed no growth inhibitory effects on colon cancer cells,^[20,129] showing that the sugar moiety strongly affects the bioactivity of flavonoids.

Accumulated evidences have indicated that the growth of hepatocarcinoma cells can be suppressed by flavones apigenin, luteolin, wogonin, and baicalin, thus being valuable for the therapeutic intervention of human hepatomas [Table 2]. Apigenin may have some implications also in the prevention of virus infection, leading to liver cancer development;^[130] wogonin possesses hepatoprotective activities against diverse pathophysiological processes associated with hepatocarcinogenesis and can be extremely competitive as anticancer drugs against malignant hepatoma.^[131,132]

Blood cells are potent target sites for flavonoids

Anticancer drugs are generally more effective against leukemia than other malignancies and in this aspect flavonoids are similar to other anticancer agents.^[24] The mean cytotoxic constants of various flavonoids on different blood cancer cells are depicted in the Figure 2 showing that many common dietary polyphenols

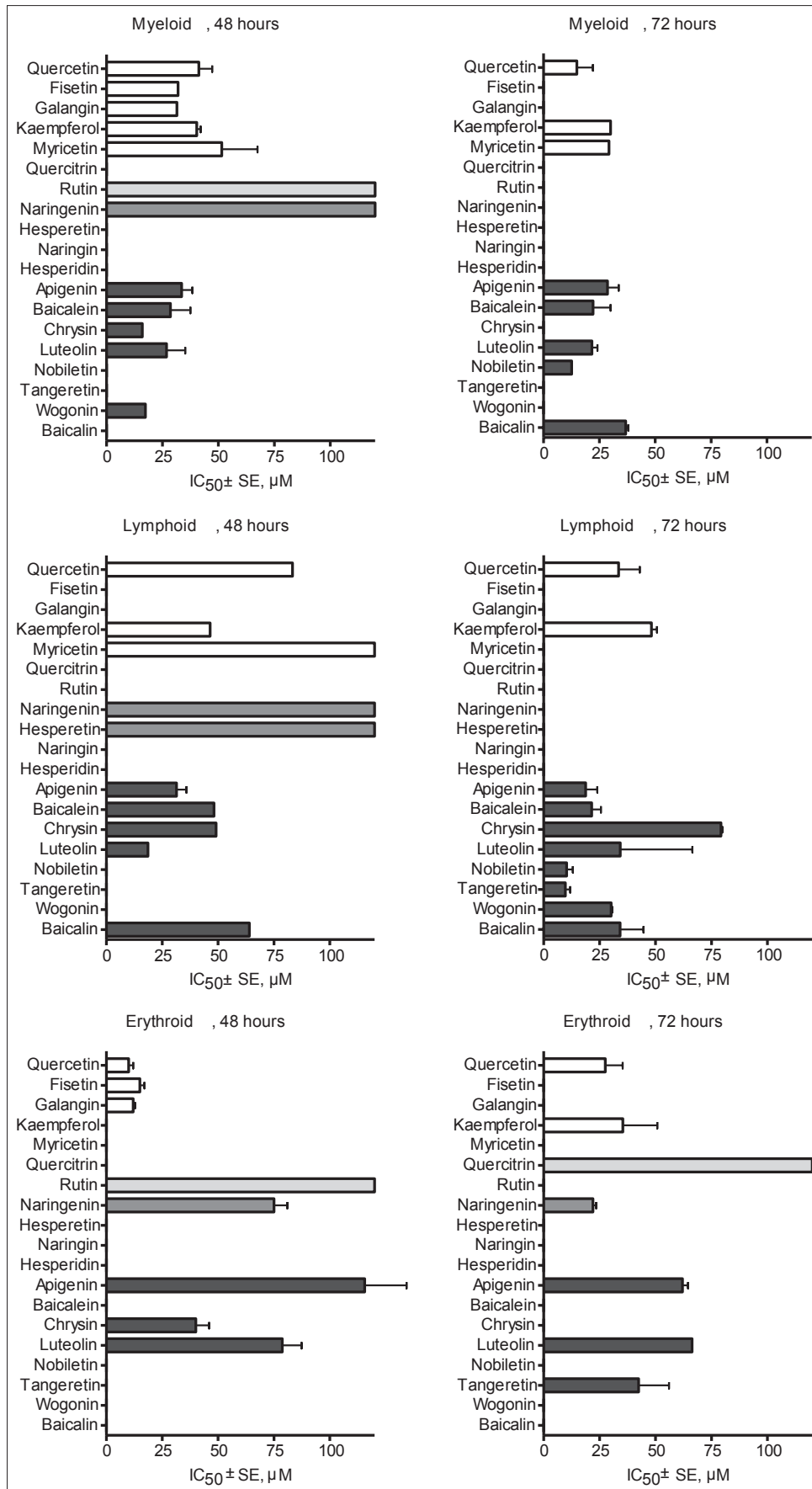


Figure 2: Cytotoxic effect of flavonoids on different human blood cancer cell lines

exhibit growth inhibitory properties against several human hematologic malignancies.

Flavonoids hold much promise for the development of new chemotherapeutics in myeloid and lymphoid leukemias.^[133-135] In general, flavonol aglycones (quercetin, kaempferol, myricetin) seem to exhibit somewhat stronger cytotoxic activity against blood cancer cells of myeloid lineage compared to lymphocytic leukemia cell lines, whereas flavonol glycosides have no effect on the viability of different blood cancer cells. In contrast to the inactivity of flavanone naringenin in myeloid and lymphoid leukemia cell lines, this dietary polyphenol exerts cytotoxicity on erythroleukemia cells, thus revealing an opposite situation to flavones (apigenin, luteolin, tangeretin) in which cases strong anticancer activity has been measured in cell lines of myeloid and lymphoid lineages but significantly lower sensitivity is expressed toward erythroleukemia cells [Figure 2]. This knowledge could be specifically applied in chemoprevention as well as clinical trials for treatment of different hematologic malignancies.

Polyphenols affecting both hormone-dependent and -independent tumor cells

Breast and prostate cancers are hormone-dependent tumors as their development and growth can be dependent on the expression of estrogen receptors (ER) and androgen receptors (AR), respectively.

Most breast cancers are heterogeneous and consist of ER-positive and -negative cells. Therefore, agents that are able to inhibit the growth of both ER-positive and -negative tumors are of great interest.^[136] Dietary flavonoids seem to display such dual activity, inhibiting both receptor-positive and -negative breast cancer cells [Table 2]. For instance, no difference in the cytotoxicity of naringenin has been found between human breast cancer cell lines expressing or not expressing ERs^[24] and the regular intake of this flavanone may slow down the rate at which breast cancer cells proliferate.^[103] High flavone intake has also been significantly correlated with a lower risk of breast cancer^[68] and apigenin, baicalein, and luteolin may be promising candidate agents in the treatment of mammary tumors.^[137-139] However, although apigenin can target both ER-dependent and -independent pathways, it seems to be somewhat more potent on ER-positive human breast cancer cell lines [Figure 3], thus providing more promise for the treatment of ER-positive tumors.

AR are the critical factors for the prostate cancer cell growth and survival and in the development of ablation-resistant prostate tumors. As presented in Table 2, flavonoids display anticancer effects both in AR-positive and -negative prostate cancer cell lines. However, flavonol aglycones (quercetin, fisetin, galangin, kaempferol, and myricetin) exert somewhat stronger cytotoxic activity on AR-dependent prostate cancer cells [Figure 4]. Indeed, quercetin has been shown to decrease the androgen receptor expression in 22rv1 human prostate cancer cells,^[140] whereas fisetin can inhibit the AR signaling pathways^[141,142] showing that these compounds may afford more health benefits in chemoprevention

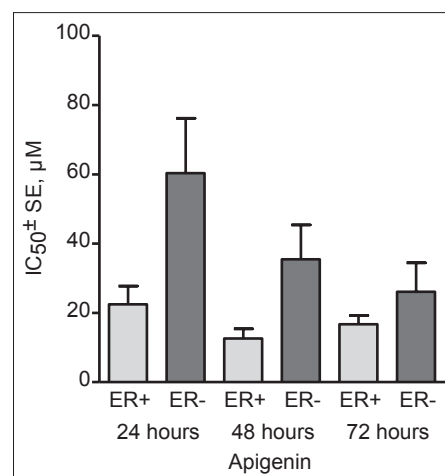


Figure 3: Cytotoxic effect of apigenin on human breast cancer cell lines depending on the expression of estrogen receptors

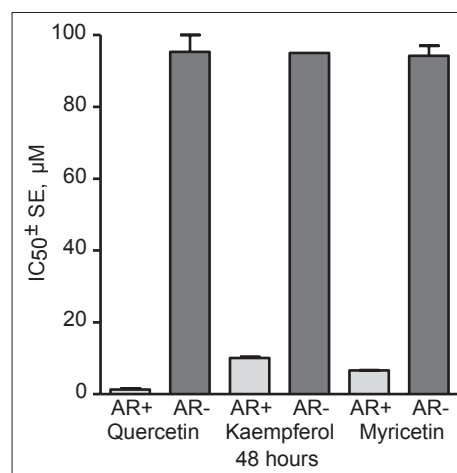


Figure 4: Cytotoxic effect of flavonols on human prostate cancer cell lines depending on the expression of androgen receptors

and earlier stages of prostate carcinogenesis when the tumor is still dependent on the presence of androgens. In contrast, flavanone naringenin seem to display only very low potency toward AR-positive human prostate cancer cells, suppressing at the same time the growth of androgen-independent human prostate cancer lines. Flavones like apigenin, baicalein, and baicalin express rather similar pattern of growth inhibition of both AR-positive and -negative prostate carcinoma cells, thus being independent on androgen receptor status.^[66,143,144] Flavonoid treatment may offer an alternative strategy to suppress androgen-insensitive prostate tumor growth and flavonoids like naringenin, apigenin, baicalein, chrysin, and luteolin may be developed as promising chemotherapeutic agents against advanced and androgen-independent human prostate tumors.

With regards to the structure of flavonoids and nature of substituents, it is especially important to point out the fact that methylation of the hydroxyl groups does not reduce the anticancer capacity but even increases it.^[61,69] Therefore, polymethoxylated flavonoids, such as tangeretin and nobiletin,

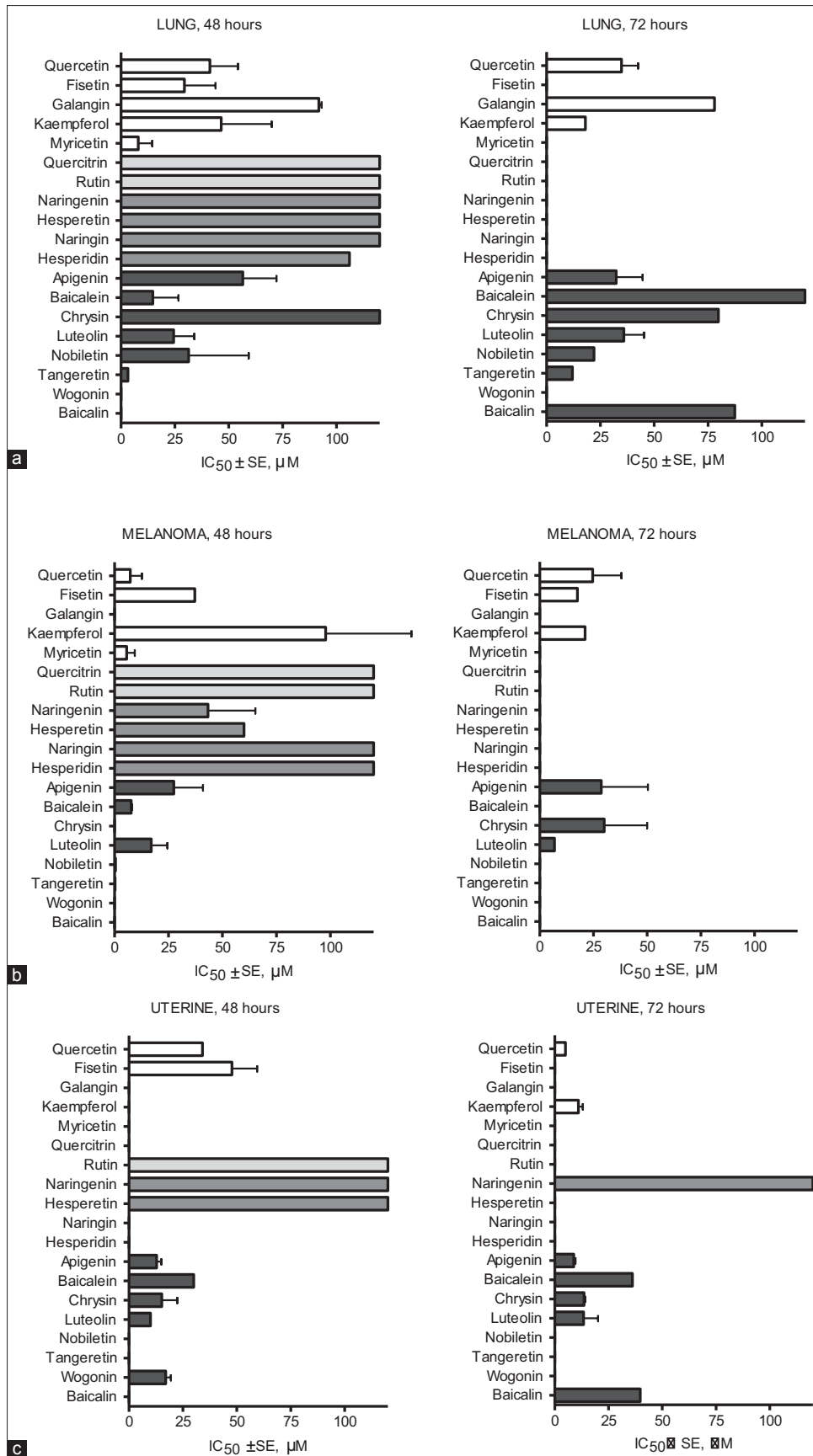


Figure 5: Cytotoxic effect of flavonoids on different human lung cancer cell lines (a), melanoma cell lines (b), and uterine cancer cell lines (c)

can be much more potent inhibitors of tumor cell growth than free hydroxylated flavonoids^[69,145] [Table 2].

Lung and uterine cancer as well as melanoma cells are strongly affected by flavonoids

Cytotoxic effects of flavonoids on malignant cell lines derived from human lung and cervical cancers as well as melanoma are depicted in Figure 5. Several flavonol aglycones are able to cause decrease in cell viability with half-maximal cytotoxic doses in low micromolar range [Table 2], revealing the most potent cytotoxic activity for myricetin in lung cancer cells and quercetin in melanoma and cervical cancer cells. Flavanones display no growth inhibitory effect on lung and cervical cancer cell lines, expressing at the same time some cytotoxicity on human melanoma cells.

Several members of the flavone group display high cytotoxic activity against cervical cancer cells. Apigenin is probably more potent and sensitive in killing cervical cancer cells than cells of melanoma and lung cancer; the same seems to be true also for chrysin. Luteolin exerts high-level activity both in cervical cancer as well as melanoma cell lines, showing that these flavones may have good perspectives as lead compounds of potent antitumor agents for the respective target sites. On the other hand, polymethoxylated flavones nobiletin and tangeretin are among the most effective at inhibiting cancer cell growth of melanoma and lung (tangeretin) and it is also the reason why these dietary polyphenols have emerged as potential drug candidates for treatment of these malignancies [Table 2, Figure 5].

CONCLUSIONS AND FURTHER PERSPECTIVES

Flavonoids can play important beneficial roles in human nutrition and health status and chemoprevention is one of the most realistic and promising approaches for the prevention of malignant disorders.^[76,118] Diet–health relationships are very complex as food items usually act through multiple pathways and each ingredient can have different molecular targets. It is also the reason why phytochemical combinations may offer greater chemoprevention than administration of single agents alone.^[110] Both additive as well as synergistic interactions between several dietary flavonoids have been reported,^[101,146] contributing to the health benefits of fruits and vegetables. Therefore, consumers may gain more significant health benefits from whole foods than from intake of dietary supplements.^[146] However, individual phenolic compounds may also act antagonistically with other components,^[147,148] and further efforts are necessary to understand their action modes as well as to provide further information for the cancer prevention in future.^[149]

Flavonoids are not only promising food-derived cancer preventive compounds but could also be considered as candidates for chemotherapeutic agents, revealing potential clinical significance in the cancer treatment.^[73,150] Polyphenolic compounds like quercetin, myricetin, apigenin, baicalein, chrysin, luteolin, nobiletin, and tangeretin might be valuable agents in anticancer strategies and

studies of their clinical use for development of novel drugs should be continued. Beneficial effects have been described also by combining certain flavonoids with standard chemotherapeutic drugs leading to decrease in the dosage and associated toxicity while targeting specific resistance mechanisms. In this way, the genotoxic damage caused by standard chemotherapeutics to normal cells can be diminished, thereby reducing the chance of developing of secondary cancers.^[45,151] Further work is certainly needed to develop and produce novel drugs from natural sources introducing structural variations into the backbone of flavonoids and modifying their structures to further improve biological activity and exhibit more potent anticancer effects.

Despite a rather short period of investigation of the anticancer action of flavonoids (for instance, apigenin was first proposed to interfere with the process of carcinogenesis only in 1980s),^[45] this field has undergone an extensive development. The cytotoxic data of flavonoids compiled within the current work and relationships presented in this review article cannot only be useful in chemoprevention to choose the food items containing most active natural polyphenols on malignant cells of certain cancer types, considering the individual genetic cancer risks and familial anamnesis but also in the selection of parent compounds to design and synthesize novel chemotherapy drugs starting from the valuable material given to us by the nature.

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