Content of Potentially Anticarcinogenic Flavonoids of 28 Vegetables and 9 Fruits Commonly Consumed in The Netherlands

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The content of the potentially anticarcinogenic flavonoids quercetin, kaempferol, myricetin, apigenin, and luteolin of 28 vegetables and 9 fruits was determined by RP-HPLC with UV detection. Fresh foods were purchased in a supermarket, a grocery, and a street market and combined to composites. Processed foods were purchased additionally. Sampling was carried out in spring, summer, winter, and spring of the following year. Quercetin levels in the edible parts of most vegetables were generally below 10 mg/kg except for onions (284–486 mg/kg), kale (110 mg/kg), broccoli (30 mg/kg), French beans (32–45 mg/kg), and slicing beans (28–30 mg/kg). Kaempferol could only be detected in kale (211 mg/kg), endive (15–91 mg/kg), leek (11–56 mg/kg), and turnip tops (31–64 mg/kg). In most fruits the quercetin content averaged 15 mg/kg, except for different apple varieties in which 21–72 mg/kg was found. The content of myricetin, luteolin, and apigenin was below the limit of detection (<1 mg/kg) except for fresh broad beans (26 mg/kg myricetin) and red bell pepper (13–31 mg/kg luteolin). Seasonal variability was low for most vegetables except for leafy vegetables with highest flavonoid levels in summer. These collective data provide a base for an epidemiological evaluation of possible anticarcinogenic effects of flavonoids.

INTRODUCTION

Flavonoids are diphenylpropanes (C_6–C_3–C_6; Figure 1) occurring ubiquitously in food plants and are a common component in the human diet. Flavonoids occur in foods generally as *O*-glycosides with sugars bound usually at the C3 position. Average intake of all flavonoids is estimated to be 1 g/day (Kuhnau, 1976). Precise data on the occurrence of flavonoids in vegetables and fruits are, however, lacking. Food-derived flavonoids such as the flavonols quercetin, kaempferol, and myricetin have antimutagenic and anticarcinogenic effects in vitro and in vivo (Kato et al., 1983; Huang et al., 1983; Fujiki et al., 1986; Mukhtar et al., 1988; Verma et al., 1988; Francis et al., 1989; Wei et al., 1990; Deschner et al., 1991). Epidemiological research on the relation between flavonoid intake and cancer risk in humans is needed to support the findings of these experimental studies. In a large number of epidemiological studies investigating relations between diet and cancer, a protective effect of the consumption of vegetables and fruits on various forms of cancer is found (Steinmetz and Potter, 1991). This protective effect is generally attributed to vitamin C and β-carotene present in these foods. However, the significance of other potentially protective compounds such as flavonoids present in vegetables and fruits has become an important issue (Wattenberg, 1985, 1990).

So far, little attention has been paid to quantitative aspects of the determination of flavonoids in foods. Furthermore, the limited data published were mainly obtained with thin-layer chromatography followed by a spectrophotometric measurement (Wöldecke and Herrmann, 1974; Herrmann, 1976; Starke and Herrmann, 1976). More recently, Bilyk and co-workers published results of flavonoid analyses in foods based on high-performance liquid chromatography (HPLC) and ultraviolet detection (Bilyk et al., 1984; Bilyk and Sapers, 1985, 1986) in a limited number of foods.

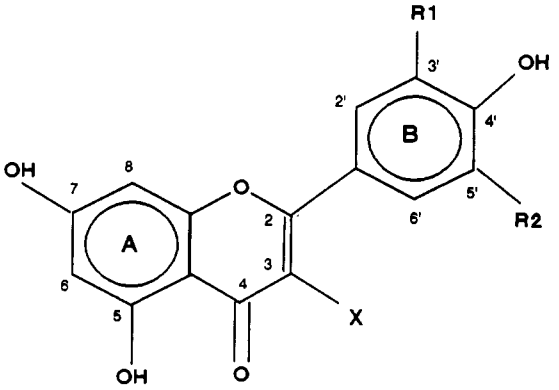

Figure 1. Structure of flavonoids. Flavonols: X = OH; quercetin, R1 = OH, R2 = H; kaempferol, R1 = H, R2 = H; myricetin, R1 = OH, R2 = OH. Flavones: X = H; apigenin, R1 = H, R2 = H; luteolin, R1 = OH, R2 = H.

Flavonoids consist mainly of anthocyanidins, flavonols, flavones, catechins, and flavanones (Herrmann, 1988). We selected three major flavonols, quercetin, kaempferol, and myricetin, and two major flavones, luteolin and apigenin, because these flavonoids are most widely investigated in anticarcinogenesis studies. We developed a HPLC method for the identification and quantification of these flavonoids in freeze-dried foods (Hertog et al., 1992). We have now measured the content of these flavonoids of 28 types of vegetables and 9 types of fruits commonly consumed in The Netherlands and studied the effect of season and processing on flavonoid levels.

MATERIALS AND METHODS

Sources and Preparation of Samples. Vegetables and fruits were selected for sampling on the basis of data provided by a nationwide food consumption survey conducted among a representative population sample. Two-day dietary records were collected for 5898 subjects (2000 households) in 1987–1988 (Hulshof and Van Staveren, 1991). The survey provided data on

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food consumption, locations where particular foods were purchased, and whether foods were bought fresh or processed, i.e., canned, in glass jars, or frozen. Twenty-eight types of vegetables and 9 types of fruits commonly consumed in The Netherlands were selected (Tables I and II). Citrus fruits were excluded because they contain almost exclusively flavanones (Herrmann, 1976).

Foods were sampled in four periods (April 1991; August 1991; December 1991; and April 1992) unless, according to the survey, a particular food was bought less than 1% of the yearly total in that specific period. However, fresh garden beans and fresh peas were purchased only in July 1991 because they were not available in other periods. Although broccoli is not commonly consumed in The Netherlands, it is gaining popularity and was therefore sampled only in April 1992. All foods were generally only purchased as fresh products; whenever the survey indicated that a particular food was consumed at more than 5% as a processed product, this product was purchased additionally. No varietal differences were studied with the exception of apples (six varieties) and pears (three varieties), which were bought in the period when the specific variety was most easily available.

Fresh foods (1 kg, or a minimum of three units) were bought on the same day at three locations: an outlet of a nationwide supermarket chain (Albert Heijn), a local grocery, and an open-air street market. Fresh foods were cleaned within 24 h, nonedible parts removed, and samples combined per product to a composite in proportions reflecting sales in the three locations. Typically, for most foods the sample bought at the supermarket accounted for 65%, the grocery sample for 20%, and the street market sample for 15% of the composite sample. Food samples were chopped under liquid nitrogen and immediately stored at −20 °C for less than 2 weeks until they were lyophilized.

Processed foods were purchased in the supermarket within 1 week after the fresh products. Three major brands (one unit each) of each product were bought in cans or glass jars or frozen as indicated in the survey. The three brands were mixed in equal portions (net weight) and immediately stored at −20 °C for less than 2 weeks until lyophilized.

After lyophilization, samples were allowed to equilibrate in open air and ground to pass a 0.5-mm sieve. Sugar-containing foods were frozen in liquid nitrogen and ground to a fine powder. Moisture was measured by drying at 80 °C in a vacuum oven. The food samples were stored at −20 °C for less than 4 months until analyzed.

Methods of Analysis. Five major food flavonoids, viz. quercetin, kaempferol, myricetin, luteolin, and apigenin, were determined in freeze-dried foods after extraction and acid hydrolysis of the flavonoid glycosides. Development, optimization, and validation of this method were described in detail before (Hertog et al., 1992). In brief, flavonoid glycosides were extracted and hydrolyzed to their aglycons with HCl in 50% aqueous methanol. Subsequently, the resulting aglycons were quantified by RP-HPLC on a Nova-Pak C_{18} column using acetonitrile/phosphate buffer (25/75 v/v, pH 2.4), as mobile phase, and UV detection (370 nm). To confirm peak identity, sample extracts were reinjected, using methanol/phosphate buffer (45/65 v/v, pH 2.4) as mobile phase. In addition, peak identity and purity were confirmed using a photodiode array detector to record UV spectra of the flavonoids in samples on-line.

As completeness of hydrolysis depends on the type of glycoside, optimum hydrolysis conditions in samples with an unknown flavonoid glycosylation pattern had to be determined. All samples were first analyzed after hydrolysis in 1.2 M HCl for 2 h. Subsequently, samples containing flavonols were reanalyzed after 4 h of hydrolysis. A 10% higher flavonoid content in the second analysis than in the first indicated the presence of flavonol glucuronides. In that case the sample was analyzed a third time using 2.0 M HCl and a hydrolysis period of 2 h. Also, if the first analysis revealed the presence of the flavones apigenin and luteolin, the samples were reanalyzed after 4 h of hydrolysis in 2.0 M HCl.

Limit of detection was defined as the amount of flavonoids resulting in a peak height of 3 times the standard deviation of the baseline noise.

Analytical Quality Control. Control samples were included with each series of samples. Batches of three different control samples sufficient for the whole project were made up of lyophilized vegetables containing the various flavonoid glycosides. Control sample A, containing flavonol glucosides, was made by mixing onion and leek (1:9 w/w). Celery, containing the flavone glycosides luteolin and apigenin, was used as control sample B for the analysis of foods containing flavones. Control sample C, containing flavonol glucuronides, was composed of lettuce and endive (1:1 w/w). Control samples were stored at −20 °C. At the start of the project the flavonoid content of the control samples was determined by five duplicate analyses on different days within a period of 2 weeks to obtain within-laboratory standard deviation of reproducibility (SD_R).

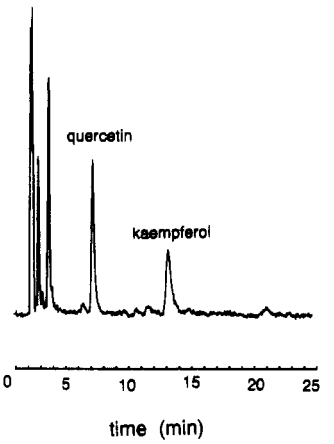

Figure 2. Typical chromatogram of a French bean extract monitored in 25% acetonitrile/phosphate buffer (pH 2.4). Detection at 370 nm; 0.01 AUFS; flow rate 0.9 mL/min.

For each series of analyses, stability of flavonoid calibration standards in methanol was checked spectrophotometrically at 375 (flavonols) and 340 nm (flavones) after dilution of the stock solution to 10 μg/mL in methanol. Standard solutions proved to be stable for over 3 months at 4 °C. Myricetin had degraded up to 10% after 1 month, and the stock solution was therefore made up freshly before every period of analysis.

Each series of analyses included one control sample corresponding to the glycosides expected and three calibration standards placed at the beginning and ending of the series. All determinations were carried out in duplicate. Differences between duplicates of more than 15% were not accepted. Series of analyses were repeated whenever the flavonoid content of the control sampled exceeded the confidence limits (mean ± 3 SD_R). Accepted results of the control samples are reported in Table III. Regression analysis of results of the control sample did not reveal any significant correlation between flavonoid content and time of analysis. An exception was luteolin in control sample B which, at the end of the project, had been degraded to 71% of the original level. This is also reflected in a high CV of the long-term variability. However, the apigenin content in the same control sample remained stable over the 1.5-year period. Control sample A was used for both analyses with hydrolysis periods of 2 and 4 h as described under Methods of Analysis. In general, long-term variability of the method was low (CVs < 10%). It is concluded that stability of flavonoids in freeze-dried foods stored at −20 °C is adequate over a 1.5-year period. The low variation in flavonoid levels of the control samples demonstrates the absence of a significant long-term variability of flavonoid analysis in the laboratory.

RESULTS AND DISCUSSION

For almost all products the initial step using 1.2 M HCl and a hydrolysis period of 2 h yielded the highest flavonoid levels. Only lettuce, endive, leek, broccoli, French beans, and slicing beans had to be hydrolyzed with 2.0 M HCl for 2 h. These results suggest that the major glycosides present in lettuce, endive, leek, broccoli, French beans, and slicing beans are glucuronides. This is in accordance with Herrmann (1988) with the exception of broccoli and leek, in which the major glycosides were reported to be quercetin

Table I. Flavonoid Content[a] of 28 Vegetables Sampled in Four Periods

product	scientific name	quercetin April 1991	quercetin Aug 1991	quercetin Dec 1991	quercetin April 1992	quercetin mean[b]	kaempferol April 1991	kaempferol Aug 1991	kaempferol Dec 1991	kaempferol April 1992	kaempferol mean[b]
mushroom	*Agaricus campester* Fr.	<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
processed		<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
onion	*Allium cepa* L.	332	347	284	486	347 ● 63	<2	<2	<2	<2	<2
leek	*Allium porrum* L.	<1	<1	<1	<1	<1	31	56	11	16	30 ± 23
red beet	*Beta vulgaris* L. cv. Rubra L.	<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
turnip tops	*Brassica campretis* L.	10			4.6	7.3	64			31	48
kale	*Brassica oleracea* L. cv. Acephala DC.			110		110			211		211
processed				47	43	45			156	212	184
sauerkraut	*Brassica oleracea* L. cv. Alba DC.	<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
white cabbage	*Brassica oleracea* L. cv. Alba DC.	<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
cauliflower	*Brassica oleracea* L. cv. Botrytis L.	<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
Brussels sprout	*Brassica oleracea* L. cv. Gemmifera DC.			<1		<1			7.4		7.4
broccoli	*Brassica oleracea* L. cv. Italica L.				30	30				72	72
Swedish turnip	*Brassica napus* L. cv. Napobrassica RCh	<1	<1		<1	<1	<2	<2		<2	<2
red cabbage	*Brassica oleracea* L. cv. Rubra DC.	6.2	5.9	3.8	1.9	4.6 ± 1.1	<2	<2	<2	<2	<2
processed		2.4	2.6	2.7	3.9	2.8 ± 0.3	<2	<2	<2	<2	<2
green cabbage	*Brassica oleracea* L. cv. Sabellica Schulz	<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
endive	*Chicorium endiva* L.	<1	1.3	<1	<1	<1.3	15	95	21	30	46 ● 42
chicory	*Chicorium intybus* L.	<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
cucumber	*Cucumus sativus* L.	<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
lettuce	*Lactuca sativa* L. cv. Capitata L.	1.9	30	6.7	7.3	14 ± 14	<2	<2	<2	<2	<2
French bean	*Phaseolus vulgaris* L.	45	32	41	42	39 ± 6	14	<2	13	8.8	<12
processed		27	19	11	15	17 ± 5	<2	3.8	<2	<2	<3.8
slicing bean	*Phaseolus vulgaris* L.	28	30			29	<2	<2			<2
pea	*Pisum sativum* L.	<1				<1	<2				
processed		<1	<1	4.3	<1	<4.3	<2	<2	<2	<2	<2
purslane	*Portulacea oleracea* L.	<1	<1			<1	<2	<2			<2
radish	*Raphanus sativus* L. cv. Radicula Pers.	<1	<1	<1	<1	<1	3.9	7.7	6.2	5.5	6.2 ± 1.5
tomato	*Salanum lycopersicum* L.	4.6	11	8.2	4.9	8.0 ± 3.1	<2	<2	<2	<2	<2
spinach	*Spinacia oleracea* L.	<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
processed		<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
broad bean	*Vicia faba* L.	20				20	<2				
processed		6.6	6.3	3.9	6.2	5.5 ± 1.4	<2	8.0	6.0	<2	<7

		luteolin April 1991	luteolin Aug 1991	luteolin Dec 1991	luteolin April 1992	luteolin mean[b]	myricetin April 1991	myricetin Aug 1991	myricetin Dec 1991	myricetin April 1992	myricetin mean[b]
no vegetables contained luteolin, apigenin, or myricetin except for											
red bell pepper	*Capsicum annuum* L.	14	13	7.0	14	11 ± 4	<1	<1	<1	<1	<1
carrot	*Daucus carota* L.	1.4	<1	<1	<1	<1.4	<1	<1	<1	<1	<1
processed		<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
broad bean	*Vicia faba* L.	<1				<1	26				26

[a] Mean (mg/kg of fresh edible part) of duplicate determinations. <1, <2 = limit of detection. Blank spaces: not available/sampled in that period. [b] Annual mean ± SD, April 1991 and April 1992 were averaged prior to calculation of mean and SD.

3-*O*-sophoroside 7-*O*-glucoside and kaempferol 3-*O*-β-D-glucoside, respectively (Starke and Herrmann, 1976). A typical chromatogram of a vegetable extract (French beans) is shown in Figure 2.

Table I reports the flavonoid content of fresh and processed vegetables sampled in the four periods. As April 1991 and April 1992 represent the same season, results of these periods were first averaged before the annual mean values and standard deviations given were calculated. Standard deviations are reported whenever a food was sampled in all four periods. The flavonoid contents of fruits are reported in Table II. No standard deviations are given because fresh fruits were generally bought in August only. Different apple and pear varieties were bought in all periods. The mean flavonoid content of these fruits was calculated by averaging the values of all varieties. Standard deviation thus reflects standard deviation of the varieties.

The major flavonoid that we found in vegetables is quercetin, followed by kaempferol. Myricetin could only be detected in fresh broad bean (26 mg/kg), and luteolin was found only in red bell pepper (11 mg/kg). We could detect apigenin only in celery (108 mg/kg) that was used in developing our method of analysis and that was applied as control sample B in this study. The mean quercetin content of onions (347 mg/kg) and the mean kaempferol content of fresh kale (211 mg/kg) were 5–10-fold higher than in most other vegetables. High mean levels of quercetin were also found in kale (110 mg/kg), broccoli (30 mg/kg), fresh French beans (39 mg/kg), and fresh slicing beans (29 mg/kg). The mean kaempferol contents of endive (46 mg/kg), leek (30 mg/kg), and turnip tops (48 mg/kg) were higher than in most other vegetables. None of the flavonoids investigated could be detected in chicory, spinach, pea, red beet, mushroom, cucumber, carrot, and all brassicas, with the exception of broccoli, kale, red cabbage, and turnip tops.

In fruits only quercetin was found with the exception of strawberries where also kaempferol is present (12 mg/kg) and white and black grapes where also a low content

Table II. Flavonoid Content[a] of Nine Fruits (Including Peel) Sampled in Four Periods

		quercetin					kaempferol				
product	scientific name	April 1991	Aug 1991	Dec 1991	April 1992	mean[b]	April 1991	Aug 1991	Dec 1991	April 1992	mean[b]
strawberry	*Fragaria ananassa* Duch.	10	8.4		7.7	8.6	7.0	16		12.	12
apple[c]	*Malus pumila* Mill.					36 ± 19					<2
Granny Smith		24			24		<2			<2	
James Grieve			21					<2			
Golden Delicious			25					<2			
Elstar				32					<2		
Jonagold				72					<2		
Cox's Orange				41					<2		
applesauce		22	18	21	20	20 ± 2	<2	<2	<2	<2	<2
red currant	*Ribes rubrum-hybriden*		13			13		<2			<2
apricot	*Prunus armeniaca* L.		25			25		<2			<2
processed		<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
pear[c]	*Pyrus communis* L.					6.4 ± 3.4					<2
Conference		3.3			3.2		<2			<2	
Beurré Hardy			10					<2			
Doyenne du Comice				5.8					<2		
sweet cherry	*Prunus cerasus* L.		15			15		<2			<2
processed		24	30	38	34	32 ± 5	<2	<2	<2	<2	<2
plum	*Prunus domestica* L.		9			9		<2			<2
peach	*Prunus persica batsch*		<1			<1		<2			<2
processed		<1	<1	<1	<1	<1	<2	<2	<2	<2	<2
grape, white	*Vitis vinifera* L.		12	12		12		<2	<2		<2
black			15			15		<2			<2

		myricetin				
product	scientific name	April 1991	Aug 1991	Dec 1991	April 1992	mean[b]
no fruits contained luteolin, apigenin, or myricetin except for						
grape, white	*Vitis vinifera* L.		4.5	<1		4.5
black			4.5			4.5

[a] Mean (mg/kg of fresh edible part) of duplicate determinations. <1, <2 = limit of detection. Blank spaces: not available/sampled in that period. [b] Annual mean ± SD; April 1991 and April 1992 were averaged prior to calculation of mean and SD. [c] Different varieties purchased in different periods.

Table III. Results of Analytical Quality Control Samples[a]

	control sample[b]					
	A (flavonol glucosides)		B (flavone glucosides)		C (flavonol glucuronides)	
	quercetin	kaempferol	luteolin	apigenin	quercetin	kaempferol
mean at start	381 (n = 5)	344 (n = 5)	333 (n = 5)	1780 (n = 5)	121 (n = 5)	142 (n = 5)
SD_R	19	28	15	73	9	12
CV_R, %	4.9	8.2	4.6	4.1	7.3	8.3
CV_r, %	2.5	5.7	3.3	2.8	3.1	4.6
mean series	375 (n = 11)	354 (n = 7)	236 (n = 4)	1740 (n = 4)	131 (n = 5)	135 (n = 5)
CV_R, %	5.1	9.4	14.0	6.2	7.2	5.2
CV_r, %	3.0	2.9	3.8	3.4	4.1	4.9

[a] Mean (mg/kg of dry weight), within-laboratory standard deviation of reproducibility (SD_R), within-laboratory coefficient of variation of reproducibility (CV_R), and repeatability (CV_r) at the start of the project (period of 2 weeks) and mean and coefficient of variation obtained in the whole project (1.5 years). [b] Each determination was carried out in duplicate.

of myricetin (4.5 mg/kg) was found. None of the flavonoids investigated could be detected in peaches. Differences in quercetin content in three pear varieties and six apple varieties were low. The mean quercetin contents for all varieties in apples and pears were 36 ± 19 and 6.4 ± 3.4 mg/kg, respectively. In general, apple varieties purchased in December had highest quercetin levels. Jonagold apples had a quercetin content twice that of other varieties. No significant differences could be noted between the quercetin contents of white and black grapes. We failed to detect kaempferol in fruits, except for strawberries, as described by Wildanger and Herrmann (1973) for some fruits such as cherry, plum, peach, and red currant. Quantities reported by Wildanger and Herrmann are, however, very low (<10 mg/kg of fresh weight).

In general, our values are somewhat lower than values reported earlier by Herrmann and co-workers (Wöldecke and Herrmann, 1974; Herrmann, 1976; Starke and Herrmann, 1977). However, Herrmann usually reported a large range of flavonoid levels which makes a comparison difficult. Besides, the thin-layer chromatographic method with spectrophotometric measurement applied by Herrmann and co-workers lacks precision and accuracy. It should be noted that in our study only the edible parts were analyzed, whereas Herrmann and co-workers generally analyzed the whole foods. Our values for various foods are higher compared to values reported by Bilyk and co-workers (Bilyk et al., 1984; Bilyk and Sapers, 1985, 1986). Discrepancies may be due to different European or American cultivars or varietal differences. It should also be noted that hydrolysis conditions were not optimized in the studies reported by Bilyk and co-workers.

Variations in flavonoid levels due to seasonal influences were large in leafy vegetables such as lettuce (1.9–30 mg/kg quercetin), endive (15–95 mg/kg kaempferol), and leek (11–56 mg/kg kaempferol). Flavonoid quantities found

in lettuce, endive, and leek sampled in summer were 3–5 times higher than in other seasons. Seasonal variability was, however, low in red cabbage. As the formation of flavonoids is light-dependent, flavonoids occur predominantly in the leaves, and growing plants in glass houses reduces the flavonoid content (Herrmann, 1976). Year-to-year variation measured by comparing results of April 1991 and April 1992 was generally within the range of the seasonal variability of the vegetables.

In general, flavonoid levels in processed foods were approximately 50% lower than in fresh products. However, processed sweet cherries had higher quercetin levels than fresh sweet cherries. Quercetin levels in applesauce corresponded well with those found in most varieties of apples. No quercetin could be found in processed apricots, but 25 mg/kg quercetin was found in fresh apricots. Possibly, these discrepancies are due to varietal differences. No information was available on the variety used in fruit processing. Variation over the year was low in most processed foods.

In this study emphasis was placed on the identification and quantification of five major potentially anticarcinogenic flavonoids in the edible parts of various commonly consumed plant foods. Together with data on the content of flavonoids in several beverages, currently determined at our laboratory, a calculation of the daily intake of these potential anticarcinogens can be made. Our data thus provide a base for epidemiological studies investigating the relation between flavonoid intake and cancer risk.

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