CAFFEIC ACID

1. Exposure Data

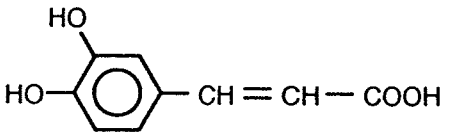
1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 331-39-5

Chem. Abstr. Name: 3-(3,4-Dihydroxyphenyl)-2-propenoic acid

Synonyms: Caffeic acid; 5(4)-(2-carboxyethenyl)-1,2-dihydroxybenzene; 4-(2′-carboxyvinyl)-1,2-dihydroxybenzene; 3,4-dihydroxybenzeneacrylic acid; 3,4-dihydroxycinnamic acid; 3-(3,4-dihydroxyphenyl)propenoic acid; 3-(3,4-dihydroxyphenyl)-2-propenoic acid



$C_9H_8O_4$ Mol. wt: 180.15

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Yellow prisms or plates from water (Lide, 1991)

(*b*) *Melting-point*: Decomposes at 225 °C (Lide, 1991)

(*c*) *Solubility*: Sparingly soluble in cold water; very soluble in hot water and cold ethanol (Budavari, 1989)

(*d*) *Stability*: Caffeic acid exists in *cis* and *trans* forms, *trans* being the predominant naturally occurring form (Janssen Chimica, 1991). Solutions of caffeic acid and its derivatives (e.g., chlorogenic and isochlorogenic acids) are unstable in sunlight and ultraviolet light. The *trans* form of caffeic acid is partially converted to the *cis* form, which in turn is partially converted to the lactone, aesculetin (Grodzinska-Zachwieja *et al.*, 1973; Hartley & Jones, 1975; Borges & Pinto, 1989).

(*e*) *Reactivity*: Caffeic acid inhibited the formation of *N*-nitrosodimethylamine *in vitro* from simulated gastric juice and nitrite and *in vivo* in rats given aminopyrine and nitrite (Kuenzig *et al.*, 1984). With lower concentrations of caffeic acid than of reactants, caffeic acid can, however, catalyse nitrosamine formation (Dikun *et al.*, 1991).

1.1.3 *Trade names, technical products and impurities*

Caffeic acid is not known to be a significant commercial product. It is available as the *trans* isomer in research quantities at purities ranging from 97% to > 99%; the *cis* isomer of

caffeic acid is not available commercially (Fluka Chemie AG, 1990; Riedel-de Haen, 1990; Janssen Chimica, 1991; Lancaster Synthesis, 1991; TCI America, 1991; Aldrich Chemical Co., 1992).

1.1.4 *Analysis*

Since ultraviolet light partially converts the *trans* isomers of several cinnamic acids, including caffeic acid, to their respective *cis* forms (Kahnt, 1967), it is important in any study of cinnamic acid derivatives in plant materials to have an accurate, rapid method for the determination of both the *cis* and *trans* isomers. Hartley and Jones (1975) separated *cis* from *trans* isomers of caffeic acid as their trimethylsilyl derivatives by gas chromatography with flame ionization detection. Conkerton and Chapital (1983) reported the separation of *cis* from *trans* isomers of caffeic acid by reverse-phase high-performance liquid chromatography (HPLC), using ultraviolet and electrochemical detection in series. Borges and Pinto (1989) reported the separation of *cis*- from *trans*-caffeic acids and aesculetin by isocratic HPLC with ultraviolet detection at 350 nm. Hydroxycinnamic acids, including caffeic acid, were separated from maize tissue samples on a reverse-phase HPLC column with ultraviolet detection at 254 nm (Hagerman & Nicholson, 1982).

An improved capillary gas chromatography procedure with flame ionization detection was developed for the analysis of nonvolatile organic acids and fatty acids in flue-cured tobacco hydrolysates. Two major nonvolatile organic acids, citric and malic acids, and two minor acids, quinic and caffeic acids, were readily quantified as their trimethylsilyl derivatives in an aqueous extract of tobacco (Court & Hendel, 1986).

Caffeic acid has been determined in grape juice, apple juice and pear juice using reverse-phase HPLC with diode array detection (Spanos & Wrolstad, 1990a,b; Spanos *et al.*, 1990).

Ficarra *et al.* (1990) reported the use of HPLC with diffuse infrared reflectance spectroscopy for qualitative and quantitative analysis of naturally occurring phenolic compounds, including caffeic acid, in the medicinal plant *Crataegus oxyacantha* L.

1.2 Production and use

1.2.1 *Production*

No information was available to the Working Group about the worldwide production, trade or consumption of caffeic acid.

1.2.2 *Use*

Several studies have been done to develop drugs based on caffeic acid for use in the treatment of asthma and allergies (Koshihara *et al.*, 1984; Murota & Koshihara, 1985). The antibacterial effect of caffeic acid and of its oxidation products was studied in four bacteria, *Staphylococcus aureus*, *Streptococcus faecalis*, *Salmonella typhimurium* and *Escherichia coli*. Bactericidal activity appeared only after oxidation of caffeic acid and under alkaline conditions (Cuq & Jaussan, 1991).

1.3 Occurrence

1.3.1 *Plants*

Caffeic acid occurs naturally in a wide range of plants, free and in various combined forms (Conkerton & Chapital, 1983). Caffeic acid and chlorogenic acids are constituents of numerous species, including Umbelliferae, Cruciferae, Cucurbitaceae, Polygonaceae, Compositae, Labiatae, Solanaceae, Leguminosae, Saxifragaceae, Caprifoliaceae, Theaceae and Valerianaceae (Herrmann, 1956; Litvinenko *et al.*, 1975).

Caffeic acid has been identified in plants used for medicinal purposes, including *Davallia mariesii* Moore (Davalliaceae), a fern used in Korean folk medicine for the treatment of the common cold, neuralgia and stomach cancer and in China as a traditional medicine for treatment of lumbago, rheumatism, toothache and tinnitus (Cui *et al.*, 1990); the roots of *Carissa spinarum* L. (Apocynaceae), a thorny, evergreen shrub used medicinally in India as a purgative and for the treatment of rheumatism (Raina *et al.*, 1971); the flowers of *Ixora javanica*, also used in Indian medicine, as an antitumour agent, gastric sedative, intestinal antiseptic and astringent (Nair & Panikkar, 1990); *Centaurium umbellatum* Gil. (Gentianaceae), a medicinal plant used in numerous countries combined with other plants (Hatjimanoli & Debelmas, 1977); and *Artemisia rubripes* Nakai, a Chinese plant used medically (Koshihara *et al.*, 1984).

Caffeic acid has been found in the flowers, leaves and buds of the medicinal plant *Crataegus oxyacantha* L. (a Rosaceae with cardiovascular effects) (Ficarra *et al.*, 1990); in the flowers of *Tussilago farfara* L. (an antispasmodic) with caffeoyl tartric acid (Didry *et al.*, 1980); in the essential oil of flowers of *Cytisus scoparius* L. (Kurihara & Kikuchi, 1980); in the leaves of *Melissa officinalis* L. (a Labiatae which inhibits viral development and tumour cell division) with chlorogenic acid (Chlabicz & Gałasiński, 1986) and in timothy grass (*Phleum pratense* L.) with chlorogenic acid isomers (Mino & Harada, 1974); in the seeds of *Argyreia speciosa* Sweet (elephant creeper, a Convolvulaceae with hypotensive and spasmolytic activity (Agarwal & Rastogi, 1974); in the essential oil of *Foeniculum vulgare* (Umbelliferae) (Trenkle, 1971); in the herb *Veronica chamaedrys* L. (Świątek *et al.*, 1971); and in the roots of *Arctium lappa* L. (burdock, a Compositae or Asteraceae used as a diuretic) with chlorogenic acid (Leung, 1980).

1.3.2 *Fruits, vegetables and seasonings*

Caffeic acid is present in a variety of fruits, vegetables and seasonings, predominantly in the form of ester conjugates, including chlorogenic acids (esters of caffeic acid and quinic acid) and related compounds. These conjugates may be hydrolysed upon ingestion, leading to variable uptakes of caffeic acid. Table 1 summarizes the levels of caffeic acid and its conjugates in various fruits and vegetables, as determined by thin-layer chromatography following enzymic, acid and/or alkaline hydrolysis.

Caffeic acid (free and conjugated) has been found at concentrations > 1000 ppm (mg/kg) in thyme, basil, aniseed, caraway, rosemary, tarragon, marjoram, savory, sage, dill and absinthe (Ames *et al.*, 1991). Other agricultural products that have been found to contain caffeic acid and conjugates include sweet potatoes (Hayase & Kato, 1984), sunflower seeds

and meal (Pomenta & Burns, 1971; Felice *et al.*, 1976), soya beans (Pratt & Birac, 1979), tobacco (Andersen & Vaughn, 1970), spinach, red peppers, apricots, coconut and rolled oats (Kusnawidjaja *et al.*, 1969; Ames *et al.*, 1991).

Table 1. Occurrence of caffeic acid and its conjugates in various fruit and vegetables

Botanical species	Plant part	Concentration as caffeic acid (mg/kg, fresh weight)	Type of hydrolysis
Vegetables			
Bean, broad bush	Hulls	12–14	Enzymatic
	Unripe fruit	< 0.5–9	Enzymatic
Beetroot, red	Whole vegetable	5–17	Enzymatic
	Outside	5	Enzymatic
	Heart	4	Enzymatic
Beetroot, sugar	Whole vegetable	3–4	Enzymatic
Broccoli	Florets	8	Enzymatic
		10	Enzymatic followed by alkaline/acid
Brussels sprouts	-	34–44	Enzymatic
		35–50	Alkaline/acid
Cabbage, Chinese	Outer leaves	11–42	Enzymatic
		52	Enzymatic followed by alkaline/acid
	Inner leaves	4–11	Enzymatic
		11	Enzymatic followed by alkaline/acid
Red	Outer leaves	6–11	Enzymatic
		16–24	Alkaline/acid
	Head	12–16	Enzymatic
		16–17	Alkaline/acid
Savoy	Outer leaves	9–14	Enzymatic
		14–36	Alkaline/acid
	Head	4–7	Enzymatic and alkaline/acid
White	Outer leaves	< 0.5–31	Enzymatic
		< 0.5–62	Alkaline/acid
	Head	< 0.5–10	Enzymatic
		< 0.5–12	Alkaline/acid
Carrot	Whole vegetable	18–96	Enzymatic
	Rind	27–141	Enzymatic
	Central cylinder	8–73	Enzymatic
Cauliflower	Leaves	9–29	Enzymatic
		58	Alkaline/acid
		90	Enzymatic followed by alkaline/acid
	Florets	1–3	Enzymatic
		4	Alkaline/acid
		6	Enzymatic followed by alkaline/acid

Table 1 (contd)

Botanical species	Plant part	Concentration as caffeic acid (mg/kg, fresh weight)	Type of hydrolysis
Vegetables (contd)			
Celery	Whole vegetable	89–104	Enzymatic
	Outside	87–122	Enzymatic
	Heart	84–109	Enzymatic
	Root	168	Enzymatic
Chives	Green leaves	< 0.5	Enzymatic or enzymatic followed by alkaline/acid
Fennel	Tuber	100	Enzymatic followed by alkaline/acid
Garlic	Dry bulb skin	< 20	Enzymatic or enzymatic followed by alkaline/acid
	Fleshy tissue of bulb	14	Enzymatic
		7	Enzymatic followed by alkaline/acid
Horseradish	Whole vegetable	10–11	Enzymatic
	Peel	14	Enzymatic
	Heart	4	Enzymatic
Kale	Stalk and midrib	9	Enzymatic
		13	Enzymatic followed by alkaline/acid
	Leaf and stalk	77	Enzymatic
		92	Alkaline/acid
	Leaf and blade	125	Alkaline
		51–163	Enzymatic
		305	Enzymatic followed by alkaline/acid
Kohlrabi	Leaves	15–66	Enzymatic
		34–113	Alkaline/acid
	Tuber	< 0.5–2	Enzymatic
		2–5	Alkaline/acid
Lettuce	Leaves	767–1570	Enzymatic
		804–1440	Alkaline/acid
Onion	Green leaves	< 0.5–15	Enzymatic
		< 0.5	Alkaline/acid
		19	Enzymatic followed by alkaline/acid
Parsley	Whole plant	6	Enzymatic
	Leaf	< 0.5	Enzymatic
Pea	Unripe seeds	< 0.5–1	Enzymatic
	Hulls	< 0.5	Enzymatic

Table 1 (contd)

Botanical species	Plant part	Concentration as caffeic acid (mg/kg, fresh weight)	Type of hydrolysis
Vegetables (contd)			
Potato	Peel	163–280	Enzymatic
		167–196	Alkaline/acid
		205	Enzymatic followed by alkaline/acid
	Whole tuber	3–30	Enzymatic
		5–33	Alkaline/acid
		8	Enzymatic followed by alkaline/acid
Radish	Whole vegetable	13–17	Enzymatic
	Peel	47–52	Enzymatic
	Heart	3–9	Enzymatic
	Leaves	376–417	Enzymatic
		394–396	Enzymatic followed by alkaline/acid
Radish, black	Whole vegetable	5–8	Enzymatic
	Peel	6–7	Enzymatic
	Heart	7	Enzymatic
	Leaves	163–247	Enzymatic
		156–220	Enzymatic followed by alkaline/acid
Rhubarb	Leaves	8–13	Enzymatic
		6	Alkaline/acid
		16	Enzymatic followed by alkaline/acid
	Outer stem	< 0.5	Enzymatic
Rutabaga	Whole vegetable	2	Enzymatic
	Peel	3	Enzymatic
	Heart	4	Enzymatic
Scorzonera	Whole vegetable	49–212	Enzymatic
	Outside	106	Enzymatic
	Heart	62	Enzymatic
Fruit			
Blueberry	Fruit	83–588	Enzymatic
Courgette (zucchini)	Whole fruit	10	Enzymatic
Currant, black	Fruit	14–93	Enzymatic
red	Fruit	8–16	Enzymatic
white	Fruit	10–21	Enzymatic
Eggplant (aubergine)	Ripe fruit	360–436	Alkaline/acid
Gooseberry,			
green	Fruit	24–32	Enzymatic
red	Fruit	29–32	Enzymatic
yellow	Fruit	23–27	Enzymatic

Table 1 (contd)

Botanical species	Plant part	Concentration as caffeic acid (mg/kg, fresh weight)	Type of hydrolysis
Fruit (contd)			
Grapefruit	Fruit	11–40	Enzymatic
	Peel	14–51	Enzymatic
Lemon	Fruit	13–27	Enzymatic
	Peel	16–35	Enzymatic
Orange	Fruit	19–50	Enzymatic
	Peel	12–36	Enzymatic
Pepper, sweet	Green fruit	3–7	Enzymatic
	Red fruit	4–10	Enzymatic
Strawberry	Fruit	< 0.5–14	Enzymatic
Sweet melon	Peel	3	Enzymatic
	Fruit	< 0.5	Enzymatic
Tomato	Unripe green fruit	13–79	Enzymatic
		44	Alkaline/acid
	Ripe red fruit	32–97	Enzymatic
	Peel	97	Enzymatic
	Pulp	41	Enzymatic
	Seeds	119	Enzymatic
Watermelon	Peel or fruit	< 0.5	Enzymatic

From Schmidtlein & Herrmann (1975a,b,c); Stöhr & Herrmann (1975a,b,c,d)

Cynara scolymus L. (Compositae or Asteraceae, artichoke) contains up to 2% *O*-diphenolic derivatives such as caffeic acid. 1,3-Dicaffeoylquinic acid and 3-caffeoylquinic acid (chlorogenic acid) are believed to be among the active constituents (Leung, 1980; Hinou *et al.*, 1989),

The content of caffeic acid in the peel of potato tubers changes with the physical state of the tuber: It is highest during profound dormancy, drops during emergence from dormancy and remains low during sprouting of the tubers. During dormancy, the largest amount is contained in the eyes of the tubers (18.7 μg/g crude weight), a smaller amount in the peel (12.5 μg/g crude weight) and the smallest amount in the pulp (2.3 μg/g crude weight). At the end of dormancy, the peel contains the largest amount of caffeic acid (3.7 μg/g crude weight), the eyes a smaller amount (2.8 μg/g crude weight) and the pulp the least (0.7 μg/g crude weight) (Morozova *et al.*, 1975). Increased biosynthesis of caffeic acid and chlorogenic acid was reported in Irish potato tubers and of caffeic acid, chlorogenic acid and isochlorogenic acid in sweet potato roots after infection or stress (Kuc, 1972).

Chlorogenic acid, which is metabolized to caffeic acid, is present in apricots, cherries, plums and peaches at concentrations ranging approximately from 50 to 500 ppm (mg/kg) (Ames *et al.*, 1991). It is also present in coffee beans, potatoes, apples and tobacco leaves in significant quantities: 34–140 mg/kg fresh weight in several varieties of potato, 120–310 mg/l juice produced from apples, 890 mg/kg fresh, mature apples and 5590–6740 mg/kg dry tea

shoots (Iwahashi *et al.*, 1990). Neochlorogenic acid, which is also metabolized to caffeic acid, is present at concentrations ranging from approximately 50 to 500 ppm (mg/kg) in apples, pears, peaches, apricots, plums, cherries, Brussels sprouts, kale, cabbage and broccoli (Ames *et al.*, 1991).

Relatively small changes occurred in the caffeic and quinic acid contents of sunflower kernels during storage; however, the chlorogenic acid content decreased during storage at 5 °C, 15 °C and 40 °C for 120 days (Pomenta & Burns, 1971).

The occurrence of caffeic acid conjugates in coffee beans has been reviewed (IARC, 1991). The conjugates of caffeic acid are present in green and roasted beans, the total percentage of chlorogenic acids in commercial roasted coffee samples ranging from 0.2 to 3.8% (Trugo, 1984; Maier, 1987).

1.3.3 *Beverages*

Caffeic acid is present in free and conjugated forms in beverages made from agricultural plants of which it is a constituent. Assuming that one cup of coffee contains 10 g of ground coffee, a level of 15–325 mg chlorogenic acids per cup can be calculated on the basis of the percentage range given above (Viani, 1988). Actual data from the USA give an average of 190 mg total chlorogenic acids per cup of brewed coffee (Clinton, 1985).

Caffeic acid is also found in fruit juices and wine. Apple juice has been reported to contain caffeic acid at 0–10 mg/l (Kusnawidjaja *et al.*, 1969) and chlorogenic acid at 20–60 mg/l, but the levels may be much higher (~200 mg/l), especially in fermented juice (Kusnawidjaja *et al.*, 1969; Brause & Raterman, 1982; Cilliers *et al.*, 1990).

In 50 samples of commercial white wines, the average concentration of caffeic acid was 2.5 mg/l. German Riesling wines contained the highest concentration (4.1 mg/l), followed by Japanese *koshu* wine (3.1 mg/l), Chardonnay wine (1.7 mg/l) and Sémillon wine (0.9 mg/l) (Okamura & Watanabe, 1981). Italian wines and a sherry were also found to contain caffeic acid (Cartoni *et al.*, 1991).

The influence of variety, maturity, processing and storage on the phenolic composition of pear, grape and apple juice has been investigated (Spanos & Wrolstad, 1990a,b; Spanos *et al.*, 1990). The concentration of chlorogenic acid increases by about six fold when apple juices are processed by diffusion extraction at different temperatures over that found by conventional pressing. In grape juices, the addition of sulfur dioxide during processing resulted in higher levels of caffeic acid.

1.3.4 *Other sources*

Caffeic acid has also been identified in wood smoke condensates (Ohshima *et al.*, 1989) and in the bee product, propolis, presumably from resin gathered from caffeic acid-containing plants (Čižmárik & Matel, 1970).

1.4 Regulations and guidelines

No information was available to the Working Group concerning the regulatory status of caffeic acid.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 30 male and 30 female B6C3F$_1$ (C57Bl/6N x C3H/HeN F$_1$) mice, six weeks of age, were fed a diet containing 0 or 2% [20 g/kg of diet] caffeic acid (purity, ≥ 98%) for 96 weeks (intakes, 2120 mg/kg bw per day for males and 3126 mg/kg bw per day for females). Squamous-cell papillomas and carcinomas occurred in the forestomachs of treated mice (4/30 papillomas and 3/30 carcinomas in males and 0/29 papillomas and 1/29 carcinomas in females), but not in controls. The incidences of epithelial hyperplasia of the forestomach were increased significantly ($p < 0.01$) in both treated males and females. Renal-cell adenomas were found in 8/29 ($p < 0.01$) females and in 0/29 controls; one renal adenocarcinoma was seen in a treated male. Significant increases in the incidence of renal tubular-cell hyperplasia were seen in both treated males and treated females. An increased incidence of alveolar type II-cell tumours (adenomas plus carcinomas) of the lung (8/30; $p < 0.05$) was reported in males but not in females. Spontaneous incidences of alveolar-cell tumours in male B6C3F$_1$ mice have been reported to be 2.2–13.9% (Hagiwara *et al.*, 1991).

3.1.2 *Rat*

Groups of 30 male and 30 female Fischer 344 rats, six weeks of age, were fed a diet containing 0 or 2% [20 g/kg of diet] caffeic acid (purity, ≥ 98%) for 104 weeks (intakes, 678 mg/kg bw per day for males and 814 mg/kg bw per day for females). Squamous-cell papillomas and carcinomas occurred in the forestomach in 23/30 (papillomas) and 17/30 (carcinomas) males and in 24/30 (papillomas) and 15/30 (carcinomas) females. No neoplastic change was noted in the forestomachs of an untreated group of 30 males and 30 females. The frequency of forestomach hyperplasia was also increased significantly in animals of each sex as compared to the control level ($p < 0.01$). Renal tubular-cell adenomas were seen in four treated males but in no untreated male or in females. Significant increases in the incidence of renal tubular-cell hyperplasia were seen in both treated males and treated females (Hagiwara *et al.*, 1991).

3.2 Administration with known carcinogens

3.2.1 *Sequential exposure*

(*a*) *Mouse*

Three groups of 30 female CD-1 mice, seven weeks of age, were treated topically with 200 nmol [51 mg] 7,12-dimethylbenz[*a*]anthracene (DMBA) in 200 µl acetone. After one

week, the mice were treated topically with 5 nmol [3 mg] 12-*O*-tetradecanoylphorbol 13-acetate (TPA) with or without simultaneous caffeic acid [purity unspecified] at 10 or 20 μmol [1.8 or 3.6 mg] twice a week for 19 weeks. The mean number of skin tumours per mouse treated with TPA and the high dose of caffeic acid was significantly lower than that in the group treated with TPA alone: 1.12, 4.43 and 6.18 tumours/mouse in the groups treated with TPA plus 20 μmol caffeic acid, TPA plus 10 μmol caffeic acid and TPA alone, respectively (Huang *et al.*, 1988).

(*b*) *Rat*

Two groups of 20 female Sprague-Dawley rats, 50 days of age, received 25 mg/kg bw DMBA in 0.5 ml sesame oil by gavage. One week later, the animals were fed a diet containing 0.5% [5 g/kg of diet] caffeic acid (purity, > 99%) for 51 weeks. The mammary glands, ear ducts, stomach, liver and kidneys were examined. The incidence of papillomas of the forestomach was significantly increased (6/19) in animals treated with DMBA plus caffeic acid as compared to rats treated with DMBA alone (0/19; $p < 0.01$) No other significant increase in tumour incidence was found (Hirose *et al.*, 1988).

Three groups of 15 male Fischer 344 rats, six weeks of age, were administered 150 mg/kg bw *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) in dimethyl sulfoxide by gavage. One week later, animals were fed a diet containing 0.5% [5 g/kg of diet] caffeic acid (purity, > 98%) or caffeic acid plus other phenolic antioxidants (0.2% catechol plus 0.5% butylated hydroxyanisole plus 0.25% 2-*tert*-butyl-4-methylphenol) for 35 weeks or the basal diet. The oesophagus, stomach, intestines, liver and kidneys were examined. Squamous-cell carcinomas of the forestomach occurred in 1/15 animals in the group treated with MNNG alone, in 4/15 in the group receiving MNNG plus caffeic acid (no significant difference from controls given MNNG alone) and in 12/15 in the group receiving MNNG plus caffeic acid together with phenolic antioxidants ($p < 0.01$). No other increase in tumour incidence was found (Hirose *et al.*, 1991).

3.2.2 *Prior or concomitant exposure*

Mouse

Female ICR/Ha mice, nine weeks of age, were fed a diet containing 0.06 mmol/g [10 g/kg of diet] caffeic acid (purity, 99%). From experimental day 8, the mice were also given 1 mg benzo[*a*]pyrene by gavage twice a week for four weeks. The diet containing caffeic acid was removed three days after the last benzo[*a*]pyrene treatment. Mice were killed at 211 days of age. In the 17 effective mice, the number of forestomach tumours (≥ 1 mm)/mouse [histology unspecified] was significantly decreased by caffeic acid ($p < 0.05$) (3.1 *versus* 5.0 tumours/mouse among 38 mice treated with benzo[*a*]pyrene alone) (Wattenberg *et al.*, 1980). [The Working Group noted the limited reporting.]

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

In rats, chlorogenic acid is hydrolysed in the stomach and intestine to caffeic and quinic acids (Czok *et al.*, 1974). A number of metabolites have been identified (Fig. 1). Glucuronides of *meta*-coumaric acid and *meta*-hydroxyhippuric acid appear to be the main metabolites in humans. After oral administration of caffeic acid to human volunteers, *O*-methylated derivatives (ferulic, dihydroferulic and vanillic acids) were excreted rapidly in the urine, while the *meta*-hydroxyphenyl derivatives appeared later. The dehydroxylation reactions were ascribed to the action of intestinal bacteria (Arnaud, 1988).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

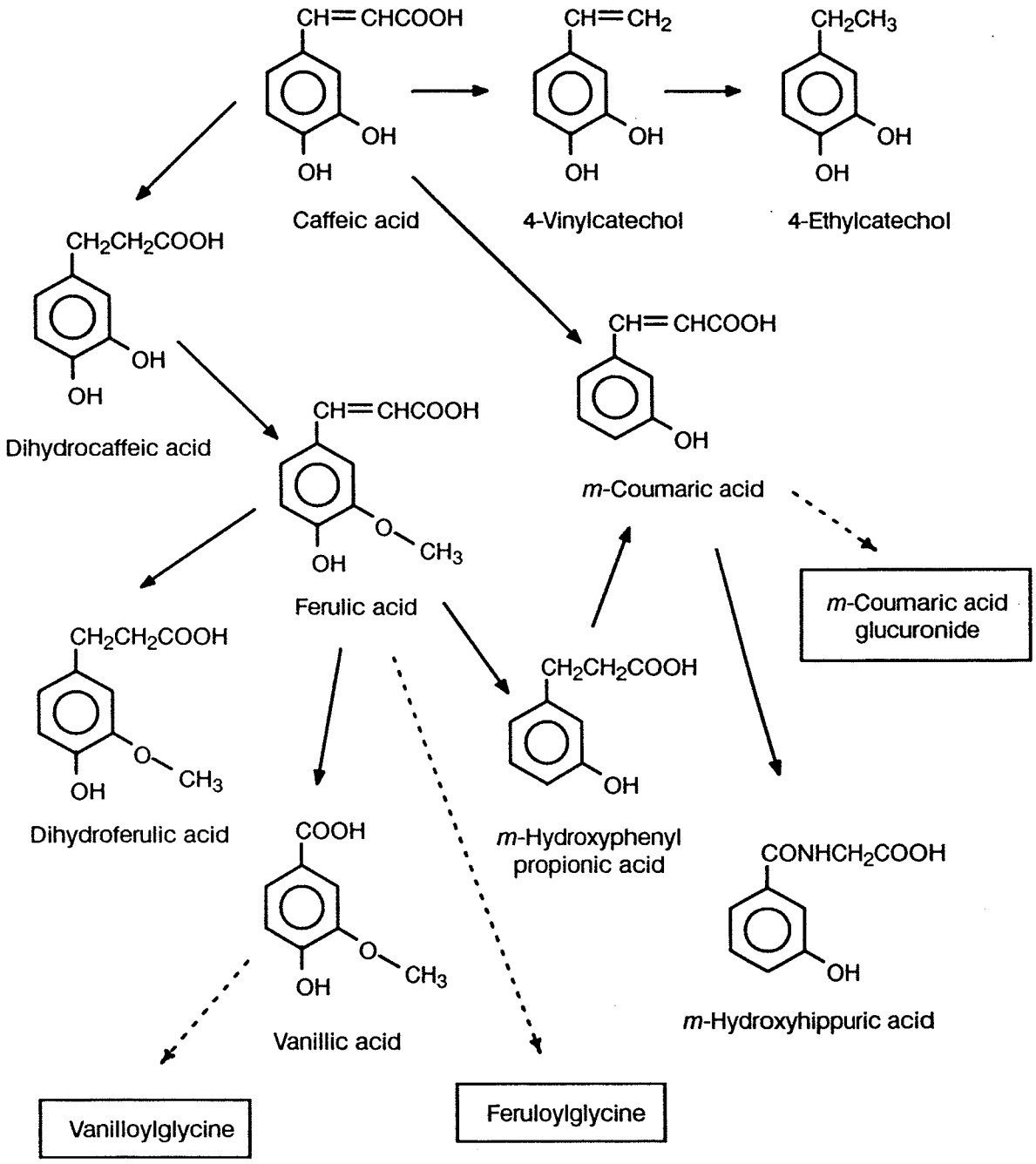
4.2.2 *Experimental data*

Five male Fischer 344 rats, six weeks of age, were given 20 g/kg of diet caffeic acid (purity, > 98%) in basal diet for four weeks. The forestomachs of all treated animals showed epithelial hyperplasia. No hyperplasia was detected in the five untreated controls (Hirose *et al.*, 1987).

A group of 15 male Syrian golden hamsters, seven weeks of age, was fed a diet containing 1% [10 g/kg diet] caffeic acid (purity, > 98%) for 20 weeks. The dose level of 1% was selected as one-fourth the LD_{50} in rats. The stomachs and urinary bladders were processed for histopathological and autoradiographic examinations. Mild epithelial hyperplasia of the forestomach was noted in 14/15 treated animals (severe in one) and in 7/15 untreated animals ($p < 0.001$). Assessment of ^{3}H-thymidine incorporation revealed an increase in the number of labelled cells in the forestomach and pyloric region of the glandular stomach as compared with untreated rats, but this was not statistically significant (Hirose *et al.*, 1986).

Caffeic acid effectively inhibits lipoxygenase and thereby inhibits the biosynthesis of leukotrienes, which are involved in immunoregulation and in a variety of diseases, including asthma, inflammation and allergic conditions. It blocks platelet aggregation by inhibiting the production of thromboxane A2, which can cause bronchoconstriction (Koshihara *et al.*, 1984; Murota & Koshihara, 1985). Caffeic acid has been widely used as a pharmacological inhibitor in a variety of organ and cell systems, and Sugiura *et al.* (1989) have shown that caffeic acid and several of its derivatives (at IC_{50} of 10^{-8}–10^{-7}M) specifically inhibit the 5-lipoxygenase. Caffeic acid (at 10^{-4}M [0.2 g]) inhibited the proliferation of malignant human haematopoietic cell lines, as measured by ^{3}H-thymidine incorporation (Snyder *et al.*, 1989); at a concentration of 17.5 μM [3.2 mg], it modified the differentiation of HL-60 cells to mature granulocytes (Miller *et al.*, 1990) by affecting leukotriene formation. The cloning efficiency of T-lymphocyte progenitor cells is also inhibited *in vitro* by caffeic acid and restored by leukotriene B4, indicating a regulatory role for arachidonic acid metabolites

Fig. 1. Proposed metabolic pathways of caffeic acid



From Arnaud (1988)

(Miller *et al.*, 1989). Several investigators have demonstrated that caffeic acid at 10^{-4}M inhibits lipid peroxidation induced by superoxide anion and formation of hydroxyl radicals *in vitro* (Iwahashi *et al.*, 1990; Toda *et al.*, 1991; Zhou & Zheng, 1991).

4.3 Reproduction and developmental toxicity

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 2)

When tested alone, caffeic acid was not mutagenic to *Salmonella typhimurium* and did not induce gene conversion in *Saccharomyces cerevisiae* D7. Forward mutations were induced in cultured mouse lymphoma L5178Y cells, and chromosomal aberrations were induced in cultured Chinese hamster ovary cells. The clastogenic effect could not be ascribed to the hydrogen peroxide that was present at low concentrations in freshly prepared caffeic acid solutions (Hanham *et al.*, 1983). Caffeic acid did not induce micronuclei in bone-marrow or intestinal cells of mice treated *in vivo*.

The effects of simultaneous exposure of cells to some transition elements and caffeic acid have also been studied. In the presence of manganese ($MnCl_2$) chelated with glycine, caffeic acid induced mutations in *S. typhimurium*, gene conversion in *S. cerevisiae* D7 and chromosomal aberrations in Chinese hamster ovary cells (Stich *et al.*, 1981a,b).

The phenethyl ester of caffeic acid inhibited adenovirus-induced transformation in rat embryo fibroblasts (Su *et al.*, 1991).

Caffeic acid decreased MNNG-induced mutation in *S. typhimurium* (Francis *et al.*, 1989). Treatment of Chinese hamster ovary K-1 cells with caffeic acid increased the incidence of sister chromatid exchange induced by mitomycin C and ultraviolet radiation. In contrast, the number of x ray-induced sister chromatid exchanges was reduced by post-treatment with caffeic acid during the G_1 phase of the cell cycle (Sasaki *et al.*, 1989).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Caffeic acid is found in many fruits, vegetables, seasonings and beverages consumed by humans, principally in conjugated forms such as chlorogenic acid.

5.2 Human carcinogenicity data

No data were available to the Working Group.

Table 2. Genetic and related effects of caffeic acid

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–[b]	–	5000.0000	Stich *et al.* (1981a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000.0000	Fung *et al.* (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000.0000	Fung *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000.0000	Fung *et al.* (1988)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5000.0000	Fung *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	150.0000	MacGregor & Jurd (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–[b]	–	5000.0000	Stich *et al.* (1981a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000.0000	Fung *et al.* (1988)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	(+)[b]	–	40000.0000	Stich *et al.* (1981a)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	–	307.0000	Fung *et al.* (1988)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+[c]	–	200.0000	Stich *et al.* (1981b)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	250.0000	Hanham *et al.* (1983)
MVM, Micronucleus test, B6C3F$_1$ mouse bone marrow *in vivo*	–		2400.0000, diet	Raj *et al.* (1983)
MVM, Micronucleus test, C56Bl/6J mouse intestine *in vivo*	–		4800.0000, diet	Wargovich *et al.* (1985)
MVM, Micronucleus test, C56Bl/6J mouse intestine *in vivo*	–	4	800.0000, diet	Wargovich *et al.* (1983)

+, positive; (+), weak positive; –, negative; 0, not tested

[a]In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

[b]Positive responses in the presence of Mn^{++}-glycine complex (10^{-4} M Mn^{++})

[c]Positive response enhanced in the presence of Mn^{++}-glycine complex

5.3 Animal carcinogenicity data

Caffeic acid was tested for carcinogenicity by oral administration in the diet in one study in mice and one study in rats. In mice, it produced renal-cell adenomas in females and a high incidence of renal tubular-cell hyperplasia in animals of each sex. An increase in the combined incidence of squamous-cell papillomas and carcinomas of the forestomach was seen in male mice, and a high incidence of hyperplasia of the forestomach was seen in both males and females. In rats, it produced squamous-cell papillomas and carcinomas of the forestomach in animals of each sex and a few renal-cell adenomas in males.

Oral administration of caffeic acid in combination with known carcinogens resulted in enhancing or inhibiting effects depending upon the carcinogen and the time of administration.

5.4 Other relevant data

Humans and experimental animals metabolize caffeic acid to the same metabolites and hydrolyse chlorogenic acid to caffeic acid.

Caffeic acid did not induce micronuclei in mice treated *in vivo*. It produced gene mutation and chromosomal aberrations in cultured rodent cells. It did not induce gene mutation in bacteria.

5.5 Evaluation[1]

No data were available on the carcinogenicity of caffeic acid to humans.

There is *sufficient evidence* in experimental animals for the carcinogenicity of caffeic acid.

Overall evaluation

Caffeic acid is *possibly carcinogenic to humans (Group 2B).*

6. References

Agarwal, S.K. & Rastogi, R.P. (1974) Ergometrine and other constituents of *Argyreia speciosa* Sweet. *Indian J. Pharm.*, **36**, 118–119

Aldrich Chemical Co. (1992) *Aldrich Catalog/Handbook of Fine Chemicals 1992–1993*, Milwaukee, WI, p. 480

Ames, B.N., Profet, M. & Gold, L.S. (1991) Dietary carcinogens and mutagens from plants. In: Hayatsu, H., ed., *Mutagens in Food: Detection and Prevention*, Boca Raton, FL, CRC Press, pp. 29–50

---

[1]For definition of the italicized terms, see Preamble, pp. 26–29.

Andersen, R.A. & Vaughn, T.H. (1970) Rapid electron capture determination of caffeic acid and quercetin moieties in plants. *J. Chromatogr.*, **52**, 385–392

Arnaud, M.J. (1988) The metabolism of coffee constitutents. In: Clarks, R.J. & Macrae, R., eds, *Coffee*, Vol. 3, *Physiology*, London, Elsevier, pp. 33–55

Borges, M.F.M. & Pinto, M.M.M. (1989) Isocratic high performance liquid chromatography separation of esculetin and *cis/trans* isomers of caffeic acid. *J. liq. Chromatogr.*, **12**, 2345–2354

Brause, A.R. & Raterman, J.M. (1982) Verification of authenticity of apple juice. *J. Assoc. off. anal. Chem.*, **65**, 846–849

Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Rahway, NJ, Merck & Co., p. 248

Cartoni, G.P., Coccioli, F., Pontelli, L. & Quattrucci, E. (1991) Separation and identification of free phenolic acids in wines by high-performance liquid chromatography. *J. Chromatogr.*, **537**, 93–99

Chlabicz, J. & Gałasiński, W. (1986) The components of *Melissa officinalis* L. that influence protein biosynthesis *in-vitro*. *J. Pharm. Pharmacol.*, **38**, 791–794

Cilliers, J.J.L., Singleton, V.L. & Lamuela-Raventos, R.M. (1990) Total polyphenols in apples and ciders; correlation with chlorogenic acid. *J. Food Sci.*, **55**, 1458–1459

Čižmárik, J. & Matel, I. (1970) Examination of the chemical composition of propolis. I. Isolation and identification of the 3,4-dihydroxycinnamic acid (caffeic acid) from propolis. *Experentia*, **26**, 713

Clinton, W.P. (1985) The chemistry of coffee. In: *11e Colloque Scientifique International sur le Café, Lomé, 1985*, Paris, Association Scientifique International du Café, pp. 87–92

Conkerton, E.J. & Chapital, D.C. (1983) High-performance liquid chromatography separation of the *cis-trans* isomers of cinnamic acid derivatives. Ultraviolet and electrochemical detection. *J. Chromatogr.*, **281**, 326–329

Court, W.A. & Hendel, J.G. (1986) Capillary gas chromatography of nonvolatile organic acids, fatty acids and certain carbohydrates in flue-cured tobacco. *Tobacco int.*, **188**, 58–61

Cui, C.-B., Tezuka, Y., Kikuchi, T., Nakano, H., Tamaoki, T. & Park, J.-H. (1990) Constituents of a fern, *Davallia mariesii* Moore. I. Isolation and structures of davallialactone and a new flavanone glucuronide. *Chem. pharm. Bull.*, **38**, 3218–3225

Cuq, J.L. & Jaussan, V. (1991) Caffeic acid oxidation and antibacterial effects (Fr.). *Sci. Alim.*, **11**, 25–36

Czog, G., Walter, W., Knoche, K. & Degener, H. (1974) Reabsorption of chlorogenic acid in the rat (Ger.). *Z. Ernährungswiss.*, **13**, 108–112

Didry, N., Pinkas, M. & Torck, M. (1980) Phenolic components from *Tussilago farfara* (Fr.). *Ann. pharm. Fr.*, **38**, 237–241

Dikun, P.P., Ermilov, V.B. & Shendrikova, I.A. (1991) Some approaches to prevention of endogenous formation of *N*-nitrosamines in humans. In: O'Neill, I.K., Chen, J. & Bartsch, H., eds, *Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105), Lyon, IARC, pp. 552–557

Felice, L.J., King, W.P. & Kissinger, P.T. (1976) A new liquid chromatography approach to plant phenolics. Application to the determination of chlorogenic acid in sunflower meal. *J. agric. Food Chem.*, **24**, 380–382

Ficarra, P., Ficarra, R., Villari, A., De Pasquale, A., Monforte, M.T. & Calabrò, M.L. (1990) High-performance liquid chromatography and diffuse reflectance spectroscopy of flavonoids in *Crataegus oxyacantha* L. III. Analysis of 2-phenyl-chroman derivatives and caffeic acid. *Farmaco*, **45**, 237–245

Fluka Chemie AG (1990) *Fluka Chemika-BioChemika 1990/91*, Buchs, p. 266

Francis, A.R., Shetty, T.K. & Bhattacharya, R.K. (1989) Modification of the mutagenicity of aflatoxin B_1 and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine by certain phenolic compounds. *Cancer Lett.*, **45**, 177–182

Fung, V.A., Cameron, T.P., Hughes, T.J., Kirby, P.E. & Dunkel, V.C. (1988) Mutagenic activity of some coffee flavor ingredients. *Mutat. Res.*, **204**, 219–228

Grodzinska-Zachwieja, Z., Kahl, W. & Klimczak, M. (1973) Spectrophotometric investigation of changes of caffeic, chlorogenic and isochlorogenic acids under the influence of some physico-chemical factors. *Pol. Pharmacol. Pharm.*, **25**, 299–305

Hagerman, A.E. & Nicholson, R.L. (1982) High-performance liquid chromatographic determination of hydroxycinnamic acids in the maize mesocotyl. *J. agric. Food Chem.*, **30**, 1098–1102

Hagiwara, A., Hirose, M., Takahashi, S., Ogawa, K., Shirai, T. & Ito, N. (1991) Forestomach and kidney carcinogenicity of caffeic acid in F344 rats and C57Bl/6N × C3H/HeN F_1 mice. *Cancer Res.*, **51**, 5655–5660

Hanham, A.F., Dunn, B.P. & Stich, H.F. (1983) Clastogenic activity of caffeic acid and its relationship to hydrogen peroxide generated during autooxidation. *Mutat. Res.*, **116**, 333–339

Hartley, R.D. & Jones, E.C. (1975) Effect of ultraviolet light on substituted cinnamic acids and the estimation of their *cis* and *trans* isomers by gas chromatography. *J. Chromatogr.*, **107**, 213–218

Hatjimanoli, M. & Debelmas, A.-M. (1977) Phenolic acids from *Centaurium umbellatum* Gil. (Fr.). *Ann. pharm. Fr.*, **35**, 107–111

Hayase, F. & Kato, H. (1984) Antioxidative components of sweet potatoes. *J. nutr. Sci. Vitaminol.*, **30**, 37–46

Herrmann, K. (1956) On caffeic acid and chlorogenic acid (Ger.). *Pharmazie*, **11**, 433–449

Hinou, J., Harvala, C. & Philianos, S. (1989) Polyphenolic substances from *Cynara scolymus* L. leaves (Fr.). *Ann. pharm. Fr.*, **47**, 95–98

Hirose, M., Inoue, T., Asamoto, M., Tagawa, Y. & Ito, N. (1986) Comparison of the effects of 13 phenolic compounds in induction of proliferative lesions of the forestomach and increase in the labelling indices of the glandular stomach and urinary bladder epithelium of Syrian golden hamsters. *Carcinogenesis*, **7**, 1285–1289

Hirose, M., Masuda, A., Imaida, K., Kagawa, M., Tsuda, H. & Ito, N. (1987) Induction of forestomach lesions in rats by oral administrations of naturally occurring antioxidants for 4 weeks. *Jpn. J. Cancer Res. (Gann)*, **78**, 317–321

Hirose, M., Masuda, A., Fukushima, S. & Ito, N. (1988) Effects of subsequent antioxidant treatment on 7,12-dimethylbenz[*a*]anthracene-initiated carcinogenesis of the mammary gland, ear duct and forestomach in Sprague-Dawley rat. *Carcinogenesis*, **9**, 101–104

Hirose, M., Mutai, M., Takahashi, S., Yamada, M., Fukushima, S. & Ito, N. (1991) Effects of phenolic antioxidants in low dose combination on forestomach carcinogenesis in rats pretreated with *N*-methyl-*N'*-nitrosoguanidine. *Cancer Res.*, **51**, 824–827

Huang, M.-T., Smart, R.C., Wong, C.-Q. & Conney, A.H. (1988) Inhibitory effect of curcumin, chlorogenic acid, caffeic acid, and ferulic acid on tumor promotion in mouse skin by 12-*O*-tetradecanoylphorbol-13-acetate. *Cancer Res.*, **48**, 5941–5946

IARC (1991) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 51, *Coffee, Tea, Mate, Methylxanthines and Methylglyoxal*, Lyon, pp. 41–197

Iwahashi, H., Ishii, T., Sugata, R. & Kido, R. (1990) The effects of caffeic acid and its related catechols on hydroxyl radical formation by 3-hydroxyanthranilic acid, ferric chloride, and hydrogen peroxide. *Arch. Biochem. Biophys.*, **276**, 242–247

Janssen Chimica (1991) *Catalog Handbook of Fine Chemicals*, Beerse, p. 449

Kahnt, G. (1967) *trans-cis*-Equilibrium of hydroxycinnamic acids during irradiation of aqueous solutions at different pH. *Phytochemistry*, **6**, 755–758

Koshihara, Y., Neichi, T., Murota, S.-I., Lao, A.-N., Fujimoto, Y. & Tatsuno, T. (1984) Caffeic acid is a selective inhibitor for leukotriene biosynthesis. *Biochim. biophys. Acta*, **792**, 92–97

Kuc, J. (1972) Compounds accumulating in plants after infection. In: Aje, S.J. & Kadis, S., eds, *Microbial Toxins*, New York, Academic Press, pp. 211–247

Kuenzig, W., Chau, J., Norkus, E., Holowaschenko, H., Newmark, H., Mergens, W. & Conney, A.H. (1984) Caffeic and ferulic acid as blockers of nitrosamine formation. *Carcinogenesis*, **5**, 309–313

Kurihara, T. & Kikuchi, M. (1980) Studies on the constituents of flowers. XIII. On the components of the flower of *Cytisus scoparius* Link (Jpn.). *Yakugaku Zasshi*, **100**, 1054–1057

Kusnawidjaja, K., Thomas, H. & Dirscherl, W. (1969) Occurrence of vanillic acid, ferulic acid, and caffeic acid in food plants (Ger.). *Z. Ernährungswiss.*, **9**, 290–300

Lancaster Synthesis (1991) *MTM Research Chemicals/Lancaster Catalogue 1991/92*, Windham, NH, p. 504

Leung, A.Y. (1980) *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics*, New York, John Wiley & Sons, pp. 35–36

Lide, D.R., ed. (1991) *CRC Handbook of Chemistry and Physics*, 72nd ed., Boca Raton, FL, CRC Press, p. 3–181

Litvinenko, V.I., Popova, T.P., Simonjan, A.V., Zoz, I.G. & Sokolov, V.S. (1975) Tannins and derivatives of hydroxycinnamic acid in *Labiatae* (Ger.). *Planta med.*, **27**, 372–380

MacGregor, J.T. & Jurd, L. (1978) Mutagenicity of plant flavonoids: structural requirements for mutagenic activity in *Salmonella typhimurium*. *Mutat. Res.*, **54**, 297–309

Maier, H.G. (1987) The acids of coffee. In: *12e Colloque Scientific International sur le Café, Montreux, 1987*, Paris, Association Scientifique Internationale du Café, pp. 229–237

Miller, A.M., Elfenbein, G.J. & Barth, K.C. (1989) Regulation of T-lymphopoiesis by arachidonic acid metabolites. *Exp. Hematol.*, **17**, 198–202

Miller, A.M., Kobb, S.M. & McTiernan, R. (1990) Regulation of HL-60 differentiation by lipoxygenase pathway metabolites *in vitro*. *Cancer Res.*, **50**, 7257–7260

Mino, Y. & Harada, T. (1974) The occurrence of caffeic acid and its derivatives in the leaves of timothy, *Phleum pratense* L. *J. Jpn. Grassl. Sci.*, **20**, 193–198

Morozova, É.V., Korableva, N.P. & Metlitski, L.V. (1975) Determination of the content of natural growth inhibitors of the potato tuber-caffeic acid and scopoletin. *Appl. Biochem. Microbiol.*, **10**, 397–401

Murota, S. & Koshihara, Y. (1985) New lipoxygenase inhibitors isolated from Chinese plants. Development of new anti-allergic drugs. *Drugs exp. clin. Res.*, **11**, 641–644

Nair, S.C. & Panikkar, K.R. (1990) Antitumour principles from *Ixora javanica*. *Cancer Lett.*, **49**, 121–126

Ohshima, H., Friesen, M., Malaveille, C., Brouet, I., Hautefeuille, A. & Bartsch, H. (1989) Formation of direct-acting genotoxic substances in nitrosated smoked fish and meat products: identification of simple phenolic precursors and phenyldiazonium ions as reactive products. *Food chem. Toxicol.*, **27**, 193–203

Okamura, S. & Watanabe, M. (1981) Determination of phenolic cinnamates in white wine and their effect on wine quality. *Agric. Biol. Chem.*, **45**, 2063–2070

Pomenta, J.V. & Burns, E.E. (1971) Factors affecting chlorogenic, quinic, and caffeic acid levels in sunflower kernels. *J. Food Sci.*, **36**, 490–492

Pratt, D.E. & Birac, P.M. (1979) Source of antioxidant activity of soybeans and soy products. *J. Food Sci.*, **44**, 1720–1722

Raina, M.K., Bhatnagar, J.K. & Atal, C.K. (1971) Isolation of caffeic acid from the roots of *Carissa spinarium* L. *Indian J. Pharm.*, **33**, 76–77

Raj, A.S., Heddle, J.A., Newmark, H.L. & Katz, M. (1983) Caffeic acid as an inhibitor of DMBA-induced chromosomal breakage in mice assessed by bone-marrow micronucleus test. *Mutat. Res.*, **124**, 247–253

Riedel-de Haen (1990) *Laboratory Chemicals 1990*, Seelze, p. 481

Sasaki, Y.F., Imanishi, H., Ohta, T. & Shirasu, Y. (1989) Modifying effects of components of plant essence on the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. *Mutat. Res.*, **226**, 103–110

Schmidtlein, H. & Herrmann, K. (1975a) On the phenolic acids in vegetables. I. Hydroxycinnamic acids and hydroxybenzoic acids of Brassica species and leaves of other Cruciferae (Ger.). *Z. Lebensmittel. Untersuch.-Forsch.*, **159**, 139–148

Schmidtlein, H. & Herrmann, K. (1975b) On the phenolic acids of vegetables. II. Hydroxycinnamic acids and hydroxybenzoic acids of fruit and seed vegetables (Ger.). *Z. Lebensmittel. Untersuch.-Forsch.*, **159**, 213–218

Schmidtlein, H. & Herrmann, K. (1975c) On the phenolic acids of vegetables. IV. Hydroxycinnamic acids and hydroxybenzoic acids of vegetables and potatoes (Ger.). *Z. Lebensmittel. Untersuch.-Forsch.*, **159**, 255–263

Snyder, D.S., Castro, R. & Desforges, J.F. (1989) Antiproliferative effects of lipoxygenase inhibitors on malignant human hematopoietic cell lines. *Exp. Hematol.*, **17**, 6–9

Spanos, G.A. & Wrolstad, R.E. (1990a) Influence of variety, maturity, processing, and storage on the phenolic composition of pear juice. *J. agric. Food Chem.*, **38**, 817–824

Spanos, G.A. & Wrolstad, R.E. (1990b) Influence of processing and storage on the phenolic composition of Thompson seedless grape juice. *J. agric. Food Chem.*, **38**, 1565–1571

Spanos, G.A., Wrolstad, R.E. & Heatherbell, D.A. (1990) Influence of processing and storage on the phenolic composition of apple juice. *J. agric. Food Chem.*, **38**, 1572–1579

Stich, H.F., Rosin, M.P., Wu, C.H. & Powrie, W.D. (1981a) A comparative genotoxicity study of chlorogenic acid (3-*O*-caffeoylquinic acid). *Mutat. Res.*, **90**, 201–212

Stich, H.F., Rosin, M.P., Wu, C.H. & Powrie, W.D. (1981b) The action of transition metals on the genotoxicity of simple phenols, phenolic acids and cinnamic acids. *Cancer Lett.*, **14**, 251–260

Stöhr, H. & Herrmann, K. (1975a) On the phenolic acids in vegetables. III. Hydroxycinnamic acids and hydroxybenzoic acids of root vegetables (Ger.). *Z. Lebensmittel. Untersuch.-Forsch.*, **159**, 218–224

Stöhr, H. & Herrmann, K. (1975b) The phenolics of fruits. V. The phenolics of strawberries and their changes during development and ripeness of the fruits (Ger.). *Z. Lebensmittel. Untersuch.-Forsch.*, **159**, 341–348

Stöhr, H. & Herrmann, K. (1975c) The phenolics of fruits. VI. The phenolics of currants, gooseberries and blueberries. Changes in phenolic acids and catechins during development of black currants (Ger.). *Z. Lebensmittel. Untersuch.-Forsch.*, **159**, 31–37

Stöhr, H. & Herrmann, K. (1975d) On the occurrence of derivatives of hydroxycinnamic acids, hydroxybenzoic acids, and hydroxycoumarins in citrus fruits (Ger.). *Z. Lebensmittel. Untersuch.-Forsch.*, **159**, 305–306

Su, Z.-Z., Grunberger, D. & Fisher, P.B. (1991) Suppression of adenovirus type 5E1A-mediated transformation and expression of the transformed phenotype by caffeic acid phenethyl ester (CAPE). *Mol. Carcinog.*, **4**, 231–242

Sugiura, M., Naito, Y., Yamaura, Y., Fukaya, C. & Yokoyama, K. (1989) Inhibitory activities and inhibition specificities of caffeic acid derivatives and related compounds toward 5-lipoxygenase. *Chem. pharm Bull.*, **37**, 1039–1043

Świątek, L., Broda, B. & Frej, E. (1971) Chemical constituents of *Veronica chamaedrys* L. (Pol.). *Acta pol. pharm.*, **28**, 189–194

TCI America (1991) *TCI America Organic Chemicals 91/92 Catalog*, Portland OR, p. 238

Toda, S., Kumura, M. & Ohnishi, M. (1991) Effects of phenolcarboxylic acids on superoxide anion and lipid peroxidation induced by superoxide anion. *Planta med.*, **57**, 8–10

Trenkle, K. (1971) *Foeniculum vulgare*: organic acids, especially phenylcarbonic acids (Ger.). *Planta med.*, **20**, 289–301

Trugo, L.C. (1984) *HPLC in Coffee Analysis*, PhD Thesis, University of Reading

Viani, R. (1988) Physiologically active substances in coffee. In: Clarke, R.J. & Macrae, R., eds, *Coffee*, Vol. 3, *Physiology*, London, Elsevier Applied Science, pp. 1–31

Wargovich, M.J., Goldberg, M.T., Newmark, H.L. & Bruce, W.R. (1983) Nuclear aberrations as a short-term test for genotoxicity to the colon: evaluation of nineteen agents in mice. *J. natl Cancer Inst.*, **71**, 133–137

Wargovich, M.J., Eng, V.W.S. & Newmark, H.L. (1985) Inhibition by plant phenols of benzo[*a*]pyrene-induced nuclear aberrations in mammalian intestinal cells: a rapid in vivo assessment method. *Food chem. Toxicol.*, **23**, 47–49

Wattenberg, L.W., Coccia, J.B. & Lam, L.K.T. (1980) Inhibitory effects of phenolic compounds on benzo[*a*]pyrene-induced neoplasia. *Cancer Res.*, **40**, 2820–2823

Zhou, Y.-C. & Zheng, R.-L. (1991) Phenolic compounds and an analog as superoxide anion scavengers and antioxidants. *Biochem. Pharmacol.*, **42**, 1177–1179