

## Ellagic Acid, an Anticarcinogen in Fruits, Especially in Strawberries: A Review

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The various roles of ellagic acid as an anticarcinogenic plant phenol, including its inhibitory effects on chemically induced cancer, its effect on the body, occurrence in plants and biosynthesis, allelopathic properties, activity in regulation of plant hormones, formation of metal complexes, function as an antioxidant, insect growth and feeding inhibitor, and inheritance are reviewed and discussed in relation to current and future research.

Ellagic acid (C<sub>14</sub>H<sub>6</sub>O<sub>6</sub>) is a naturally occurring phenolic constituent of many species from a diversity of flowering plant families. Interest in ellagic acid has increased greatly during the last decade due to its effectiveness as an antimutagen and anticarcinogen and its potential as an inhibitor of chemically induced cancer. Much has been learned since 1980 concerning the clinical attributes of ellagic acid, but relatively little is known about the physiological, genetic, and ecological aspects of ellagic acid and its naturally occurring derivatives in the plant. We know that ellagic acid is present in a wide variety of plants and its presence or absence may be significant taxonomically, but we are only beginning to notice intraspecific variation.

Ellagic acid exists in plants in a great many derivative forms that differ in volatility, mobility, and reactivity in plant as well as in animal systems. Research has progressed at a rapid rate among medical research programs studying ellagic acid as a potential anticarcinogen or in blood clotting research. Exploring dietary sources of ellagic acid, the

digestibility of natural forms of ellagic acid, and the distribution and organ accumulation or excretion in animal systems is in progress at several institutions. Recent interest in ellagic acid in plant systems has been largely for fruit-juice processing and wine industry applications. However, new studies also suggest that ellagic acid participates in plant hormone regulatory systems, allelopathic and autopathic effects, insect deterrent principles, and insect growth inhibition, all of which indicate the urgent need for further research to understand the roles of ellagic acid in the plant.

Carcinogenic and mutagenic factors, whether natural or products of industry, are ubiquitous in our environment. We may minimize our exposure to these carcinogens, but it is unlikely that they will ever be eliminated. Many efforts have been directed toward improving dietary habits to minimize cancer risk. In addition, the identification of naturally occurring anticarcinogens and antimutagens present in the diet is becoming increasingly important. A comprehensive knowledge of the cancer inhibitory properties of anticarcinogens necessitates an understanding of their action, and their physiological roles in plants.

### Ellagic acid: Anticarcinogen/antimutagen

Ellagic acid has shown promise as an inhibitor of chemically induced cancer in *in vivo* studies with rats and mice and in *in vitro* studies with rat, mouse, and human tissue explants (Table 1). Antimutagenicity studies are generally done by assessing the inhibition by ellagic acid of potentially mutagenic chemicals in cultures of the bacterium *Salmonella typhimurium*.

Data have been reviewed on the effectiveness of ellagic acid as an anticarcinogen and antimutagen and on its mode of action as an inhibitor of chemically induced cancer (De Flora and Ramel, 1988; Hayatsu et al., 1988; Stoner, 1989).

### Mode of inhibition

The inhibition of cancer by ellagic acid appears to occur through the following mechanisms:

*a.* Inhibition of the metabolic activation of carcinogens. For example, ellagic acid inhibits the conversion of polycyclic aromatic hydrocarbons [e.g., benzo (*a*) pyrene, 7,12-dimethylbenz (*a*) anthracene, and 3-methylcholanthrene], nitroso compounds (e.g., *N*-nitrosobenzylmethylamine and *N*-methyl-*N*-nitrosourea), and aflatoxin B<sub>1</sub> into forms that induce genetic damage (Dixit et al., 1985; Teel et al., 1985; Mandal et al., 1987, 1988).

*b.* Carcinogen detoxification by stimulation of enzyme (e.g., glutathione *s*-transferase) activity is increased toward benzo(*a*) pyrene-4,5-oxide and 1-chloro-2,4-dinitrobenzene substrates in mice (Das et al., 1985).

*c.* Binding to reactive metabolic forms of the carcinogen to form a harmless complex that is incapable of reacting with cellular DNA, i.e., acts as a scavenger. Ellagic acid reacts with benzo (*a*) pyrene diol epoxide by taking a sterically favorable position to form a covalently linked product in which the reactive epoxide ring of the pyrene is opened, rendering the carcinogen harmless (Sayer et al., 1982).

*d.* Occupation of sites in DNA that might otherwise react with carcinogens or their metabolites. Ellagic acid inhibited the binding of *N*-methyl-*N*-nitrosourea to salmon sperm DNA by reacting with the O<sup>6</sup> position in guanine and preventing methylation at that site (Dixit and Gold, 1986; Teel, 1986).

### Conflicting evidence

Although ellagic acid shows promise as an inhibitor of chemically induced cancer, conflicting data have been presented in the literature on its effectiveness in preventing carcinogenesis or even DNA-adduct formation (Table 1). The high affinity of the strongly nucleophilic 4-OH group for electrophilic

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Table 1. Anticarcinogenic and antimutagenic activity of ellagic acid.

Carcinogen	Tissue: donor	Response <sup>a</sup>	Reference
Benzo (a) pyrene	Skin; rat	AC	Del Tito et al., 1983
	Lung explants; mouse	AC	Dixit et al., 1985; Teel et al., 1985
		AC	Chang et al., 1985
	Skin; mouse	AC	Mukhtar et al., 1984b
	Skin explant; mouse	AC	Lesca, 1983
	Lung, skin; mouse	AC	Teel et al., 1986a, 1986b
	Lung explant; human	AC	Wood et al., 1982
Salmonella (Ames) test	AM	Smart et al., 1986a	
Aflatoxin B <sub>1</sub>	Lung, skin; mouse	NE	San and Chan, 1987;
	Salmonella (Ames) test	AM	Mandal et al., 1987
	Tracheobronchial explants; rat, human	AC	Mandal et al., 1987
7,12-Dimethylbenz (a) anthracene	Mammary; rat	NE	Singletary and Liao, 1989
Nitroso compounds	Rat	AC	Barth and Fox, 1988; Mandal et al., 1988, 1990
	Salmonella (Ames test)	AM	Dixit and Gold, 1986
3-Methylcholanthrene	Skin; mouse	AT	Mukhtar et al., 1984a, 1986
	Skin; mouse	NE	Smart et al., 1986b
N-2-fluorenylacetamide	Liver: rat	AC	Tanaka et al., 1988

<sup>a</sup>AC = anticarcinogenic effect; AM = antimutagenic effect; AT = antitumorigenic; NE = no AC or AM effects detected.

metabolizes that are non-DNA-reactive substances may effectively remove ellagic acid from biological systems and prevent it from acting as an anticarcinogen (Hayatsu et al., 1988). Absorption of ellagic acid into the body from a dietary source also appears to be limited. Ellagic acid fed orally to mice was found to be poorly absorbed and is eliminated as free ellagic acid and in conjugated forms (Tee] and Martin, 1988; Smart et al., 1986a), which may prevent tissues from attaining sufficiently high concentrations for it to be effective as an in-vivo anticarcinogen. Synthetic lipophilic derivatives of ellagic acid, especially 3-*o*-decylellagic acid, have greater affinities for lung and other tissues than has ellagic acid proper (Smart et al., 1986a).

### Human immunodeficiency virus inhibition

Ellagic acid and some ellagitannins have shown inhibitory properties against replication of human immunodeficiency viruses (HIV) (Asanaka et al., 1988; Take et al., 1989) and of avian myeloblastosis virus (AMV) reverse transcriptase and cellular DNA polymerases  $\alpha$  and  $\beta$  (Take et al., 1989). Ellagic acid, unlike antibiotics such as Colistin or Enduracidine A, inhibits DNA polymerases nonspecifically. The antiviral activity of some ellagitannins may be due to inhibition of adsorption of HIV onto cells, as well as inhibition of reverse transcriptase activity (Asanaka et al., 1988; Take et al., 1989). Studies by Asanaka et al. (1988) with mice suggest that the ellagitannin oenotherin B may be effectively used by oral administration for inhibition of HIV and herpes virus.

### Other effects on the body

Ellagic acid also has been found to control hemorrhage in animals (Girolami et al., 1966) and humans (Cliffton, 1967). In promoting

clotting, ellagic acid activates the Hageman clotting factor (Factor XII) in blood (Bock et al., 1981). Ellagic acid is used widely in blood research to study factors affecting clotting, or thrombosis. It also may have some hypotensive (lowering blood pressure) and sedative effects according to preliminary research with rodents (Bhargava et al., 1968).

### Occurrence in plants

Ellagic acid is a naturally occurring phenolic constituent of many flowering plant species (Bate-Smith, 1961 b). In the family Rosaceae (Bate-Smith, 1961a) and in the Fagaceae (Giannasi and Niklas, 1981), ellagic acid has been used as a chemotaxonomic guide. In the Rosaceae, it was found to be widely distributed in the subfamily Potentilleae (e.g. species of *Potentilla*, *Comarella*, *Duchesnea*, and *Fragaria*) and in the closely related genera *Rubus*, *Geum*, and *Waldsteinia*. Ellagic acid was also detected in the Rosaceous genera *Purshia*, *Filipendula*, *Acaena*, *Alchemilla*, *Agrimonia*, *Poterium*, and *Rosa*, but not among >70 *Prunus* spp. examined. These early studies focused on determining the presence of ellagic acid and were not quantitative. Recent studies have focused on quantification of ellagic acid in human dietary sources, especially fruits and nuts (Boyle and Hsu, 1990; Daniel et al., 1989; Maas et al., 1991; Wang et al., 1990).

Ellagic acid is a derivative of gallic acid, a trihydroxybenzoic acid, and its presence indicates a close relationship with plants possessing the trihydroxyflavonoid constituents, myricetin and leucodelphinidin. This relationship was found to hold for many members of the Saxifragaceae, Cunoniaceae, and Myrothamnaceae that are closely related to the Rosaceae. However, while members of the Leguminosae possess trihydroxy substituted phenolics, they lack ellagic acid (Bate-Smith, 1961a).

### Biosynthesis

Chemically, ellagic acid (Fig. 1) is 2,3,7,8-tetrahydroxy[1]benzo-pyrano-[5,4,3-cde] [1] benzopyran-5,10-dione, C<sub>14</sub>H<sub>6</sub>O<sub>8</sub>, with a molecular weight of 302.19. It can be prepared from natural sources (*Eucalyptus* bark, walnuts, etc.) by sodium persulfate oxidation of gallic acid or by acid hydrolysis of crude tannin (Zee-Cheng and Cheng, 1986). In nature, ellagic acid may occur in free form, but more commonly in the form of ellagitannins as esters of the diphenic acid analog on glucose.

Ellagic acid is formed by oxidation and dimerization of gallic acid; thus, it is a dilactone of the dimer of gallic acid. Oxidation is hastened by alkaline conditions, whereas hydrolysis and lactonization is favored by acidic conditions (Tulyathan et al., 1989). Ishikura et al. (1984) postulate two pathways for gallic acid formation; through B-oxidation of phenylpropanoid and through dehydrogenation of shikimic acid in *Rhus* and *Acer*. The preferential pathway may be determined by leaf age, although temperature studies were not undertaken. The pathway from phenylalanine to cinnamic acid via phenyllactic acid is a possible pathway in strawberries. Activity of the delaminating enzyme phenylalanine ammonia-lyase (PAL) corresponds to the accumulation of anthocyanin in strawberry fruit (Given et al., 1988; Hyodo, 1971) and of flavonoids and cinnamic acids in strawberry leaf disks (Creasy, 1971); however, the relationship has not been determined between PAL activity and ellagic acid production.

Tannins and associated polyphenols in plant extracts have been widely studied for their medicinal and antimutagenic and anticarcinogenic properties (Hayatsu et al., 1988; Ito et al., 1989; Iwu and Anyanwu, 1982 Okuda et al., 1989; Sigman et al., 1984). Geraniin, a tannin constituent of many plants, including *Geranium thunbergii* Sieb. and Zucc., which is one of the most frequently used medicinal plants in Japan, produces ellagic acid abundantly by hydrolysis (Okuda et al., 1984). Geraniin, on hydrolysis, also produces gallic acid, which may form a dimer than can convert to ellagic acid.

Our studies (Maas et al., 1991) and the work of others (e.g. Daniel et al., 1989; Nemeč, 1973) have shown that ellagic acid occurs in strawberries, but we do not know its

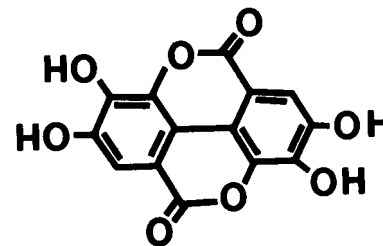


Fig. 1. Ellagic acid.

function or route of synthesis in strawberries. In other plants, ellagic acid has been shown to occur in several derivative forms (Table 2).

The listing of derivatives of ellagic acid illustrates some of the complexity involved in determining the function of ellagic acid in plants, and which forms may be most effective as anticarcinogens.

### Allelopathy, fungistasis, and auto-inhibition

Ellagic acid, as a derivative of gallic acid and as a phenol, probably shares some of the properties of these constituents. Hydrolyzable tannins, especially gallotannins, have been implicated as allelopathic agents (Rice, 1984). A recent review (Rice, 1984) of allelopathy lists the involvement of hydrolyzable tannins, including ellagic acid, as plant growth and seed germination inhibitors and growth inhibitors of N-fixing and vitrifying bacteria. Ellagitannins produced by the white oak (*Quercus alba* L.) apparently protect the heartwood of the tree from fungal decay (Hart and Hillis, 1972). They suggest that the ellagitannins inhibit certain fungal enzymes due to their protein-binding capacities.

Ellagic acid was identified as one constituent of a *Xanthium* sp. exhibiting allelopathy (Inam et al., 1987). However, ellagic acid by itself was ineffective in inhibiting root growth or protein synthesis of lettuce seedlings, while ferulic and cinnamic acids were effective (Cameron and Julian, 1980; Krogmeier and Bremner, 1989). These studies do

illustrate, however, that experimentation has been done mostly with ellagic acid in its free form and not with glycoside derivatives such as those produced by the plant. Auto-inhibition of rooting in chestnut tree cuttings was related to the presence of 3,3,4-tri-*o*-methyl-ellagic acid (Vieitez et al., 1987; Vieitez and Ballester, 1988). In tests with beans, this ellagic acid derivative reduced the number of roots by 32% when added to the rooting medium at  $10^{-5}$  M. When added to indoleacetic acid (IAA) at equimolar concentrations ( $10^{-5}$  M), the rooting activity of the auxin was reduced by 31.570. Similarly, phenolic exudates hamper in-vitro propagation of geraniums (*Pelargonium × hortum*). Hildebrandt and Harney (1989) identified ellagic acid and several gallic acid derivatives in exudates as responsible for the inhibitory activity. The naturally abundant tannin, geraniin, in *Pelargonium* spp. readily hydrolyzes to release ellagic and gallic acids (Okuda et al., 1984).

### Plant hormone regulation

Ellagic acid was among the polyphenolic substances thought to function in the regulatory degradation system of IAA in strawberries (Runkova et al., 1972). Polyphenols in this system inhibited degradation of IAA by peroxidases, whereas monophenols (e.g., *p*-hydroxyphenylacetic acid and *p*-hydroxybenzoic acid) enhanced peroxidase degradation of IAA in strawberry tissues. Forcing photosynthesis to occur at a high rate with illumination caused production of increased amounts of polyphenols, while low or no illumination favored degradation of polyphenols and synthesis of monophenols as an integral part of the IAA regulatory system.

### Metal complexes

Because of the ability of its four phenolic groups to readily form complexes with metals, such as Mg and Ca, ellagic acid can cause the formation of insoluble aggregates. These ellagic acid-metal ion complexes have been implicated in promoting blood clotting (Bock et al., 1981) and in causing harmful scale accumulation on metal surfaces in the wood pulping process (Hewitt and Nelson, 1965; Press and Hardcastle, 1969). In general, orthodihydroxyphenols chelate with many metals. Ellagic acid has been shown to form complexes with mono-, di-, and trivalent metals as well as with various organic solvents (Nelson, 1965); it also forms a fluorescent complex with sodium borate (borax) that was found to be useful for its identification in samples (Wolfbeis and Hochmuth, 1986).

### Antioxidant

Their metal chelating capacity together with their ability to react with free radicals gives many polyphenols effective antioxidant properties. Ellagic acid has been shown to function as an antioxidant (Osawa et al., 1987; Suet et al., 1988), that is, as an oxidative sub-

strate. It can terminate oxidations mediated by free radicals in a system, thus protecting other constituents from oxidation. This may be the mechanism of MA degradation inhibition described above. The oxidation mechanisms of ellagic and gallic acids during wine aging and related food processing have been determined by Tulyathan et al. (1989). They present a scheme of gallic acid oxidation and dimerization and of dilactone (ellagic acid) formation to explain regenerative polymerization in wines as a natural process when wines are made alkaline (Singleton, 1987). Gallic acid and ellagitannins are extracted by ethanol, along with other phenols, in wine aged with white-oak heartwood cooperage (Quinn and Singleton, 1985). Ellagitannins extracted though barrel aging may survive for at least several years in the wine.

Ellagic acid also has been shown to act as an exogenous antioxidant. It may prevent oxidation of edible oil, fats, methyloleate, lard, and soybean and performs as well as or better than  $\alpha$ -tocopherol or *t*-butylanisole (Dziedzic and Hudson, 1984; Kurechi and Kunugi, 1983). In mammalian systems, ellagic acid and its derivatives show inhibitory activity against lipid peroxidation in mitochondria and microsomes (Okuda et al., 1983) and the cytochrome P450-dependent monooxygenase system.

Preferential oxidation of polyphenolic constituents of the pellicle of the walnut (*Juglans regia* L.) may protect the walnut kernel against decomposition (Jurd, 1956). Complete hydrolysis of walnut pellicle tannins yielded 50% of its weight as ellagic acid, 15% as gallic acid, plus methyl gallate and a considerable amount of glucose.

### Insect growth and feeding inhibition

Ellagic acid is an endogenous inhibitor of insect growth and a deterrent of insect feeding on certain plants (Klocke et al., 1986). Several semi-arid species of *Geranium*, *Erodium*, *Tamarix*, *Quercus*, *Cistus*, and *Heliothis* possess the ellagitannin, geraniin, which acts as a protoxin that releases insect growth inhibitors, particularly ellagic acid, upon hydrolysis. Ellagic acid inhibits growth of the polyphagous herbivorous tobacco budworm [*Heliothis virescens* (Fabr.) (Noctuidae)]. Klocke et al. (1986) have shown that several members of the rose family inhibit the growth of insects, e.g., species of *Amelanchier*, *Cercocarpus*, *Rosa*, and several other genera. *Fragaria* spp. were not included. However, several *Fragaria chilensis* clones were shown recently to be resistant to root-chewing insects (Shanks et al., 1984).

Inhibition mechanisms of ellagic acid to chewing insects and aphids may be quite different. For example, differential sensitivity among aphid species to several ellagitannins and related phenolic compounds and derivatives was shown in feeding-deterrent studies (Jones and Klocke, 1987). The ellagitannins geraniin and pedunculagin were active against *Schizaphis graminum* and *Myzus persicae*, but not against *Acrythosiphon pisum*. Ellagic and

Table 2. Examples of naturally occurring derivatives of ellagic acid.

3,4,4'-trimethylellagic acid <sup>2</sup>
3,4,5,5'- <i>o</i> -tetramethyl-3',4'- <i>o</i> , <i>o</i> -methylideneboruleoellagic acid <sup>2</sup>
3,4,5- <i>o</i> -trimethyl-3',4'- <i>o</i> , <i>o</i> -methylidene flavellagic acid <sup>2</sup>
3,3'-4- <i>tri-o</i> -methylellagic acid <sup>3</sup>
3,4,4'- <i>tri-o</i> -methylellagic acid <sup>3</sup>
3,3'- <i>di-o</i> -methylellagic acid 4'-rutinoside <sup>4</sup>
3,4,3'- <i>tri-o</i> -methylellagic acid <sup>3</sup>
5'-methoxy-3,4,3'- <i>tri-o</i> -methylflavellagic acid <sup>3</sup>
3,4,3'- <i>tri-o</i> -methylflavellagic acid <sup>3</sup>
ellagic acid 3,3'- <i>di-o</i> -methyl ether <sup>3</sup>
<i>tri-o</i> -methylellagic acid <sup>3</sup>
3,3'- <i>di-o</i> -methylellagic acid 4'-beta-D glucoside <sup>3</sup>
tetramethylellagic acid <sup>3</sup>
tetra- <i>o</i> -methylellagic acid <sup>3</sup>

<sup>2</sup>From *Agrostistachys hookeri*; 3,3',4-*o*-trimethylellagic acid cytotoxic to cultured P-388 lymphocytic leukemia cells. Choi et al., 1988.

<sup>3</sup>From chestnut (*Castanea* sp.) cuttings; inhibits rooting of cuttings. Vieitez et al., 1987.

<sup>4</sup>From *Euphorbia acaulis* rhizomes. Bindra et al., 1988.

<sup>5</sup>From *Rhabdodendron macrophyllum*. Filho et al., 1985.

<sup>6</sup>From *Polygonum hydropiper* root. Fukuyama et al., 1983.

<sup>7</sup>From *Acalypha indica* leaves, twigs. Talapatra et al., 1981.

<sup>8</sup>From *Anogeissus latifolia* heartwood. Deshpande et al., 1981.

<sup>9</sup>From several species. Geevanada et al., 1980.

<sup>10</sup>From *Geum elatum*. Painuly et al., 1984.

gallic acids, however, were inactive against *M. persicae* and *A. pisum*.

## Inheritance

The manner of ellagic acid inheritance is not known. Strawberry (Maas et al., 1991), and blackberry and apple (Maas et al., unpublished), and muscadine grape (Boyle and Hsu, 1990) cultivars differ in amounts of ellagic acid in tissues. We presume by analogy with other metabolites that cultivar differences are characteristic of each cultivar and that inheritance of relative ellagic acid content has either a high general or high specific combining ability (Galletta and Maas, 1990). Analogous inheritance mechanisms could occur with, ascorbic acid (vitamin C) and total soluble carbohydrates. Since the major portion of ellagic acid is presumably derived from a single metabolic pathway through gallic acid, we may find in strawberry that specific combining ability is of greater importance than general combining ability in ellagic acid inheritance, just as with ascorbic acid inheritance. The same may be true for gallic acid and geraniin inheritance, but probably not for massed derivatives of either constituent (e.g., ellagitannins as a group). If this hypothesis is correct, breeding for high (or low) ellagic acid content of fruit, or any other structure, should be highly successful. However, one unexpected observation in our examination of strawberry tissues was that no correlation was found among ellagic acid contents of fruit pulp, achenes, and leaf tissue (Maas et al., 1990). This may indicate that selection for ellagic acid content can be highly specific for tissue type, e.g., for high fruit content but low leaf content, etc. The reverse situation may be advantageous in muscadine grapes where ellagic acid is one component of the troublesome phenolics extracted with juice for commercial processing (Boyle and Hsu, 1990; Spiers, 1988), and of precipitates in wine made from loganberry (Singleton et al., 1966).

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