Chapter 1

Ellagitannins Renewed the Concept of Tannins

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1.1 Old and New Concepts of Tannins

The pharmacological activities of tannins described in medicinal books before the recent achievements on ellagitannin chemistry were mostly those of gallotannins and condensed tannins of poor chemical uniformity. The gallotannins extracted from Chinese or Turkish gall, sometimes called tannic acid, are variable mixtures of polygallates of carbohydrates. They cause irritation on skin and mucous membranes, although they have been utilized in some traditional medicinal applications, and are technically defined on the basis of their general capacity to bind to proteins and nitrogen basic compounds such as alkaloids. The condensed tannins, mixtures of oligomeric and polymeric flavanols (e.g., catechins), are chemically more unstable and heterogeneous, thus conforming to the
old concept of tannins. They were mainly used for leathering and staining, although some plants containing them have been used as traditional medicines. Phlorotannins are highly unstable oligomers of phloroglucinol (i.e., 1,3,5-trihydroxybenzene) produced by algae that have never been isolated without being first converted into their methyl or acetyl derivatives, and as such they constitute a third but rather peculiar group of tannins.

As for ellagitannins, although some members of this class of hydrolyzable tannins were obtained early on, it is the isolation and structural determination of over 500 pure compounds since 1975 from various plants, many of which used in traditional medicines, that brought remarkable changes in the definition and concept of “tannins” (Haslam, 1989, Okuda, 1995, 1999a, 2005, Okuda et al., 1990, 1991, 1992a, 1993a, 1995, 2000, Quideau and Feldman, 1996).

1.1.1 About the chemical stability of ellagitannins

Geraniin, from Geranium thunbergii, which is one of the most popular medicinal plants used in Japan, was isolated as crystals, thus allowing its precise chemical analyses (Okuda et al., 1982a) and X-ray crystallography (Luger et al., 1998). The purified crystalline geraniin was surprisingly found to give almost no astringent taste, while its capacity to bind to hemoglobin and basic compounds, as evaluated by the relative astringency (RA) and relative affinity to methylene blue (RMB) index values (see Section 1.6.2), are comparable to those of other main tannins (Okuda et al., 1985). The biological and pharmacological activities, successively found for geraniin and other purified ellagitannins, were remarkably different from those of the “tannins” vaguely imagined in the past. The biogenetic sequences of these newly found tannins allowed propositions about the chemical and biological correlations among hydrolyzable tannins produced in nature. The old concept of “tannins”, which merely meant mixtures of hardly identifiable and unstable phenolics, has now been replaced by a new concept through which tannins, particularly ellagitannins, can be considered in a way similar to that of other types of natural organic products, such as terpenoids and alkaloids. Unlike the “tannins” of the old concept, these
isolated ellagitannins generally remain intact when in contact with air. The various biological and pharmacological properties of these tannins can be determined for each individual compound.

1.1.2 Definition of ellagitannins in the narrow and wider senses

Geraniin (Okuda et al., 1976, 1982a) can be regarded as a keystone in the ellagitannin biooxidation process, since it is structurally classified as a dehydroellagitannin that is located at a junction in the biogenesis of the whole ellagitannin family. Geraniin has also been found in several oligomeric molecules as a composing monomer. Rapid developments were made in the field of ellagitannin chemistry after the discovery of geraniin, leading to the isolation of others dehydroellagitannins, as well as products of further biogenetic oxidation, and also oligomers, up to pentamers (Yoshida et al., 1999, 2005).

While several ellagitannins had been isolated from the fruits of Terminalia chebula (i.e., myrobalans) since 1947 (Schmidt and Mayer, 1956), and also from Castanea and Quercus species of the Fagaceae family (Mayer, 1971), new techniques of isolation, spectroscopy and biological screening (Okuda et al., 1989a) enabled in more recent years rapid developments, which notably helped with the partial revision of some of their structures (Okuda et al., 1980a, Yoshida et al., 1980). Furthermore, these in-depth investigations also served to gather important insights on plant genealogy, for the structural diversity thus unveiled about ellagitannins was found to correlate to the evolution and classification of the plants that contain them (Okuda et al., 2000).
Ellagitannins can be defined in a narrow sense as hexahydroxydiphenoyl esters of carbohydrates or cyclitols, while the definition of ellagitannins in a wider sense also cover compounds derived from further oxidative transformations, including oligomerization processes (Okuda et al., 1995). It is this latter and wider definition that will be taken into account throughout this book.

1.1.3 Stereochemistry of ellagitannins – Absolute configuration of HHDP, DHHDP and chebuloyl group

Chemical and circular dichroism (CD) spectral studies have shown that the absolute configuration of the atropisomeric biaryl HHDP groups at the O-2–O-3 and O-4–O-6 positions of the α-glucopyranose core of most ellagitannins is S, such as in the molecule of pedunculagin, whereas the
configuration of the HHDP group at the O-3–O-6 positions, such as in geraniin, is \( R \). The absolute configuration at the methine carbon of the DHHDP group at the O-2–O-4 positions in geraniin, terchebin and mallotusinic acid (Okuda and Seno, 1981) is \( R \), whereas this configuration is \( S \) in isoterchebin (see structure 27 in Chapter 2) (Okuda et al., 1982e/f). The methine carbon of the chebuloyl group in the molecules of chebulinic acid and chebulagic acid, which are biogenetically derived from geraniin, retains the stereochemical features of the DHHDP group at the O-2–O-4 positions of geraniin (Yoshida et al., 1980, 1982).

1.1.4 Condensation of dehydroellagitannins with other substances

Tannins are, in general, capable of interacting with co-existing substances, and are often bound to basic compounds, proteins and other high molecular mass compounds, as well as metallic ions. Besides the binding activities indexed by the aforementioned RA and RMB values, dehydroellagitannins also express structure-specific reactivity in condensation reactions with certain co-existing substances under mild conditions.

For example, a condensation product derived from geraniin and ascorbic acid, ascorgeraniin (or elaeocarpusin) was isolated from Geranium thunbergii and also from Acer nikoense and Elaeocarpus sylvestris. This compound also co-exists with geraniin in some other Acer, Rhus and Cercidiphyllum species. It has been prepared by condensation of geraniin with ascorbic acid in a moderately acidic aqueous or a methanolic aqueous solution at room temperature, thus demonstrating that it could be produced in the plant without any enzyme intervention (Okuda et al., 1986a/b). An analog, putranjivain A, was isolated from several euphorbiaceous plants (Lin et al., 1990).
Phyllanthusiin D, a condensation product of geraniin with acetone, was isolated from acetone and aqueous acetone homogenates of *Phyllanthus flexuosus*, *Phyllanthus amarus*, and also from suspension cultures of *Geranium thunbergii* (Yazaki et al., 1991). In this case, it is likely that phyllanthusiin D is simply an artefact formed during the extraction procedure, since it was produced when geraniin was refluxed in dry acetone containing a small amount of trifluoroacetic acid. One can here also mention the condensation reaction between geraniin and ortho-phenylenediamine in weakly acidic media that yields a phenazine derivative, a reaction commonly used to determine the presence of a DHHDP group in an ellagitannin molecule.
1.1.5 Accumulation of an ellagitannin of specific structure in a plant

Often a monomeric or an oligomeric ellagitannin is the main component of a plant species, and the pharmacological activity of that plant is sometimes attributable essentially to that component. Geraniin is the main component of *Geranium thunbergii* (*Geraniaceae*), making up over 10% by weight of the dry leaf. It is also the main component in other *Geranium* species (Okuda et al., 1980b), usually accompanied by small amounts of analogs such as dehydrogeraniin, furosinin (Okuda et al., 1982d), ascorgeraniin (Okuda et al., 1986a) and geraniinic acids B and C (Ito et al., 1999a).

![Dehydrogeraniin: R = (β)-OG](image1)

![Furosinin: R = OH](image2)

![Geraniinic acid B: R¹ = COOH, R² = H](image3)

![Geraniinic acid C: R¹ = H, R² = COOH](image4)

Dimeric agrimoniin, oenotherin B (and its trimeric variant, oenotherin A, see also Section 1.3.5) and coriariin A are also the main components in *Agrimonia pilosa* (Okuda et al., 1982b), *Oenothera erythrosepala* (Hatano et al., 1990a), and *Coriaria japonica* (Hatano et al., 1986), respectively, and are usually accompanied by smaller amounts of the monomers composing these dimers and higher oligomers.
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1.2 Distribution of Ellagitannins in the Plant Kingdom

Ellagitannins of various structures, which are derived from biosynthetic stepwise oxidation of gallotannins (Okuda et al., 2000) and subsequent oligomerization processes (Okuda et al., 1993a), are generated by plant species of the Dicotyledoneae in the Angiospermae, mostly by plant species of the Choripetalae. This distribution in plants is similar to that of gallotannins, but ellagitannins are by far much richer in structural diversity and, unlike gallotannins, are isolable as pure and stable compounds. Ellagitannins are absent in most orders of Sympetalae, which rank higher in the Dicotyledoneae plant evolution system. This rather limited distribution of ellagitannins contrasts with the wider distribution observed for condensed tannins and caffetannins (caffeic acid esters), which are also found in Monocotyledoneae plant species in the Gymnospermae. It is interesting to note that ellagitannins are often the tannins identified as active principles in medicinal plants (Okuda et al., 1989b), and that the condensed tannins expressing biological activities are often those that are galloylated, thus featuring structural motifs analogous to those of hydrolyzable tannins, such as in the active condensed tannins found in rhubarb, Polygonum multiflorum, Saxifraga, stolonifera, and Diospyros kaki (Okuda, 1999a).

1.3 Formation and Classification of Ellagitannins in Plants

Ellagitannins can be classified according to their biogenetic oxidation stages (Okuda et al., 2000).

1.3.1 Oxidative biological transformations from gallotannins to ellagitannins and dehydroellagitannins

The characteristic unit of all ellagitannins, the hexahydroxydiphenoyl (HHDP) group, is the product of the first-stage biogenetic oxidation of galloyl groups. Linking one or two additional galloyl group(s) to the HHDP unit via C–O or C–C bond formation gives rise to several variations of the HHDP group, such as those shown below.
The HHDP group produced in the primary class of ellagitannins can then be oxidized to dehydrohexahydroxydiphenoyl (DHHDP) group (Fig. 1.1). The compounds that bear this DHHDP group are referred to as “dehydroellagitannins” and exemplified by inter alia geraniin, terchebin and furosinin. Among the special chemical reactivity features of the DHHDP group, a cyclohexenetrione linked to a pyrogallol, are (1) the aforementioned facile condensation with other compounds such as ascorbic acid and ortho-phenylenediamine (vide supra) that furnish ascorgeraniin and phenazine derivatives (Fig. 1.2) and (2) the equilibrium in aqueous or alcoholic solutions between five- and six-
membered hemiacetal or acetal rings. Geraniin, in its crystalline form, adopts the six-membered hemiacetal ring form, but equilibrates back into a mixture of both cyclic hemiacetals or acetals when dissolved in an aqueous or an alcoholic solution. This behavior is reminiscent of that observed for D-fructose, which adopts a cyclic pyranose structure in the crystalline state, but equilibrates between fructopyranose and fructofuranose in aqueous solutions (Okuda et al., 1982a).

Further oxidative transformations of the DHHDP group yield several other subclasses of ellagitannins, some members of which are shown in the following part of this chapter and in Chapter 2.

1.3.2 Regiospecificity of the HHDP group on the glucose core, and its correlation to plant families

The positioning of the HHDP group or its oxidized variants on the glucose core is generally the same in ellagitannins produced by plant species of the same family. Thus, one type of ellagitannins bears the HHDP group at their glucose O-2~O-4 and/or O-3~O-6 positions, and another type bears it at their O-2~O-3 and/or O-4~O-6 positions. Ellagitannins of the former type such as geraniin, corilagin and granatin B are produced by plants of the Geraniaceae, Combretaceae and Punicaceae families, as well as in most species of euphorbiaceous plants. The latter type of ellagitannins exemplified by pedunculagin and
casuarictin are found in plants of other families, e.g., Betulaceae, Coriariaceae, Cornaceae, Fagaceae, Hamamelidaceae, Lecythidiaceae, Lythraceae, Melastomataceae, Myrtaceae, Nyssaceae, Onagraceae, Rosaceae, Theaceae and Trapaceae.

Fig. 1.2  Examples of condensation reactions of the geraniin DHHDP group yielding ascorgeraniin and a phenazine derivative.

1.3.3  C-glycosidic ellagitannins and complex tannins

1.3.3.1  Occurrence of C-glycosidic tannins in plants

The C-glycosidic tannins that are exemplified by casuarinin, stachyurin and casuariin, first isolated from Casuarina stricta (Okuda et al., 1982c,
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1983a), are widely distributed in various plant species of *Casuarinaceae, Stachyuraceae, Myrtaceae, Betulaceae, Fagaceae, Hamamelidaceae, Lythraceae, Punicaceae, Melastomataceae, Rosaceae, Elaeagnaceae, Theaceae and Juglandaceae* families (Okuda et al., 1982h). Castalagin and vescalagin were found in the woody *Castanea* and *Quercus* species (Mayer, 1971). The so-called complex tannins, which commonly referred to ellagitannins having a flavanol-based motif linked to C-1 of the glucose core through a C–C bond, occur in some species of *Fagaceae, Combretaceae, Myrtaceae, Theaceae* and *Melastomataceae*, and constitute a subclass of C-glycosidic ellagitannins (Yoshida et al., 1992a).

![Diagram of tannin structures](image-url)

- **Casuarinin**: $R^1 = H$, $R^2 = OH$
- **Stachyurin**: $R^1 = OH$, $R^2 = H$
- **Castalagin**: $R^1 = H$, $R^2 = OH$
- **Vescalagin**: $R^1 = OH$, $R^2 = H$
- **Camelliatannin A**
1.3.3.2 Biomimetic synthesis of C-glycosidic ellagitannins

Casuarinin was biomimetically synthesized through an acid-catalyzed intramolecular phenol-aldehyde coupling reaction of liquidambin (Fig. 1.3, see also Fig. 9.6 in Chapter 9), an aldehydic ellagitannin presumed to be the key biosynthetic precursor of C-glycosidic ellagitannins (Okuda et al., 1987). The complex tannins camelliatannins A and B were hemisynthesized by condensation of casuarin with (−)-epicatechin (Fig. 1.3), and also by conversion of camelliatannins E and C, respectively, via a treatment with polyphosphoric acid (Fig. 1.4). The transformation of camelliatannin A into camelliatannin F, featuring a cyclopentenone ring, was achieved by heating camelliatannin A in a mixture of ethanol and acetic acid (Fig. 1.4, Hatano et al., 1995).

1.3.4 Oligomerization of ellagitannins leading to pentamers

The first oligomeric hydrolyzable tannin isolated in 1982 was agrimoniin (vide supra), which remarkably displays α-glycosidic linkages on both of its constituting monomeric units (Okuda et al., 1982b). Its isolation was followed by that of gemin A (vide infra), a dimer having both α and β linkages (Yoshida et al., 1982), and gemins B-F (Yoshida et al.,
1985a/b), as well as various oligomers up to pentamers, including a dimer of geraniin, \textit{i.e.}, acalyphidin D\textsubscript{1} (Yoshida \textit{et al.}, 1992b, 1999, 2005). Such oligomers often express specific pharmacological activities (\textit{vide infra}) that are not shared by monomeric ellagitannins and other tannins.

Fig. 1.3 Synthesis of camelliatannins A and B from casuarin and epicatechin. Casuarin derived from liquidambin via 5-\textit{O}-desgalloylation of casuarinin (see Fig. 9.6 in Chap. 9).
1.3.4.1 Oligomers as main components in a plant species

*Agrimonia pilosa* (Rosaceae), an antidiarrheic in Japan, produces agrimoniin as the main component accompanied by small amounts of potentillin, the monomer composing the agrimoniin molecule, and several other monomers. Agrimoniin is also the main component in *Agrimonia eupatria*. Oenothein B, a macrocyclic dimer, is the main component in *Oenothera erythrosepala* (Onagraceae) and is
accompanied by the trimer oenothein A and tellimagrandin I, the monomer composing these oligomers (Hatano et al., 1990a). Coriariin A is the main component in *Coriaria japonica* (*Coriariaceae*) (Hatano et al., 1986). The monomers frequently found as constituents of these oligomeric molecules are tellimagrandins I and II, pedunculagin and casuarictin as further exemplified below by the structure of gemin A.

1.3.4.2 *Oligomerization via oxidative C–O and C–C coupling modes*

The oligomerization of ellagitannins mainly occurs via C–O oxidative coupling, but C–C oxidative coupling takes place in C-glycosidic ellagitannins, including complex tannins. The C–O coupling modes can be classified on the basis of the *O*-donating polyphenolic unit of a monomer and the *O*-accepting polyphenolic unit in another monomer composing the dimer, as shown below in Fig. 1.5. Generally, a given
linking unit repeatedly participates in the construction of an oligomeric ellagitannin system.

Fig. 1.5 Formation of the GOG and GOGOG oligomeric linking units.

1.3.4.2.1 The GOG- and GOGOG-type units
The GOG-type linking units are produced by C–O coupling between two galloyl groups (Fig. 1.5), as found in the \( p \)-GOG isodehydrodigalloyl group (\( p-O \) of a galloyl group C-linked to another galloyl group, mode \( a \)) and the \( m \)-GOG dehydrodigalloyl group (\( m-O \) of a galloyl group C-linked to another galloyl group, mode \( b \)). The GOGOG-type units are formed via an additional oxidative C–O coupling of a galloyl group with a GOG group. Agrimoniin and laevigatins B, C, D (Yoshida et al., 1989a) and E, as well as gemin A, are examples of dimers featuring the GOG-type linkage, and tamarixinin A and hirtellin B (Yoshida et al., 1989a).
1991c) are examples of dimers featuring the \( m \)-GO-\( m \)-GOG-type unit, also referred to as the hellinoyl group as shown below.

![Diagram of tannin structures](image)

1.3.4.2.2 The DOG and D(OG)\(_2\)-type units

In the DOG-type linking units, which are most frequently found in oligomers, the \( O \)-donating hydroxyl group is part of an HHDP group, and a galloyl group is the acceptor. The \( m \)-DOG and the \( p \)-DOG groups have been called valoneoyl and tergalloyl groups, respectively. The prefixes \( m \) and \( p \) referred to the position of the hydroxyl oxygen atom of the HHDP group being engaged in the diaryl ether bond. Rugosins D, E, F (dimers) and G (trimer) from several *Rosa* species (Okuda et al., 1982g, 1990, Hatano et al., 1990b), tetramers trapanin B from *Trapa japonica* (Hatano et al., 1990c) and nobotanin K from *Heterocentrum roseum* (Yoshida et al., 1989), and pentamers melastoflorins A-D from *Monochaetum multiflorum* (Yoshida et al., 2005), are examples of the
m-DOG-type linked oligomers. Eucalbanin C (vide infra) is a dimer having a p-DOG linking unit (Yoshida et al., 1992c).

In a D(OG)₂-type linking unit, found in a smaller number of oligomers, two hydroxyl groups of an HHDP group engaged their oxygen atoms in diaryl ether bonds, as exemplified in oenothein A and woodfordin D from Woodfordia fruticosa (Yoshida et al., 1991a) (see Section 1.3.5).
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Rugosin D: $R = (\beta)-OG$
Rugosin E: $R = OH$

Rugosin F

Rugosin G
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Trapanin B

Melastoflorin A

Nobatanin K
1.3.4.2.3 The GOD-type unit
The linking unit resulting from a donation of a galloyl hydroxyl oxygen to form an ether linkage to an HHDP group is classified as the GOD type. Roshenins A and B (Yoshida et al., 1992d), lambertianin A and sanguin H-6 are examples of the GOD-type dimers, and lambertianin C and sanguin H-11 are trimeric and tetrameric examples (Tanaka et al., 1985, 1993).
1.3.5 Macrocyclic oligomers

Macrocyclic dimers have been isolated from plants of several families. Oenothein B (Okuda et al., 1982b), often accompanied by the trimer oenothein A (Yoshida et al., 1991a), was isolated from Oenothera and Epilobium species in Onagraceae and Lythrum anceps in Lythraceae. Oenothein B was also isolated from Woodfordia fruticosa in Lythraceae, which also yields woodfordin C (Yoshida et al., 1990a), a galloylated oenothein B, and woodfordin D, which is a galloylated oenothein A (Yoshida et al., 1991). Camellin B, which displays an analogous macrocyclic structure, has been isolated from several Thea species and from Schima wallichii in Camelliaeaceae (Yoshida et al., 1990b). Cuphiins D1 (a galloylated woodfordin C) and D2 (a regioisomer of woodfordin C) were isolated from Cuphea hyssopifolia (Lythraceae) (Chen et al., 1999). Eugeniflorins D1 (a galloylated oenothein B) and D2, an analog having a hemiacetal-forming linking unit, were obtained from Eugenia uniflora (Myrtaceae) (Lee et al., 1997). These oligomers feature the m-DOG linking unit. The m- and/or p-GOG-bearing dimers tamarixinin B, hirtellin C and iso-hirtellin C, the structures of which are evoked in the next section on oligomer transformations, also display macrocyclic motifs.
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1.3.6 Structural transformations of ellagitannin oligomers

Although ellagitannins are generally stable compounds, some oligomers do undergo structural transformations under rather mild conditions.

1.3.6.1 Isomerization of dimers via Smiles rearrangement

Hirtellin C is a macrocyclic dimer possessing both the m- and p-GOG units that was isolated from Reaumuria hirtella (Tamaricaceae). It is readily isomerized into isohirtellin C in hot water at 95 °C via a Smiles rearrangement that enables the conversion of the p-GOG unit into a m-GOG unit. This rearrangement is presumably facilitated by the release of steric effects originating from hydroxyl groups in the p-GOG linking unit. Even at pH 7.4 and at only 40 °C, this isomerization reaction was almost complete within 30 min (Yoshida et al., 1993a).

Application of this isomerization reaction was used to confirm the structure of tamarixinins B (a macrocyclic dimer) and C, both isolated from Tamarix pakistanica (Tamaricaceae). Indeed, their Smiles rearrangement led to analogs of established structures, tamarixinin B being thus converted into hirtellin C, and tamarixinin C into hirtellin A (Fig. 1.6, Yoshida, et al., 1993b).

The tergalloyl group in eucalbanin C, a p-DOG-type dimer isolated from Eucalyptus alba (Myrtaceae), was quantitatively converted into eucalbanin B of the valoneoyl m-DOG-type in a phosphate buffer (pH 7.4) at room temperature (Fig. 1.7). The dilactonized tergalloyl group in eucalbanin A was also isomerized to the dilactonized valoneoyl group in cornusiin B (Yoshida et al., 1992c).

1.3.6.2 Hydrolysis of ellagitannin oligomers into monomers

Partial hydrolysis of oligomers in boiling water or weak acids affords monomers. The linking unit usually remains attached onto one of the monomers thus released from the dimeric structure. This type of transformation, or partial degradation, is a useful tool to gather important informations in the course of the elucidation of an oligomeric structure.
Fig. 1.6 Smiles rearrangement-mediated conversions of tamarixinin B into hirtellin C and tamarixinin C into hirtellin A.

Fig. 1.7 Smiles rearrangement-mediated conversion of eucalbanin C into eucalbanin B.
Fig. 1.8 Seasonal transformations of ellagitannins in *Liquidambar formosana*. 
1.3.7 Seasonal transformations of ellagitannins in a plant

While the ellagitannin structures occurring in a plant species are generally invariable throughout a year, as observed for geraniin in *Geranium* species, seasonal structural change of main tannins occurs in some woody plants. An example is the seasonal transformations of gallo- and ellagitannins in *Liquidambar formosana*. Tellimagradins, casuarictin and gallotannins, which are abundant in young leaves in April, are replaced by casuarinin by July, and the latter, together with pedunculagin, are the main tannins in the leaves from summer to autumn until the leaves fall down. This seasonal transformation, which interestingly parallels the oxidative biogenetic route followed by ellagitannin structures, is depicted above (Fig. 1.8, Okuda et al., 1987).

1.3.8 Production of ellagitannins by tissue cultures

The callus and shoot cultures of *Heterocentron roseum*, under illumination with fluorescent lamps, produce large amounts of casuarictin (a C-glycosidic monomer) and nobotanin M (a dimer) (Yazaki and Okuda, 1990). Oenothein B and other macrocyclic dimers were produced by callus culture of *Oenothera laciniata* and shoot tissue culture of *O. tetraptera* (Taniguchi et al., 1998, 2002). Geraniin and other ellagitannins were accumulated by *Aleurites fordii* callus culture (Taniguchi et al., 2002).

1.4 Correlation of Ellagitannins of Various Oxidation Stages with Plant Evolution Systems

1.4.1 Classification of hydrolyzable tannins based on the oxidation stages of their polyphenolic functions

Hydrolyzable tannins of various biogenetic oxidative stages can be classified into types I to IV according to the degree of oxidation of their polyphenolic groups. The different polyphenolic groups and examples of compounds of each type are as follows (Okuda et al., 2000):
Type I: gallotannins (galloyl group, e.g., 1,2,3,4,6-penta-\(O\)-galloyl-\(\beta\)-D-glucose, \textit{i.e.}, PGG)
Type II: ellagitannins (HHDP group, \textit{e.g.}, pedunculagin)
Type III: dehydroellagitannins (DHHDP group, \textit{e.g.}, geraniin)
Type IV: oxidized ellagitannins [chebuloyl group, \textit{e.g.}, chebulagic acid, geraniinic acids A and B, phyllanthusiins A-C, repandusinic acid, heterophylliin E]

In addition to these oxidative transformations, various additional transformations occur in plants, yielding monomers that can be classified into types I+ to IV+:

Type I+: \(C\)-glycosidic gallotannins (3,4,11-tri-\(O\)-galloylbergenin)
Type II+: \(C\)-glycosidic ellagitannins, \textit{e.g.}, casuarinin; complex tannins,
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e.g., camelliatannin A; ellagitannins linked to a phenolic or polyphenolic moiety through an ether linkage, e.g., coriariin B; gluconic acid version of ellagitannins, e.g., shephagenin A (Yoshida et al., 1996)

**Type III+**: dehydroellagitannins linked to a phenolic or polyphenolic moiety through an ether linkage, e.g., mallotusinic acid (Okuda et al., 1981)

**Type IV+**: oxidized dehydroellagitannins linked to a phenolic or polyphenolic through a C–C bond, e.g., camelliatannin F.
1.4.2 Correlation of the oxidation stages with Cronquist’s system of plant evolution

The progressive oxidative transformations of monomeric ellagitannins can be correlated with morphological plant evolution system. Since hydrolyzable tannins generally express strong antioxidation properties, the potency of which being correlated to their biogenetic oxidation stage, a correlation of their structures with the plant evolution system may be more significant than that of other plant metabolites. Thus, a search of such a correlation within subclasses of the Cronquist’s system of plant evolution for Dicotyledonae (Fig. 1.9), i.e., Rosidae, Dilleniidae, Hamamelidae, Caryophyllidae and Magnolidae (NB: ellagitannins are not found in Asteridae) unveiled the following aspects and several other features:
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i) Oxidized tannins of the types III and IV are frequently found in the Rosidae, while they are found only in a small number of plant species belonging to the Dileniidae and Hamamelidae. These oxidized tannins are not found in the Caryophyllidae and Magnolidae, the earliest subclasses of the Dicotyledonae.

ii) Correlations within a subclass are as follows. Rosales, the earliest order in the Rosidae, mostly produce type-I and type-II ellagitannins. The oxidative transformations to types III and IV progress according to the evolution of the orders, i.e., Rosales → Sapindales → Geraniales, without being accompanied by any production of oligomers, and Rosales → Euphorbiales, being accompanied by production of oligomers. The oxidative transformations in the Dilleniidae seem to progress from Dilleniales (type I) to Theales (types I, II and IV+) (Okuda et al., 2000).

Fig. 1.9  Cronquist’s plant evolution system of Dicotyledonae —– evolutionary route of ellagitannin-producing plants. □: orders to which ellagitannin-producing plants belong.

Analogous considerations may be made for the formation of C–O and C–C bonds (see Chapter 2) during oligomerization of ellagitannins, as well as during their macrocyclization, which requires formation of an additional bond:
i) Macrocyclic ellagitannin dimers, e.g., oenothein B and woodfordin C.  

ii) Macrocyclic ellagitannin trimers, e.g., oenothein A and woodfordin D.  

iii) Macrocyclic dehydroellagitannin dimers, e.g., eugeniflorin D₂ from *Eugenia uniflora*.  

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Fig. 1.10 Ellagitannins types in Geraniales and Euphorbiales plant orders.

**Geraniales**  
*Geraniaceae*  
*Geranium*: I, III, IV  

**Euphorbiales**  
*Euphorbiaceae*  
*Alchornea*: III, III+  
*Aleurites*: III, III+, IV  
*Antidesma*: III, III+  
*Euphorbia*: I, II, II+, III, III+, IV  
*Excoecaria*: I, II, II+, III, III+  
*Macaranga*: I, II, III, IV  
*Mallotus*: I, I+, II+, III, III+, IV  
*Phyllanthus*: I, II, III, IV  

1.4.3 Isolation of oxidized ellagitannin oligomers in specific plant orders

Highly oxidized ellagitannin dimers of types III, III+ and IV have been isolated from euphorbiaceous plants in Euphorbiales, besides from *Geraniaceae* in Geraniales (Fig. 1.10). Euphorbin E from *Euphorbia hirta*, composed of geraniin and oxidized isoterchebin molecules (Yoshida, *et al.*, 1990c), acalpydich D₁ (Amakura, *et al.*, 1999) composed of two geraniin molecules with an oxidized linking unit, and eurorbutin C (Hatano *et al.*, unpublished data) from *E. robusta*, a
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Macrocyclic dimer with brevifolin carboxylic acid as one of the linking units, are such examples. Many oligomers having geraniin as the composing unit have also been isolated from Euphorbiaceous plants (Yoshida et al., 1999).
1.5 Main Ellagitannin-Rich Medicinal Plants

Many plant species containing ellagitannins have been used for the treatment of diseases, especially in Asia (Okuda et al., 1992c). It is notable that the comparison of the amounts and pharmacological properties of ellagitannins and other components in plants shows that some of these ellagitannins could be playing the main role in the medicinal application of these plants (Fig. 1.11).

![Selection of ellagitannin-rich medicinal plants (main ellagitannin).](image)
The aerial part of *Geranium thunbergii* (*Geraniaceae*), producing geraniin, is one of the most popular medicinal plants in Japan, and is one of the official medicines in the pharmacopoeia, often used as an antidiarrheic. This medicinal plant has also been widely used for controlling intestinal function, mainly for preventing constipation. These medicinal effects will be principally due to protection of mucous membrane in intestine mainly by geraniin, and not retardation or acceleration of peristalsis of intestine, as observed in a pharmacological experiment with extracted intestine. The potent antioxidant activity and related activities of geraniin could also be participating in these effects. These two ways of application against constipation and diarrhea, opposite to each other at first sight, would be attributable to these activities helped by the mild property of geraniin.

*Mallotus japonicus* (*Euphorbiaceae*) is also a folk medicine used in Japan. Besides its bark that contains bergenin and oligogalloylated bergenins, utilized as an anti-ulcer medicine, its leaves that yield geraniin and mallotusinic acid (a type-III+ ellagittannin) have also been used for their stomachic effects (Okuda and Seno, 1981). Fruits of *Trapa japonica* (*Oenotheraceae*), which contain trapanin B (a tetramer), were also used as a stomachic and tonic medicine (Hatano *et al.*, 1990c).

The herb of *Agrimonia pilosa* (*Rosaceae*), yielding agrimoniin, the first isolated dimeric ellagitannin, is used as an antidiarrheic and a hemostatic medicine in Japan, although it is not as popular as *G. thunbergii*. Moreover, it has been used clinically as an anti-cancer medicine in China. *Agrimonia eupatoria*, a vulnerary, cholagogic and anti-aphtonic plant that grows in Europe and other parts of the world, also produces agrimoniin. Particularly worthnoting is the host-mediated antitumor activity observed for agrimoniin and several other analogous ellagitannins (see Section 1.7.2.3 and Chapter 6, Section 6.2).

Myrobalans, the fruits of *Terminalia chebula* (*Combretaceae*) that grows in India and Southeast Asia, yield chebulinic acid, chebulagic acid and terchebin. It is one of the most frequently used plant parts in Ayurveda, the traditional Indian medicine.

The herb of *Oenothera biennis* (*Onagraceae*), trivially called evening primrose, and other *Oenothera* species were used by Native Americans to quiet nervous sensibility. The herb of *Oenothera*
erythrosepala, from which were isolated the two macrocyclic oligomers oenothein A and B, is presumed to be a descendant from an American wild species, once cultivated.

The root peel of *Punica granatum* (*Punicaceae*) is an anthelmintic widely used against tapeworm. The ellagitannins granatins A and B and punicalin promote the anthelmintic effect of isopelletierine, which is not very effective when used alone. The fruit peel of this tree has also been used in Central and Western Asia as a gargling liquid for throat diseases.

The fruit of *Cornus officinalis* (*Cornaceae*), rich in cornusiins A, D and E (dimers), and C and F1 (trimers) (Hatano *et al*., 1989a/b), is a tonic in several prescriptions of traditional Chinese medicine. The flower of *Camellia japonica* (*Theaceae*) was used as a hemostatic in China.

The leaves of *Castanea crenata* (*Fagaceae*), which produces acutissimins A and B (Ishimaru *et al*., 1987), has been used as a tonic and an antitussive medicine, and also for treating a rash produced by lacquer poisoning. The herb of *Sanguisorba officinalis* (*Rosaceae*), which contains sanguins H-6 and H-11, has been used as a hemostatic
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and antidiarrheic in China. The herb of *Geum japonicum* (*Rosaceae*), which contains *inter alia* dimeric gemins A, B and C, was used in Japan as a diuretic. The herb of *Rubus triphyllus* (*Rosaceae*), which contains sanguins H-6 and H-11, was used as an antidiarrheic and a tonic medicine in Japan (Tanaka *et al*., 1985).

1.6 Properties and Primary Activities of Ellagitannins

The remarkable chemical stability of most ellagitannins allows accurate evaluation of their biological and pharmacological activities, in contrast to other types of tannins for which such evaluations are often difficult to perform.

1.6.1 Reduction, stabilization and precipitation of other substances by tannins, and solubilization of precipitates by excess tannin

At room temperature, ellagitannins, like other tannins, reduce metallic ions such as Cu$^{2+}$, Fe$^{3+}$ and Cr$^{6+}$ into Cu$^{+}$, Fe$^{2+}$ and Cr$^{3+}$, respectively (Okuda *et al*., 1982i). Such reductions are presumably accompanied by oxidation of the tannin molecules into quinonoid species. The discoloration of natural pigments, e.g., shikonin and β-carotene, that occurs during storage of their respective solution in ethanol in the presence of oxygen under light exposure was remarkably suppressed by addition of geraniin. This suppressing effect was further enhanced in the presence of metallic ions such as Ca$^{2+}$ and Mg$^{2+}$. The precipitates produced by mixing punicalin with Fe$^{3+}$ or Cu$^{2+}$ at a concentration of punicalin of $5.0 \times 10^{-3}$ M were solubilized at higher concentrations of punicalin, and the precipitates produced by mixing chebulinic acid with quinine, cinchonine, berberine or papaverine were also solubilized by increasing the concentration of chebulinic acid over 1.0 mg/10ml (Okuda *et al*., 1982j). Such solubilizations of precipitates are attributable to the higher solubility of the complexes formed when using higher concentrations of these tannins.
1.6.2 Indexes of tannin binding activity and reversal of tannin biological activities

The leather making activity of tannins is attributed to their aptitude to form multiple hydrogen bonds to collagen in hide. The binding of tannins with alkaloids has been exploited for preparing some medicines such as complexes of tannic acid with *inter alia* berberine and diphenhydramine in order to suppress the offensive taste of these compounds. Gallotannin mixtures have been mainly used for this purpose because of their ready availability. The efficacy with which a given tannin molecule binds to hemoglobin or methylene blue relatively to that of tannic acid JP (*i.e.*, Japanese Pharmacopoeia) (RA or RMB) or to that of geraniin (RAG or RMBG) offers convenient indexes that serve to rapidly evaluate the binding activities of various tannins (Okuda *et al*., 1985). The latter indexes RAG and RMBG are more reliable than the former ones, because of the structural uniformity of the standard compound geraniin.

The effects of tannins on enzymes can drastically vary and even be reversed depending upon the concentration at which the tannin molecule is used, as well as upon the structural class to which it belongs. For example, the inhibitory effects of the ellagitannins chebulinic acid and granatin B on *Streptococcus mutans*, a carcinogenic bacterium, at $10^{-5}$ M are less potent than those observed at $10^{-6}$ M, but they are reinforced by further increasing the concentration of these ellagitannins (Kakiuchi *et al*., 1986). Geraniin, mallotusinic acid, chebulinic acid and chebulagic acid enhanced adrenocorticotropic hormone (ACTH)-induced lipolysis in fat cells at a concentration of 20 $\mu$g/ml or 5 $\mu$g/ml, but all of these ellagitannins have no effect on the insulin-induced lipogenesis from glucose. These activities of ellagitannins are contrary to those observed with condensed tannins, which weakly inhibited ACTH-induced lipolysis, whereas they enhanced insulin-stimulated lipogenesis from glucose (Kimura *et al*., 1983).

1.6.3 Antioxidant activities

One of the most notable activities of tannins and related polyphenols is their potent antioxidant activity (Okuda *et al*., 1992b, 1993b, Okuda,
One of the roles of tannins in plant tissues, particularly in those around the vascular bundle where their concentration is generally high, might have to do with the prevention or at least the retardation of oxidation in the plant body.

The antioxidant activity of tannins was initially demonstrated by their suppression of the autoxidation of ascorbic acid (Yoshida, et al., 1981). The inhibitory effect of tannins on Cu(II)-catalyzed autoxidation of ascorbic acid was examined by kinetic studies and ESR measurements showing that the inhibitory effects by several ellagitannins (e.g., geraniin, mallotusinic acid and corilagin), and ellagic acid, which is produced by hydrolysis of ellagitannins, are markedly higher than that by polyphenols of low molecular masses, such as gallic acid, and also significantly higher than that by pentagalloylglucose (PGG). These effects are attributable to the potent radical scavenging activity of ellagitannins as substantiated by signals of stable free radicals in their ESR spectra. Unlike ellagitannins, polyphenols of low molecular masses usually gave unstable or no ESR signals. However, the antioxidant effect of ellagic acid, in spite of its rather small size, is quite high in accordance with the high stability of its free radical (Fujita et al., 1987).

The radical scavenging capacity of ellagitannins of various chemical structures has also been evaluated on the basis of their effects on the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical (Fig. 1.12). Ellagitannins generally showed more potent effects than α-tocopherol and ascorbic acid, as measured by the discoloration of the purple DPPH radical solution. The generation of stable free radical from an alkyl gallate upon scavenging the DPPH radical was demonstrated by ESR measurements and by high-yielding isolation of the dialkyl ester of hexahydroxydiphenolic acid (HHDP) produced by mutual coupling of transient C-centered galloyl radicals (Yoshida et al., 1989b). The antioxidant activity of ellagitannins, thus attributable to their radical scavenging effect, was also evidenced by their significant inhibitory action on the carbon tetrachloride- and galactosamine-induced cytotoxicities in primary cultured rat hepatocytes (Hikino et al., 1985).

The antioxidant effect of tannins on lipids in biological systems was shown by inhibition of lipid peroxidation induced by adenine 5'-diphosphate (ADP) and ascorbic acid in rat liver mitochondria, and by
inhibition of lipid peroxidation induced by ADP and NADPH in rat liver microsomes. All tannins, except some small polyphenols and methylated polyphenols among twenty-five compounds, showed significant inhibitory effects in these two systems at a concentration of 1 µg/ml, ellagitannins being generally much more potent than condensed tannins. The peroxidation was almost completely inhibited by pedunculagin and isoterchebin at a dose of 5 µg/ml (Okuda et al., 1983b).

In a study of the effects of tannins on arachidonic acid metabolism, geraniin and corilagin inhibited the formation of the lipoxygenase product 5-HETE (i.e., 5-hydroxyeicosatetraenoic acid) in rat peritoneal polymorphonuclear leukocytes, dose dependently at concentrations ranging from $10^{-3}$ to $10^{-6}$ M, whereas the formation of the cyclooxygenase products HHT, thromboxane B$_2$ and 6-keto-PGF$_{1α}$ was not inhibited at these concentrations (Kimura et al., 1986).
In an investigation of the protective effects of tannins against oxidative damage induced in mouse ocular lenses by incubating them with xanthin-xanthine oxidase, ADP and Fe$^{3+}$ (i.e., X-OX system), lipid peroxide concentration in the lens was markedly lowered by geraniin, but the effect was low when using polyphenolic small molecules (Iwata et al., 1987).

The effects of twenty-five tannins, including ellagitannins and small polyphenols, on the concentration of superoxide anion radical generated in the hypoxanthine-xanthine oxidase system, were evaluated by ESR measurements of the adduct of 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) and the radical. Increasing the ellagitannin concentration in the solution of superoxide generating mixture inhibited the appearance of signals of the DMPO adduct in a dose-dependent manner. The scavenging effect of ellagitannins on the superoxide anion radical increased generally with increase of the number of phenolic hydroxyl groups in the molecule. The radical scavenging mechanism of ellagitannins and related polyphenols on the superoxide anion radical was thus substantiated (Hatano et al., 1989c).

### 1.7. Biological and Pharmacological Activities

#### 1.7.1 Antiviral, antimicrobial and immunomodulatory activities

Monomeric and dimeric ellagitannins, as well as some gallotannins, potently inhibited *Herpes simplex* infection, as reported by Fukuchi and co-workers (Fukuchi et al., 1989). Dimeric ellagitannins efficaciously inhibited reverse transcriptase from RNA tumor virus (Kakiuchi et al., 1985). Several ellagitannins, including gemin D (a monomer), gemin A, camelliin B and nobotanins A, B and F (dimers), and trapanin B and nobotanin K (tetramers), among 87 tannins and related polyphenols, were shown to inhibit HIV-induced cytopathic effects and HIV-specific antigen expression, but condensed tannins expressed no similar activity (Nakashima et al., 1992).

Ellagitannins and other tannins exhibited interesting antimicrobial activities on some drug-resistant bacteria in the presence of some other
antimicrobial agents (see Chapter 2). Helicobacter pylori, a Gram-negative spirillum that may cause chronic gastritis, gastric ulcer, duodenal ulcer and also stomach cancer, was potently inhibited by tellimagrandin I and corilagin at a minimum inhibitory concentration (MIC) of 6.25 μg/ml.

The effect of β-lactam against MRSA (methicillin-resistant Staphylococcus aureus) acquiring multi-drug resistance was restored by corilagin and tellimagrandin I, as well as by several other polyphenols (see Chapter 2 for further details). Potent effects against leishmanises, a group of diseases with extensive morbidity and mortality in developing countries, were observed using several dehydroellagitannins, the ellagitannin hippophaenin A and also several gallotannins, while the effect of proanthocyanidins was generally less pronounced. Differences were found between Leishmania promastigotes and L. amastigotes in the anti-leishmanial activity of each polyphenol. These intriguing differences may be indicative of an activation of leishmanicidal macrophage function, which led researchers to rely on several functional bioassays, including a biochemical assay for nitric oxide (NO), a fibroblast-lysis assay for release of tumor necrosis factor (TNF-α), and a cytopathic effect inhibition assay for interferon (IFN)-like properties, for carrying out in-depth investigations of the activity of tannins on leishmanises (see Chapter 2).

1.7.2 Antitumor activities

A large amount of hard data has been gathered during the last two decades on the inhibitory activities of polyphenols, including ellagitannins and analogs, on tumor incidence and propagation. This is in sharp contrast to what was commonly thought earlier on, when precise chemical evidence of tannins was not available. Indeed, induction of cancers by some plant species was believed to be due to their high content in “tannins”. Today, the cytotoxic activity of several tannins of defined structure has been reported. Recent evidences of the antitumor activities of ellagitannins are reviewed thereafter.
1.7.2.1 *Inhibition of mutagenicity of carcinogens*

The mutagenicity of Trp-P-1 (*i.e.*, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole) and MNNG (*i.e.*, N-methyl-N'-nitro-N-nitrosoguanidine), and also that of N-OH-Trp-P-2 (*i.e.*, 3-hydroxyamino-1-methyl-5H-pyrido[4,3-b]indole), a directly-acting mutagen, were strongly inhibited by ellagitannins from medicinal plants, such as geraniin, mallotusinic acid, pedunculagin and agrimoniin, and also by (−)-epigallocatechin gallate (EGCG). Since ellagic acid was found to inhibit the mutagenicity of 7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (B[a]p diol epoxide) and since it is produced by hydrolysis of ellagitannins, variation of the antimutagenic activity of *Geranium thunbergii* was investigated along the extraction of geraniin during which its hydrolysis occurs. Interestingly, the results showed that after an initial and rapid increase of the inhibitory effect on Trp-P-1 due to an increase of the concentration of geraniin as a result of its extraction from the plant, a marked downward modulation of that effect was observed due to the hydrolysis of geraniin. An upward modulation of the inhibitory effect on B[a]p diol epoxide occurred simultaneously due to the hydrolytic release of ellagic acid from geraniin (Okuda *et al*., 1984a).

1.7.2.2 *Inhibition of tumor promotion*

Tumor promotion is a much longer process than its initiation during the two-stage chemical carcinogenesis, and its inhibition is therefore regarded as an important objective in cancer prevention. The tumor promotion on mouse skin by 12-O-tetradecanoylphorbol-13-acetate (TPA), after initiation with dimethylbenz[a]anthracene (DMBA), was significantly inhibited by ellagic acid and several ellagitannins isolated from *Cowania mexicana* and *Coleogyne ramosissima*. These compounds were also found to inhibit Epstein-Barr virus early antigen (EBV-EA) activation induced by TPA. The TPA-induced ornithine decarboxylase (ODC) activity and the TPA-stimulated hydroperoxide production were inhibited by several ellagitannins and other polyphenols (Ito *et al*., 1999b). Inhibitors of TNF-α release nowadays constitute attractive potential candidates for the development of cancer preventing strategies.
In this vein of investigation, geraniin and corilagin were identified as potent inhibitors (Okabe et al., 2001).

1.7.2.3 Host-mediated antitumor activity

Several oligomeric ellagitannins specifically inhibited tumor (Sarcoma-180 and MM2) growth after having been administrated either before or after intraperitoneal inoculation of tumor cells into mice abdomen. This effect was found only for these oligomers among over a hundred tannins and related polyphenols thus screened. Among these active oligomers were macrocyclic oligomers, such as oenothein B and woodfordin C (dimers), oenothein A and woodfordin D (trimers), and woodfordin F (tetramer) (Miyamoto et al., 1997). This effect was attributed to an enhancement of the immune response of host animals, which was supported by their stimulation of IL-1 production from human peripheral macrophages (Miyamoto et al., 1993, see Chapter 6).

1.7.3 Induction of apoptosis

Ellagitannins induced apoptotic cell death, which was characterized by internucleosomal DNA cleavage and apoptotic body in human promyelocytic leukemic HL-60 cells and evaluated by agarose gel electrophoresis and fluorescence activated cell sorter, at levels of potency higher than those determined for condensed tannins. However, the most active compound thus screened was the simple phenol gallic acid (Inoue et al., 1994, Sakagami et al., 1995, 1999).

1.7.4 Effects on liver functions and others

Intramuscular administration of geraniin significantly lowered levels of glutamyl oxaloacetic transaminase (GOT), glutamyl pyruvic transaminase (GPT) and lipid peroxides in serum (Nakanishi et al., 1999). Intramuscular injection of geraniin and ellagic acid significantly suppressed experimental hepatic injuries induced by carbon tetrachloride, D-galactosamine, and thioacetamide in rats, and a protective effect against liver damages was confirmed by histological observation (Hikino...
et al., 1985). Geraniin was also found to suppress the increase of lipid peroxide level in the serum caused by inhalation of carbon tetrachloride.

The effects of tannins as evaluated via oral administration are particularly worthy of further investigation. The oral administration of geraniin-rich extract of *Geranium thunbergii* significantly lowered the lipid peroxide level in the serum and the liver of rats in which liver injury was induced by feeding them with peroxidized oil. The levels of serum cholesterol, GOT and GPT in the rats treated with peroxidized oil were also reduced in the presence of geraniin (Kimura *et al.*, 1984).

### 1.7.5 Absorption and metabolism of ellagitannins in animals

The metabolic conversion of ellagic acid in animals into 3,8-dihydroxybenzo-[b,d]pyran-6-one and related compounds was reported in 1980 (Doyle and Griffiths, 1980). This compound and 3-hydroxy-6H-dibenzo[b,d]pyran-6-one were detected in the urine and serum of a sheep that was fed with *Terminalia oblongata* leaves containing chebulagic acid, punicalagin and teroblongin (*i.e.*, 1-α-O-galloylpunicalagin). 3-O-Glucuronide of 3-hydroxy-6H-dibenzo[b,d]pyran-6-one was also isolated from the urine and serum of the sheep (Okuda *et al.*, 1995). These aspects and other related to the bioavailability of ellagitannins are discussed in greater details in Chapters 7 and 8.

![Chemical structures](image)

3,8-Dihydroxy-6H-dibenzo[b,d]pyran-6-one: R = OH
3-Hydroxy-6H-dibenzo[b,d]pyran-6-one: R = H

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